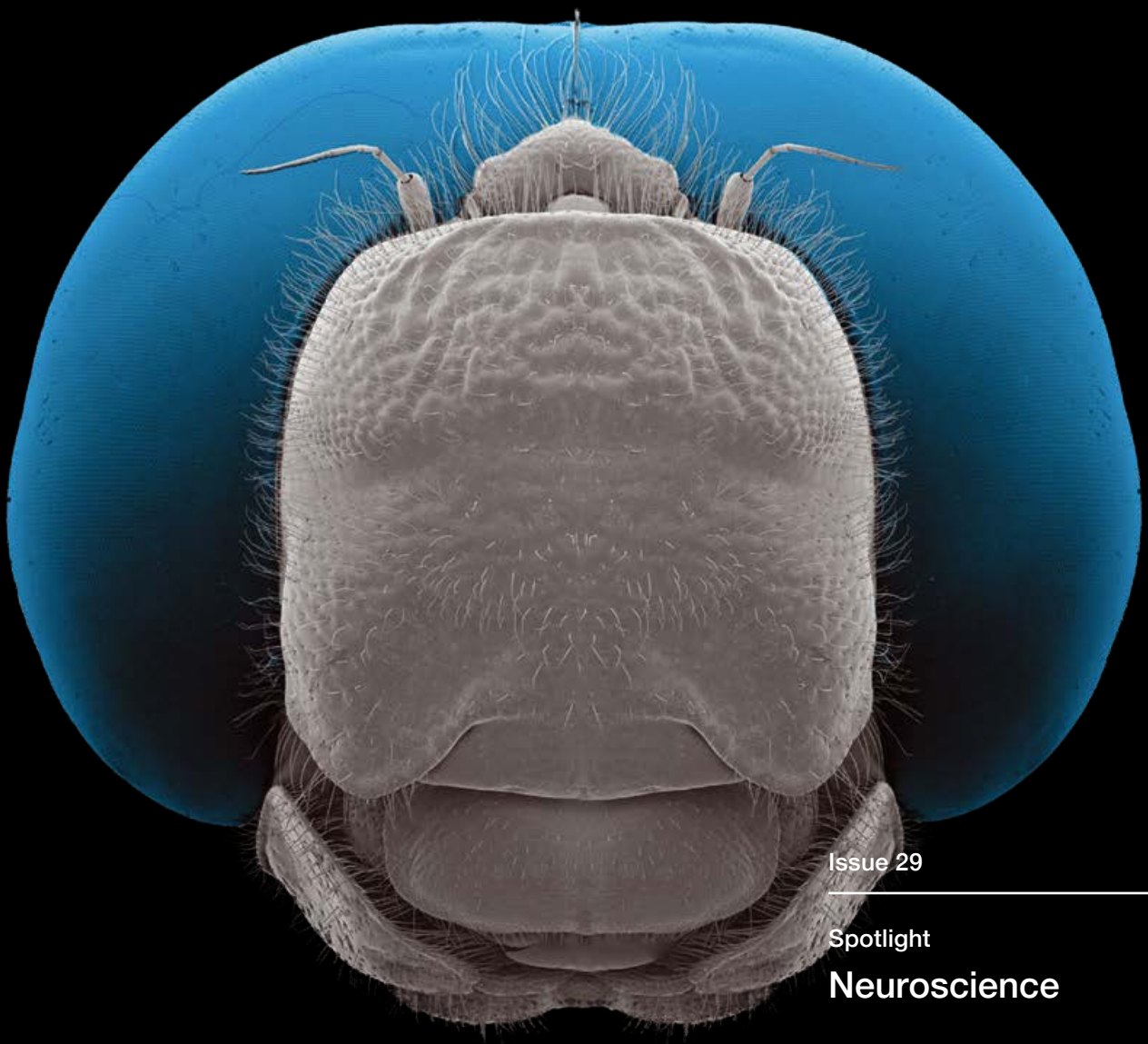
Research

Horizons

Pioneering research from the University of Cambridge



Issue 29

Spotlight

Neuroscience

Feature

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Feature

Soft solids and the science of cake

UNIVERSITY OF CAMBRIDGE
www.cam.ac.uk/research

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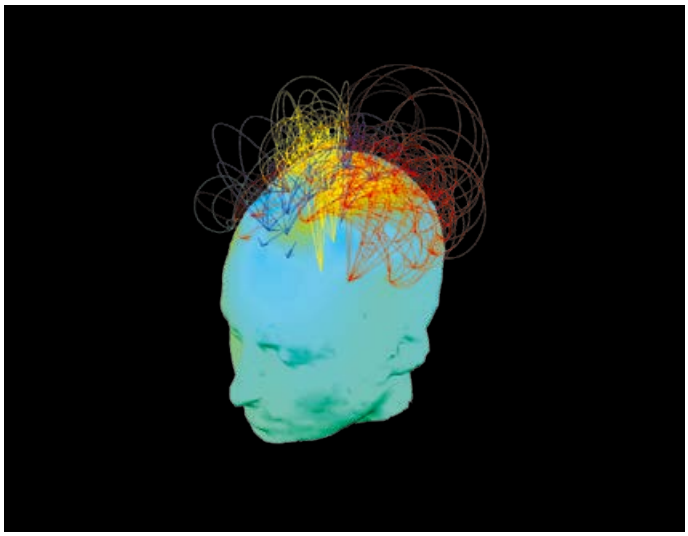

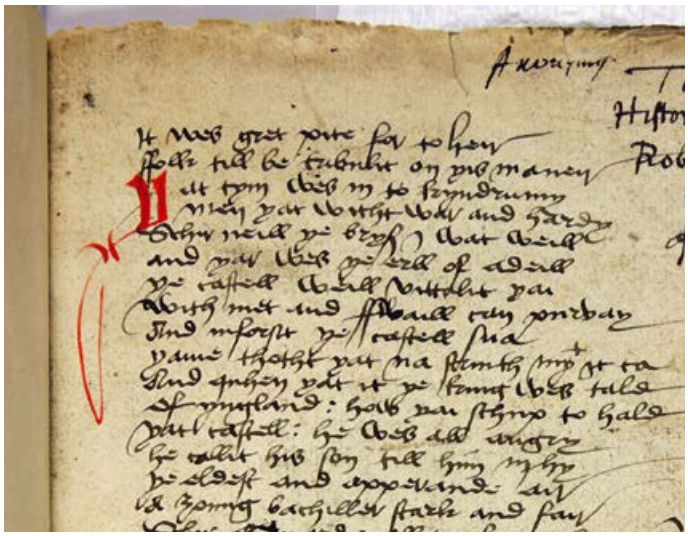

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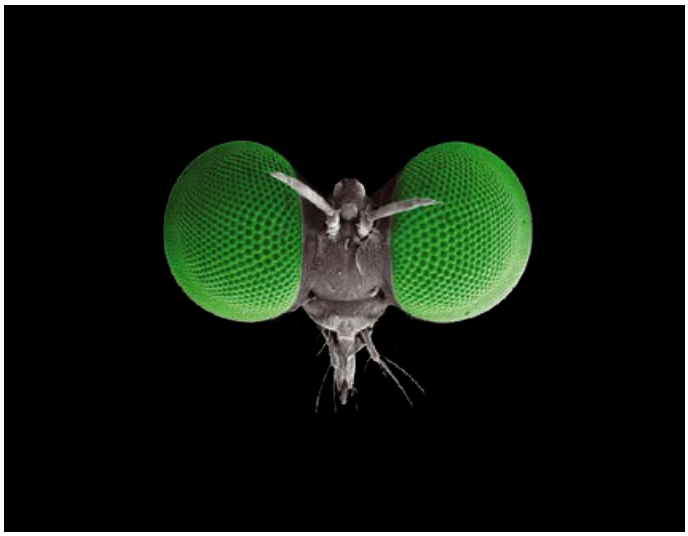

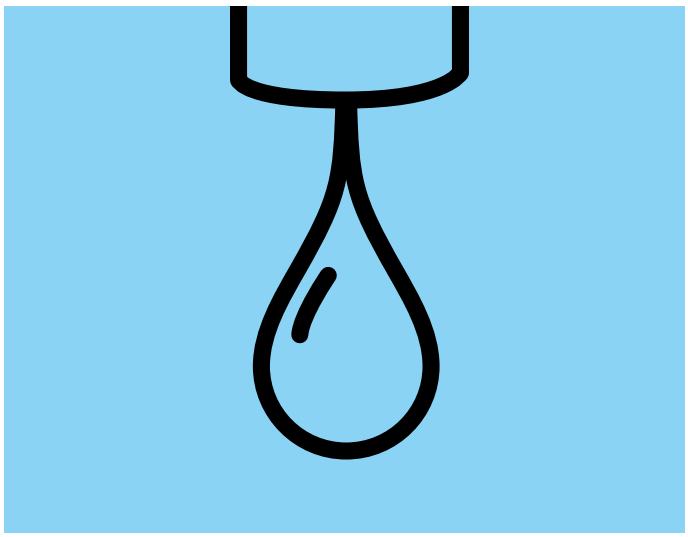

Welcome

I am delighted to welcome you to this issue of *Research Horizons*, the first in my new role as Pro-Vice-Chancellor (PVC) for Research. I am really thrilled to take this position, and especially look forward to working as part of the new PVC team. I want to express particular thanks to my predecessor, Lynn Gladden, for leaving me a great set-up to run, and also for being incredibly supportive over the last few months as I grappled to understand the role.

It's always an exciting time to be working in Cambridge, but now feels particularly so with all the developments in research infrastructure – on the Cambridge Biomedical Campus, in the City centre and in West Cambridge. The recent announcement of a £75 million investment by the government in our Cavendish Laboratory was especially pleasing.

One research area that has been growing and diversifying is neuroscience – the Spotlight focus of this issue. We have over 700 researchers in more than 60 different departments across the University and its local institutes, working in everything from biomedicine and maths, to psychiatry and philosophy, and education, engineering and economics. They are connected by Cambridge Neuroscience, which was launched in 2007 and became one of the University's first Strategic Research Initiatives in 2010.

We hope the articles give you a sense of one of the cornerstones of Cambridge Neuroscience – the need to translate fundamental advances into an understanding of the healthy and diseased brain and how we apply this knowledge. As a research chemist working in drug discovery, I appreciate the importance of making this connection happen.

Elsewhere in the magazine, we cover far-reaching territory indeed – from 20 years of exoplanet discovery to the history of paper and of polio vaccination, and from the science of cake to the story of how a headache led to the discovery of a possible treatment for thrombosis. It is really gratifying to see articles covering the work of researchers at all stages of their careers, including postdocs, whom I have long championed.

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News

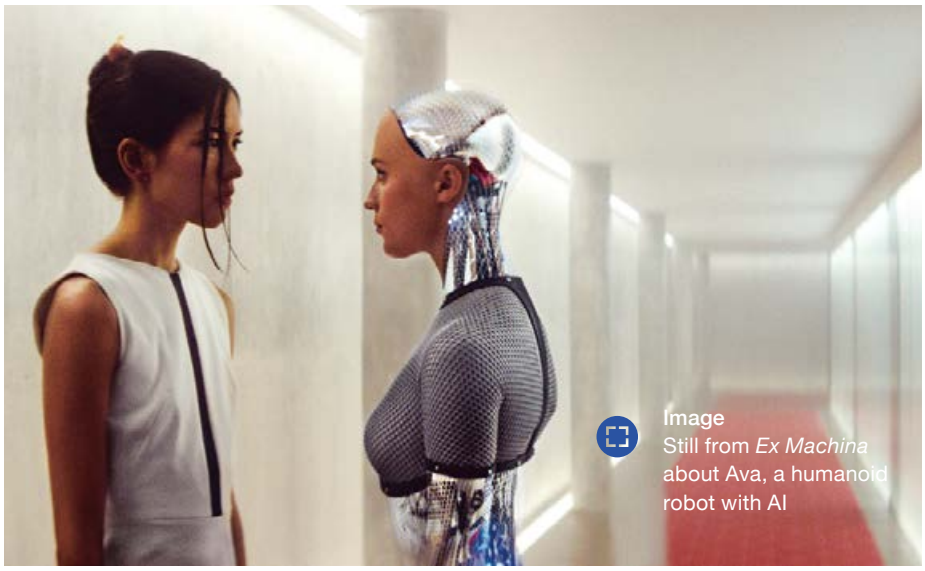


Image
Still from *Ex Machina* about Ava, a humanoid robot with AI

Facing the future of intelligence

A new research centre will explore the opportunities and challenges to humanity from the development of artificial intelligence (AI).

Human-level intelligence is familiar in biological 'hardware' – it happens inside our skulls. We live in an age in which it is feasible that similiar intelligence might one day be created in computers.

While it's hard to predict when this will happen, some researchers suggest that human-level AI will be created this century. Freed of biological constraints, such machines might become much more intelligent than humans. What would this mean for us?

Thanks to an unprecedented £10 million grant from the Leverhulme Trust, the University of Cambridge is to establish a new interdisciplinary research centre, the Leverhulme Centre for the Future of Intelligence, to explore the opportunities and challenges of this potentially epoch-making technological development.

Huw Price, the Bertrand Russell Professor of Philosophy and Director of the Centre, explains: "Machine intelligence will be one of the defining themes of our century, and the challenges of ensuring that we make good use of its opportunities are ones we all face together. At present, however, we have barely begun to consider its ramifications, good or bad."

The Centre brings together computer scientists, philosophers, social scientists and others from the Universities of Cambridge and Oxford, Imperial College London and the University of California, Berkeley, and is supported by Cambridge's Centre for Research in the Arts, Social Sciences and Humanities.

Dr Ó hÉigeartaigh, Executive Director of the University's Centre for the Study of Existential Risk (CSER), which developed the proposal for the new Centre, adds: "The Centre is intended to build on CSER's pioneering work on the risks posed by high-level AI and place those concerns in a broader context, looking at themes such as different kinds of intelligence, responsible development of technology and issues surrounding autonomous weapons and drones."

Deutschlandstudien

A new research hub in Cambridge will improve understanding of the German world past and present.

The word *Forschungszentrum* (research centre) will be heard more often in Cambridge, as a research hub and 25 new research projects commence in the arts, humanities and social sciences. What connects them all is the study of Germany.

"Arguably, Cambridge has the largest number of scholars working on Germany and German culture in the world outside Germany itself," says Professor Christopher Young, who with Professor Sir Christopher Clark co-directs the new research centre.

Now, with €1m funding from the German Academic Exchange Service (DAAD), this portfolio will be intensified across fields such as history, law, economics, divinity, philosophy, literature and linguistics. Neil MacGregor, Director of the British Museum, is patron.

Many of the projects will involve exchange visits with German scholars, positioning Cambridge as a nexus for the Anglo–German relationship and catalysing further research projects.

Two public forums per year, held in association with a German newspaper, will look at issues that are relevant to contemporary Germany. "This could be immigration, or austerity, high-tech investment or the unique development of Berlin," explains Young. "Germany is widely regarded as a model economy. Understanding the country's economic and political importance, and the challenges it faces, is a golden opportunity for us and for Europe."

"We have huge strength and depth in Germany-related research across a couple of millennia. This will be the first time such a wide portfolio has been brought together and developed. We hope the hub will act as a beacon for the study of German culture both in the UK and worldwide."

News in brief

More information at www.cam.ac.uk/research

22.01.16

Infectious diseases lab opens at the University of Makeni, Sierra Leone, in partnership with the University of Cambridge.

04.01.16

New Year's honours for Professor Alastair Compston, Professor Dame Ann Dowling, Professor David MacKay and Dr Emily Shuckburgh.

Boosting farm yields could 'sink' gas

Raising farm yields and allowing 'spared' land to be reclaimed could offset greenhouse gases produced by farming.

Land is a source of greenhouse gases if it is used to farm fertiliser-hungry crops or methane-producing cattle. But it can also be a sink for gases if agricultural yields are increased and areas of natural forests and wetlands are expanded.

New research by Professor Andrew Balmford, Department of Zoology, suggests that upping forest cover from 12% to 30% of UK land over the next 35 years – close to that of France and Germany, but still less than the European average – and restoring 700,000 hectares of wet peatland would mean these habitats could act as a carbon 'sink'. What's more it could be enough to meet government targets of 80% greenhouse gas reduction by 2050 for the farming industry.

The study originated from a Cambridge Conservation Initiative workshop, which asked leading experts to "look into their crystal balls", says Balmford. "We wanted to know what food yield increases were achievable in the 2050 timescale across crop and livestock sectors."

Prehistoric massacre

Skeletal remains from a massacre 10,000 years ago suggest the "presence of warfare" in late Stone Age foraging societies.

Partial remains of 27 individuals, including at least eight women and six children, have been unearthed in Nataruk, Kenya, by researchers from Cambridge's Leverhulme Centre for Human Evolutionary Studies (LCHES).

Massacred around 10,000 years ago, the group of prehistoric hunter-gatherers show clear signs of a violent death: extreme blunt-force trauma to crania and cheekbones, broken hands, knees and ribs, arrow lesions to the neck, and stone projectile tips lodged in the skull and thorax of two men. The hands of four had probably been bound, including a woman in the last stages of pregnancy.

The researchers believe it is the earliest scientifically dated historical evidence of human conflict – an ancient precursor to warfare – and that the group, perhaps members of an extended family, might have been attacked and killed by a rival group of prehistoric foragers.

"The deaths at Nataruk are testimony to the antiquity of inter-group violence and war," says Dr Marta Mirazón Lahr, from LCHES, who led the Nataruk study, just published in *Nature,* and directs the European Research Council funded IN-AFRICA Project.

"The Nataruk massacre may have resulted from an attempt to seize resources – territory, women, children, food stored in pots – whose value was similar to those of later food-producing agricultural societies, among whom violent attacks on settlements became part of life."

The origins of warfare are controversial: some believe that the capacity for organised violence occurs deep in the evolutionary history of our species, others that it is a symptom of the idea of ownership that came with the settling of land and agriculture.

The Nataruk massacre is the earliest record of inter-group violence among prehistoric hunter-gatherers who were largely nomadic.

Image
The skull of a hunter-gatherer showing evidence of blunt-force trauma to the head

Credit: Marta Mirazon Lahr, enhanced by Fabio Lahr

30.11.15

Winston Churchill's vast archive – held at Cambridge's Churchill College – has been added to UNESCO's list of the world's greatest cultural treasures.

26.11.15

Jaguar Land Rover adopts a 'head-up' holographic display developed at Cambridge for passenger vehicle windscreens.

25.11.15

The Government has announced that an investment of £75 million will be made in Cambridge's Cavendish Laboratory.

Terra hunter

Image
Could picking an exotic planet for your holiday destination be reality one day?

Twenty years ago, in Geneva, PhD student Didier Queloz discovered a planet orbiting another sun – something that astronomers had predicted, but never found. Today he continues his terra hunting for extreme worlds and Earth twins in Cambridge.

When the numbers began to filter through from the spectrograph that was measuring small shifts in light from distant stars, Didier Queloz at first thought they were wrong. He certainly didn't think he'd discovered an exoplanet. He checked and re-checked.

"At some point I realised the only explanation could be that the numbers were right."

Today, many regard the discovery of 51 Pegasi b by Queloz and Professor Michel Mayor at the University of Geneva in 1995 as a moment in astronomy that forever changed the way we understand the universe and our place within it. It was the first confirmation of an exoplanet – a planet that orbits a star other than our Sun. Until then, although astronomers had speculated as to the existence of these distant worlds, no planet other than those in our own solar system had ever been found.

"For centuries, we only had the one single example of our own solar system on which to base our knowledge of planets," says Queloz, who moved to Cambridge's Department of Physics two years ago. "If you wanted to understand botany, you wouldn't build the botanic picture from one single flower – you need all the others."

Of the 1,900 or so confirmed exoplanets that have now been found – a tenth of these by Queloz himself – many are different to anything we ever imagined, challenging existing theories of planet formation.

Fifty light years from Earth, the exoplanet 51 Peg resembles the gas giant Jupiter. But unlike our distant cousin, which is located in the further reaches of our solar system and takes 10 years to orbit the Sun, 51 Peg 'hugs' its sun, orbiting every four days. It's been hailed as an example of a whole new class of 'roaster planets' or 'Hot Jupiters' and has prompted scientists to wonder if large planets are able to migrate closer to their suns over millions of years.

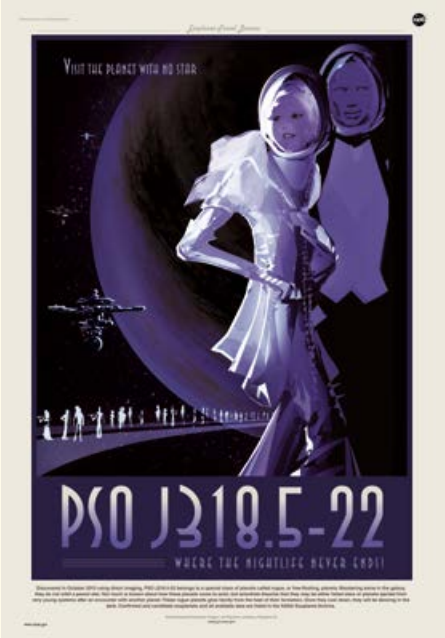
"We are constantly surprised by the diversity of the other worlds," says Queloz. Super-Earths like the volcanic planet 55 Cancri e with a temperature gradient across it of a thousand degrees; rogue planets like PSO J318.5-22, which roam freely between stars; Kepler-186f, which is lit by the light of a red star; and icy Kepler-16b with its double sunset. "For some, we don't even have names to describe what they are."

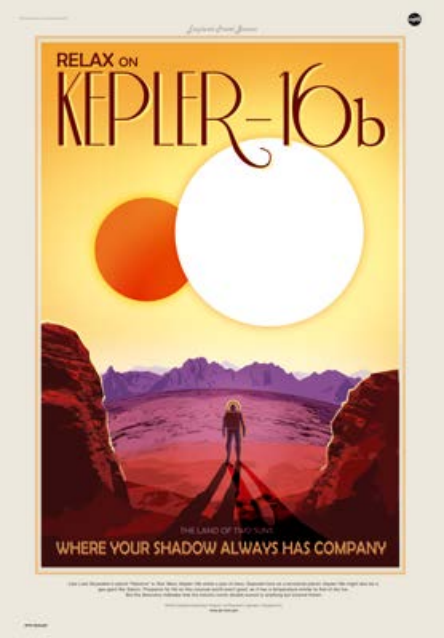
But, as yet, no planet has been discovered that could be considered a twin of our own. "We are finding planets of a similar size and mass to Earth but nothing at the right temperature – so-called Goldilocks planetary systems in the habitable zone close enough to the sun to be warmed by it but not so close that the presence of water and life is a sheer impossibility," explains Queloz.

"Of course the question everyone would like to answer is whether there is life out there, because we are curious and we can't resist – it's how we are," says Queloz.

Queloz believes that a new era of terra hunting is fast approaching. "The past 20 years has seen a 'brute

Credit: All images: courtesy of NASA/JPL-Caltech





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Film available

force' hunt for exoplanets. We are now confident that they are practically everywhere you look for them. To find an Earth twin, however, we need to look at specific planets for longer."

It's not possible to see an exoplanet directly – it's far too close to a blinding source of light, its star – so astronomers use two techniques to look indirectly. Focusing on a star, they use NASA's Kepler telescope to look for the dimming of starlight as the planet transits in front of it. From this, they calculate the planet's size and temperature.

The breakthrough that Queloz and Mayor pioneered was a technique to look for signs of 'wobble' caused by the gravitational pull exerted by the planet on the star as it orbits. The technique needed to be accurate enough to detect a wobble of only 10 m/s – the speed of a running man. To put this in context, the Earth moves at the speed of 30,000 m/s."

Current technology works well for finding large exoplanets but to find planets the size of the Earth in the habitable zone astronomers need to look at smaller stars, and they need to overcome 'stellar noise', or natural variability in the data caused by physical motions of gas at the surface of the star.

"This noise is slowing further progress but we believe that it can be overcome by careful analysis and by extending the length of time we are able to observe a planet for," adds Queloz. "Intensive runs on a small number of stars where an observation is carried out every night for years is far more valuable than unevenly spaced data taken over years."

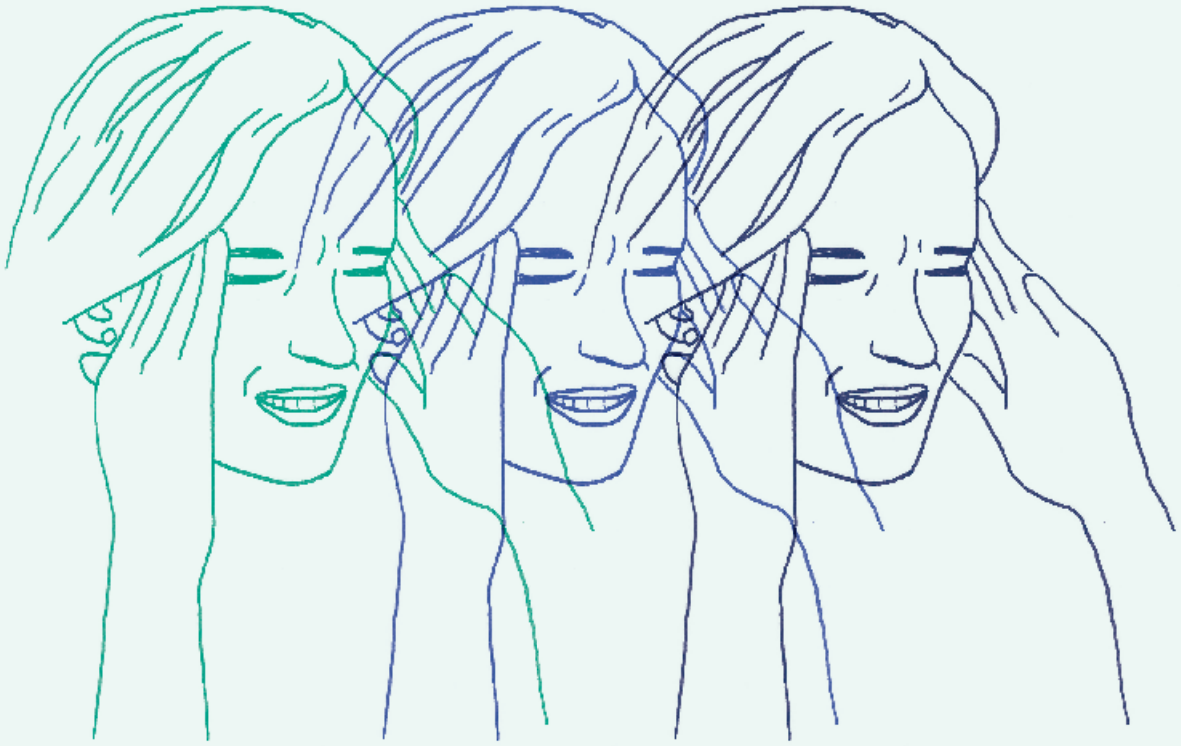
"We are constantly surprised by the diversity of the other worlds"

As techniques improve and with the launch of the James Webb Space Telescope, astronomers will be able to ask whether what we understand as the basic molecules of life – carbon, oxygen and hydrogen – are present in the atmosphere of exoplanets, opening up the possibility of understanding their astrobiology and geophysics.

"My feeling is that life will be found, although life like us may be extremely rare because otherwise we probably would have seen it by now," he adds. "It may take a long time, and many scientists, to find life, but maybe that's part of the fun – it would be too easy otherwise!"

On the door of Queloz's office is a spoof poster published by NASA in celebration of 20 years of exoplanet discoveries. Offering greetings from the Exoplanet Travel Bureau, it suggests 51 Pegasi b as a dream destination, or indeed "any planet you wish – as long as it's far beyond our solar system." Could this be reality one day? "It's far too hard to say," says Queloz. "But I would hope that sending a tiny probe of perhaps a few grams in weight might be possible in the next century."

At one stage in recent years, Queloz was almost finding an exoplanet a week. His terra hunting has slowed while he focuses on improving the equipment and techniques that he believes will help find an Earth twin. But the excitement never goes away, he says. "I must admit that every time I find a planet I feel like a child – it's a surprise because it's a new system. I used to joke with people asking me about sci-fi – the reality is far more exciting and diverse than any sci-fi movie you can imagine!"



The scientist, the clinician, his patient and her headache

How a bump on the head could lead to a drug that might save the lives of millions of people who are at risk of clotting.

The woman's headache had lasted for three weeks. She'd accidentally bumped her head on a door, and when the medics at A&E carried out a CT scan they saw a collection of blood on the surface of her brain indicating a traumatic bleed. When they analysed blood samples in a test tube, it refused to coagulate. There was something strange about this blood.

"The tests showed that her clotting was grossly abnormal," explains Dr Trevor Baglin, Consultant Haematologist at Cambridge University Hospitals, who was called in to treat the patient. "It looked like a severe form of acquired haemophilia. We thought it could be life-threatening – her clotting system did not appear to be working. Fortunately, and to our surprise, the bleed on her brain didn't progress."

Baglin called up his colleague Professor Jim Huntington at the Cambridge Institute for Medical Research. The clinician and the scientist had been working together for the previous eight years, hoping to find the solution to a medical conundrum: how to prevent the fatal clotting that leads to stroke, heart attack and deep-vein thrombosis (DVT) without putting a patient at risk of excessive bleeding.

The crux of the challenge is a remarkable balancing act that exists within our blood. On the one hand, it's essential that blood keeps moving; any blockage (called thrombosis) could stop oxygen flow to the brain or disrupt the beating of the heart. But in the event of an injury, it's imperative that the leakage is blocked to avoid huge blood loss. The haemostatic system that governs the balance between thrombosis and bleeding is a complex and highly efficient cascade of interactions between proteins and cells, inhibitors and stimulators.

Which made what was happening in the patient all the more intriguing and alarming. "We thought that the patient would present with another bleed and that next time she might die," continues Baglin. "This was our impetus to start investigating her – we needed a strategy to save her."

They drew on expertise among colleagues in Cambridge and internationally, as Huntington explains: "There was no time to write a grant and raise funding – we had to find help where we could.

"But it took time to figure it out and during all this time she kept not haemorrhaging. She even had surgery and accidentally cut part of her finger off. Each time, she clotted when she shouldn't have been able to."

They began to suspect that she was proof of something they had hypothesised about for years. "We knew there must be another way of helping people at risk of clotting than the currently available pharmacological approaches of simply inhibiting the process – these treatments are notoriously tricky to get right and can result in bleeds," says Huntington.

"We were looking for a more physiological approach – one that mimics what is happening naturally – when a 'proof of concept' walked into the clinic," adds Baglin.

"We thought it could be life-threatening – her clotting system did not appear to be working"

"...we needed a strategy to save her"

They had already identified a region called exosite 1 on thrombin, a protein that lies at the heart of the clotting cascade, as being a potential target. In a remarkable case of coincidence, the patient was making a rogue antibody that recognised exosite 1, and it was this antibody that was causing the strange behaviour of her blood.

Baglin explains further: "The reason we had identified exosite 1 as a target is because it is critical for defining what thrombin interacts with – 'the company it keeps' – which determines whether a good clot or a bad clot is formed.

"We believe that events involved in good versus bad blood coagulation are subtly different, even to the extent of where in the blood vessel – at the wall or in the centre – that the clot forms. We think that the patient's antibody exploits this difference beautifully, tilting the balance in favour of the formation of a good clot."

Using this knowledge, Baglin and Huntington decided to make a synthetic antibody, which they called ichorcumab, now known as JNJ-375. Although it differs from the patient's antibody, it binds to exosite 1 in a similar fashion.

"A third of people in the Western world die of some form of thrombosis," adds Huntington. "DVT, pulmonary embolism, ischaemic stroke, heart attack – all result from the inappropriate activity of thrombin. This antibody might deliver a high degree of anticoagulation without increased bleeding; we've never seen that before."

With the help of Cambridge Enterprise – the University's commercialisation arm – they formed a spin-out company, XO1 Ltd, raised $11 million in funding and began to develop the antibody as a new anticoagulant drug candidate. In 2015, the company was acquired by Janssen Pharmaceuticals Inc.

"There's a huge unmet need for anticoagulants," says Dr Peter DiBattiste, Global Development Head, Cardiovascular, for Janssen Research & Development LLC. "Despite the availability of anticoagulants for over 60 years, there are still many people who go untreated because of the risk of bleeding. This could really be a game changer."

JNJ-375 opens up a completely new field of candidate drugs for thrombotic diseases. Unlike current treatments, which are taken in tablet form at a specific dosage, the hope is that this drug might be administered monthly by subcutaneous injection, in the clinic or even at home. "The key thing here is that one size dosage should fit all," says Huntington. "Because of the way it works, it would be impossible to take too much and bleed."

Baglin and Huntington continue to be involved in the preclinical testing phase and in plans for clinical trials, along with many researchers who have been drawn together by this fascinating project. "We recognise the tremendous expertise that these individuals bring to the project. It's really invigorating to get the scientific input of brilliant people who have devoted their lives to thrombosis," adds DiBattiste.

Looking back, Huntington feels that the insight gleaned from the patient who'd bumped her head is a shining example of the importance of clinicians and scientists working together. "If Trevor and I had not already been collaborating then the chance of this patient's natural anticoagulant being spotted would have been quite slim. As Louis Pasteur said, 'In the field of observational research, fortune favours the prepared mind', and our minds were prepared."

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Tales from the paper trail

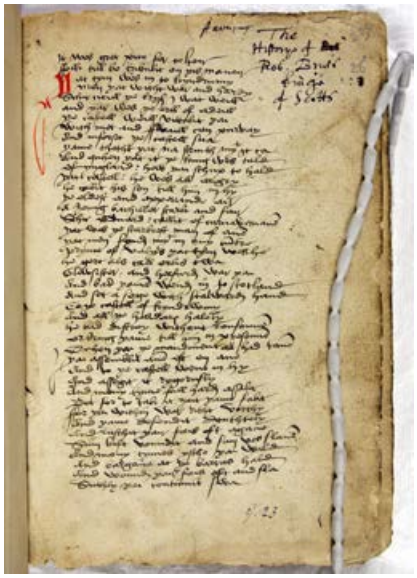
It may seem strange to describe paper as technology, but its arrival in England in about 1300 was a pivotal moment in cultural history. That story is being pieced together for the first time in a new project that also promises to reveal much about why some innovations succeed where others fail.

How's this for a measure of the pace of the tech revolution? Twenty years ago, you would have read this article only on paper; now it is also available on your tablet, smartphone or computer. The impact of digital media has become so pervasive that even remarking upon it feels trite. Where predictions that printed books and newspapers are dying once seemed far-fetched, the future now seems less certain.

If we do become a paperless society, we will be terminating a relationship with one of the most successful technologies of all time; one that has endured for 700 years in England, and much longer elsewhere. Our reliance on paper runs so deep that it seems strange to think of it as technology at all. Yet to a person living in 14th-century England, paper would have been an advanced new material. Most writing was on parchment (made from animal skin), and an alternative made of pulped rags represented a truly disruptive innovation.

"Paper was economical – not in the sense that it was cheap, but because it was lighter, more portable and enabled you to write more," explains Dr Orietta Da Rold from the Faculty of English. "Its arrival had a huge impact. People could share ideas in a way that hadn't happened before. Paper became a pivotal technology for a subsequent explosion in the transmission of knowledge."

Da Rold is leading a project called Mapping Paper in Medieval England, the pilot phase of which was carried out last year. The aim is to understand how and why paper was adopted in England and eventually became a dominant technology – more so even than electronic media have today.



Credit: St John's College Library, Cambridge

Its historical importance goes beyond paper's significance as a device for dissemination. Paper, Da Rold suggests, helped to precipitate the spread of literacy and literature. It could be used to teach and practice reading and writing, and it enabled the emergence of a reading public that consumed and shared the works of Geoffrey Chaucer, among others.

It is also a history that has never been fully explored. We know that England was slow to adopt paper, because paper-based manuscripts started to appear in archives only from about 1300 onwards, later than on the continent. How and why this happened, however, has never been properly studied.

In 2015, thanks to a Cambridge Humanities Research Grant, Da Rold and her team spent eight months trawling archives up and down the country in search of paper manuscripts written or based in England between the years 1300 and 1475, when William Caxton set up his first printing press. They found 5,841 manuscripts, of which 736 were paper.

"That's not the final number because some records don't state whether a manuscript is paper or not," Da Rold says. The information has, however, been enough to set up an electronic database – the most comprehensive of its kind – with ambitions to crowd-source more data in the future.

Working out how the use of paper spread across England means establishing where each of these manuscripts was based, which is easier said than done because both manuscripts and scribes moved. In some cases, the dialect used in the text suggests a possible point of origin, while other documents can be specifically 'localised', usually because they contain a direct reference to their source.

Da Rold has tentatively begun to plot this information onto a map of England. Refining it will be part of the project's next phase. Each sheet within a manuscript also bears a watermark – an emblem, such as an animal or a star. Tracking this watermark gives some clues as to where the paper was made, where it was used and the wider network of use.

Tentative patterns are already emerging. Some centres in the East of England, like Lincoln and Norwich, appear to have held significant stocks of paper that gradually spread westwards. "There are capillaries that go out across the country, but they don't go everywhere," Da Rold says.

Why this happened will be covered in a forthcoming book: *From Pulp to Fiction*.

Paper became a pivotal technology for a subsequent explosion in the transmission of knowledge

Da Rold has two main theories about why paper first came into use, both of which have much wider implications for understanding how any technology succeeds. First, it appears to have undergone a phase of cultural acceptance. This did not necessarily involve people using paper to write – it was just as common in late medieval England to use it to wrap up spices or jam – but the process established paper within the culture.

Second, paper was actively championed by specific groups of people who found it useful: lawyers, merchants, secretaries and anyone who needed to record financial transactions. Paper was easier for them to use than parchment. "It became convenient because people living at the time decided that it met their needs," Da Rold says.

Why England adopted paper so late remains unclear, but paper is thought to have emerged from China, then gradually spread westwards. England's position at the end of this paper trail meant that it took longer for the technology to arrive, and the medieval equivalent of a tech cluster to support its development and use may also have been lacking.

Certainly, after the first attempt at establishing an English paper mill, near Hertford, failed in 1507, paper was not produced domestically until the 17th century. This contrasts with, for example, Italy, where major centres like Fabriano emerged. These paper mills, however, drew on a network of supporting industries that helped to refine the production process. It may be that these vital clusters of ideas and expertise were what appeared faster overseas than in England, thereby determining the rate at which paper was adopted and diffused.

...a history that has never been fully explored

Importantly, the paper revolution failed to end the use of parchment overnight. Indeed, there seems to have been a prolonged period of hybridisation during which time those who wrote used paper and parchment (which had different and complementary properties) side by side.

This, Da Rold suggests, has implications not just for establishing how England became a paper-based culture, but also for understanding any process of technological acquisition. It also hints that paper should not, perhaps, be written off just yet.

"The human mind is constantly preoccupied with what is new, and at the same time instinctively conservative," she reflects. "History such as this shows that at moments of transition the most successful people are those who work with all technologies, and get the most out of everything. There is coexistence as well as friction, and sometimes there is no winner. That may explain why even though we now have iPads we are still taking notes and writing on paper."

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Image
Left: page from an edition of *The Brus*, produced in the early 15th century, and an example of an early manuscript on paper; below: a dragon-shaped watermark can be seen on the fold between the sheets of this medieval manuscript, giving clues about where the paper was made and used

Credit: Cambridge University Library

Call to arms: how lessons from history could reduce the ‘vaccination gap’

A rise in the number of outbreaks of vaccine-preventable diseases has highlighted the growing trend for parents not to have their child vaccinated. Could the activities of a group of teenagers in 1950s America inspire a fresh look at the effectiveness of pro-vaccine public health information campaigns?

An outbreak of measles in Disneyland sounds like a fairytale gone bad. Yet, in January 2015, states across the USA began reporting measles among individuals who had visited the Disneyland Resort in California the month before. All because a visitor to the resort had unwittingly carried the virus into the ‘Happiest Place On Earth’.

The virus is so contagious that 90% of those close to ‘patient zero’ had been at risk of being infected if they were not already immune. Epidemiologists later concluded that “substandard vaccination compliance” was likely to blame for the outbreak. Six months later, the state of California made vaccination mandatory: from July 2016, all children enrolling in school must be fully vaccinated.

Measles and other vaccine-preventable diseases have been on the rise globally in recent years. France, for instance, seemed close to eliminating measles in 2007, but in the following four years, reported a dramatic outbreak of more than 20,000 cases, with 80% of reported cases occurring in unvaccinated people.

These recent events have highlighted the ‘vaccination gap’ – the trend for parents not to have their child vaccinated because of anxiety about unforeseen health consequences. But without a certain threshold of vaccination in a community – so-called herd immunity – the unvaccinated become especially vulnerable.

Yet, vaccinations are considered to be one of the greatest public health achievements in history. Perhaps that’s part of the problem, says historian Dr Stephen Mawdsley: “We have largely forgotten what it’s like to face an epidemic sweeping through a population.” Vaccinations, it seems, have become a victim of their own success.

But this isn’t the first time that ‘vaccine hesitancy’ has threatened public health. “During the first half of the 20th century, America faced a terrifying disease – polio,” he adds. “As many as 57,000 new cases were being reported every year in the early 1950s. Not only

Image
Elvis Presley receives a polio vaccination

was this a painful illness, it had grave economic consequences. Thousands of survivors required expensive acute and convalescent care, and many suffered from lasting paralysis."

Although the polio virus could strike anyone, young children were particularly affected, inspiring the term 'infantile paralysis'. Despite a vaccine being available, few teenagers and adults sought its protection because they believed they were not sufficiently at risk to warrant paying for the course of three inoculations.

Mawdsley's research, just published in the *Journal of Cultural and Social History*, has uncovered how young people themselves became the answer to the problem, in what might be the first, largest and most successful case of teen health activism of the time. This fight waged against vaccine noncompliance in 1950s America, he suggests, could provide important lessons for the world today.

It was while hunting through the archives of the March of Dimes (MOD) – a fundraising campaign set up by polio survivor President Franklin D. Roosevelt and his law partner Basil O'Connor – that he made the discovery. "Who'd have thought that, after suffering terrible epidemics and fear, Americans would have a very mixed reaction towards polio vaccination? Or that those in the 'vaccination gap' would help to fill it."

A range of social, economic and political factors complicated the delivery of a comprehensive vaccination programme. Teens, in particular, were a demographic group that was difficult to reach. Two years after the vaccine was licensed in 1955, as many as 30% still had no inoculations, and a third of all new cases were in teens. The public health message wasn't getting through, and new strategies were needed.

Celebrities helped the cause. 'Presley Receives a City Polio Shot' proclaimed the *New York Times* in 1956, as the King of Rock 'n' Roll offered his arm for vaccination before appearing on the *Ed Sullivan Show*. But the real drivers of the message were a group of teenagers gathered together by the MOD-financed National Foundation for Infantile Paralysis (NFIP).

"Growing consumerism and rising purchasing power and recreational time spurred the emergence of an assertive teen culture by the late 1950s," explains Mawdsley. "Many national organisations began to recognise teens as important consumers with cultural influence. By tapping into this segment of society, the NFIP hoped to inspire a new wave of vaccination driven by peer approval."

The relationship was reciprocal. For the hundreds of young people brought together by the NFIP from all over the USA for a conference, this was a chance to challenge negative stereotypes about juvenile delinquency, and gain recognition and appreciation through grassroots activism.

Officials and teenagers debated strategies to improve vaccination, as well as how to break down race, ethnicity and gender stereotypes. The underlying ethos was that the vaccination message could penetrate teen culture only if it came from within its ranks. After the conference, the teenagers established county chapters across the country under the motto 'Teens Against Polio' (TAP), each chapter recruiting yet more teens to promote vaccination.

Some canvassed door to door or gave talks at schools; others organised car washes and peanut sales, or visited polio wards and rehabilitation centres. "No shots, no dates" was a recurring phrase, and teens were often asked at school dances to prove they were immunised before gaining entry. "By using exclusive dances as a tactic, young volunteers were able to exploit the fear of missing out as a means to increase vaccine uptake among teens," he says.

"I interviewed some former TAP volunteers, and they said that looking back it was surprising that some of these tactics were so acceptable – it showed the power of teens understanding and connecting with their own demographic."

The creativity and audacity of teens were acknowledged as cornerstones to the marketing strategy by adults, as one NFIP chapter chairman recalled: "The youngsters did have enterprise and nerve. They went in offices, stores, restaurants, hotels – any place there was a person. They barged in on bank presidents, dentists, janitors, even the jail."

Although teen health activists could not solve all the challenges facing vaccination, their strategies had a remarkable effect. As teen vaccination increased, fewer cases of polio emerged. By 1960, the annual incidence of polio had decreased by nearly 90% compared with 1950.

Mawdsley believes that lessons might be learnt from the history of the fight against polio by public health communication campaigns today. "Yes, their approaches and language were very much the product of 1950s America, but the lesson here is that a hard-to-influence group can be reached. This could be by tapping into new forms of communication such as social media, or clever approaches to promoting vaccination to people opposed to vaccination.

"TAP reinvigorated a failing public health campaign by addressing the fears, access restrictions and misinformation about polio. The teen polio crusaders were a Trojan horse in the battle for public support and donations for polio."

This research was funded by Clare Hall, Cambridge, and Cambridge Infectious Diseases.

Credit: The New York City Municipal Archives

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Film available

Soft solids and the science of cake

Credit: Divulgação Petrobras, ABr - Agência Brasil

Researchers hope that working out the behaviours of soft solids, which can act like either solids or liquids, may make for tastier cakes – and safer oil wells.

What do cake batter and a massive, offshore oil drilling rig have in common? The answer lies in a type of material known as a soft solid, which can behave either like a solid or like a liquid, depending upon the stress it is subjected to. Cake batter, molten chocolate, Marmite®, custard and the foamed concrete used in oil wells are all examples of these 'dual personality' materials.

Soft solids are non-Newtonian fluids, which don't adhere to the same rules as 'normal' liquids. Newtonian fluids – such as water or cooking oil – don't change their behaviour as a result of how they have been handled, such as having been mixed or being left stagnant for days. For example, if a bowl of water is mixed for an hour at high speed, it will flow in exactly the same way at the end of the hour as at the beginning.

Non-Newtonian fluids – such as custard, cake batter or foamed concrete – are different. Sometimes they behave like a solid, and sometimes they behave like a liquid. For example, move quickly and firmly enough and it's possible to walk on custard. But stop moving, and you will start to sink. This is because custard gets thicker or thinner depending on the rate at which you try to move it. This is one way in which non-Newtonian fluids differ.

However, the mechanisms that make soft solids distinctive in this way are complex and still not well understood, making it difficult for engineers to control their properties precisely. Being able to do so would open up a range of new opportunities, whether the goal is a fluffier cake or safer drilling for oil.

There are a wide range of soft solid materials, many of which are present in your kitchen. Researchers in Cambridge's Department of Chemical Engineering and Biotechnology are attempting to unravel how the structure of one type of soft solid – bubbly liquids – affects their properties, which may enable a far greater degree of control than is currently possible.

"Non-Newtonian fluids are mysterious things, and being able to accurately control their properties has all kinds of practical implications," says Professor Ian Wilson, who leads the research. "The connections between cake and concrete may not seem obvious at first, but the link is bubbles. It's amazing how widely this type of soft solid is found – we also see them in the natural world, in things like magma. What we're trying to do is to develop a simple method to describe a complex phenomenon, in order to get to the point where we can design these materials to do exactly what we want them to do."

When trying to lighten either a cake or cement, one answer is simple: fill it with air bubbles. In cake batters, this leads to a fluffier cake. In oil wells, it makes for lightweight cement which is used to fill in the gaps between the pipe and the rock to prevent oil and gas from escaping.

The fact that this approach is far from perfect was proven in disastrous terms when, in April 2010, an explosion at the giant offshore oil rig Deepwater Horizon in the Gulf of Mexico killed several workers and precipitated the largest accidental oil spill in the history of the oil industry. The subsequent enquiry highlighted that something went wrong with the foamed concrete used, and its failure was one of a series of events that led to the explosion of the rig and the massive oil spill in the Gulf of Mexico which followed.

What do cake batter and a massive, offshore oil drilling rig have in common?

For foamed concrete to work well, the bubbles have to be well distributed throughout the material, and they must remain stable so that they don't collapse or combine into giant holes.

Wilson and his colleague Dr Bart Hallmark have been working on a closely related, but slightly different, type of soft solid. In foamed concrete the base liquid is viscoplastic, whereas in many food products the base liquid is viscoelastic. Viscoelastic materials display both viscosity and elasticity when undergoing deformation. Adding bubbles increases the elasticity enormously – this is why cake batter climbs up your whisk when you are beating it. Much of the research in this area has focused on Newtonian base liquids, but in the food and other industries the base liquids are often viscoelastic.

Starting with honey – a viscous liquid – the researchers investigated how the amount and size of the bubbles affected its behaviour, and then attempted to model that behaviour accurately. They then moved on to gum solutions, which are used to thicken sauces. The researchers showed how the mathematical model for the base liquid behaviour – in this case, the Giesekus fluid model – responds to bubble addition.

This gives researchers a tool to understand, predict and control the properties of these soft solids. For the food industry, this may make it easier to bake moist, fluffy cakes at an industrial scale, while the approach could also be used by the huge range of industries that use bubbly liquids in their processes and products.

"By using a Giesekus model and changing the bubble size, we may be able to fine-tune the behaviours of bubbly liquids," explains Wilson. "For food production, this may help determine how a formulation or process needs to be changed to make a better cake batter: what speed to beat it at, or how best to scale the recipe up to industrial quantities so that the end product has the right structure."

However, the ramifications of this research reach far beyond the world of cakes, due to the ubiquity of bubbly liquids and related soft solids. Although foamed concrete differs from honey – it starts off as viscoplastic rather than viscoelastic – the development of models that can accurately describe these soft solids will allow engineers to design and control them, and hopefully prevent them from going wrong.

This research was originally funded by Premier Foods and developed further by a visiting Fellow, Dr Loly Torres-Pérez, courtesy of the Galician Council of Education and Culture and the European Union, and is currently funded by Schlumberger Cambridge Research.

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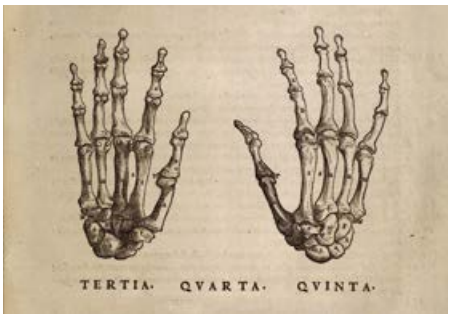
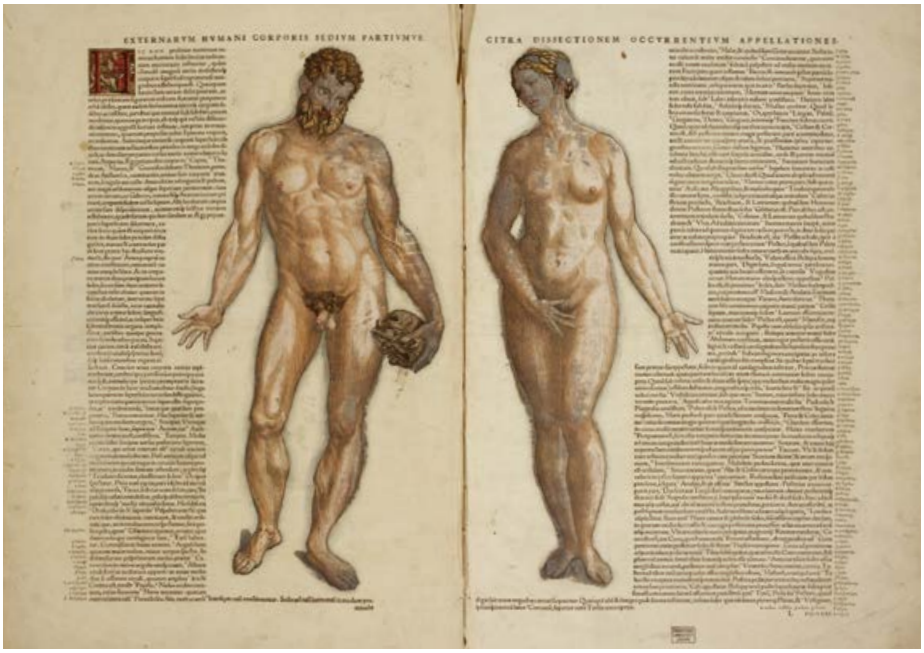
Things Lines of Thought





Images
Andreas Vesalius' *Epitome* and *Fabrica*

One of the world's most influential books on anatomy – written by the man who turned the dissection of the human body into an art form – is also one of the earliest examples of the humble 'pop-up' book.

In 2016, Cambridge University Library is celebrating its 600th anniversary as one of the world's great libraries. Among its nine million books, journals and maps lie many of the most significant medical works of the modern world, which drew inspiration from Arabic and Greek predecessors, and which in turn continue to inspire each new generation of medics.

One of the books is Andreas Vesalius' *Epitome*, a companion piece to his famous *Seven books on the fabric of the human body* (commonly known as *Fabrica*).

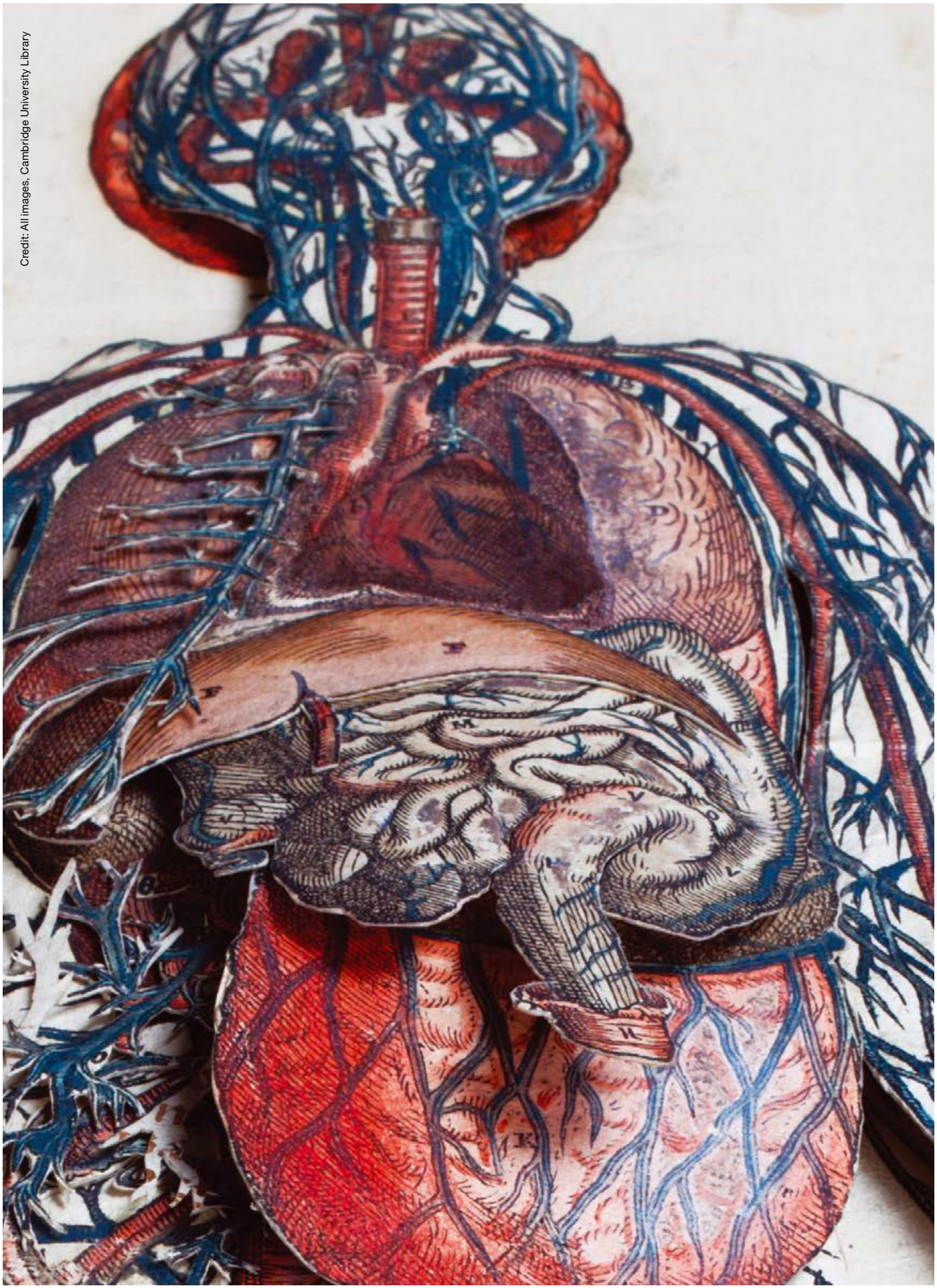
This copy of the *Epitome* is thought by many to have first belonged to Philip II of Spain – husband of Queen Mary, and son of Holy Roman Emperor Charles V.

It includes the same kind of beautiful woodcuts of the human body as the *Fabrica*, but its innovation lay in an attached sheet that readers were encouraged to cut up and glue together onto a base figure to make a layered paper manikin. The manikin made in the University Library's copy has, unlike others, miraculously survived the intervening years since its first publication in 1543.

"The book originally came with additional sheets of paper, with a full-size figure of blood vessels surrounded by images of individual organs and some veins," explains Cambridge's Professor Sachiko Kusukawa, from the Department of History and Philosophy of Science. "The intricate details made them a challenge to cut out and would have made them very flimsy – so the Cambridge manikin has been backed with a 14th-century legal manuscript."

The *Epitome*, which has been digitised on the Cambridge Digital Library, will be one of the star attractions in the forthcoming *Lines of Thought* exhibition celebrating 600 years of Cambridge University Library, which will run from 11 March to 30 September, 2016.

www.lib.cam.ac.uk



Credit: All images, Cambridge University Library

A TANGLED TALE

It's over a hundred years since the first case of Alzheimer's disease was diagnosed, and since then we've learned a great deal about the protein 'tangles' and 'plaques' that cause the disease. So why do we still not have any effective drugs – let alone a cure – for the disease?

You may have heard of the 'dementia tsunami'. It's heading our way. As our population ages, the number of cases of dementia is set to rocket, overwhelming our health services and placing an enormous burden on our society.

Only, it's not quite so simple. A study published last year by Professor Carol Brayne from the Cambridge Institute of Public Health suggested that better education and living standards meant people were at a lower risk of developing the disease than previously thought and so, despite our ageing population, numbers were likely to stabilise – and could even perhaps fall slightly.

Of course, even this more optimistic outlook does not hide the fact that millions of people worldwide will be diagnosed with dementia each year and millions are already living with the condition. An effective treatment still seems like a distant prospect.

"Dementia isn't one disease: it's a constellation of changes in an individual's brain, with many underlying causes," says Brayne. "Most people, by the time they're in their eighties or nineties, have some of these changes in their brains, regardless of whether or not they ever develop dementia."

For this reason, Brayne believes we need a radical approach to tackling brain health throughout the course of our lifetime, with a greater emphasis on reduction in the risk of dementia achieved through measures in society that are related to better health in general, such as social and lifestyle changes, in addition to the focus on early therapeutic approaches to preventing or treating the disease through a pharmaceutical approach.

By far the most common and well-known form of dementia is Alzheimer's disease. Symptoms include memory problems, changes in behaviour and progressive loss of independence. At a biological level, the disease sees a build-up of two particular types of proteins in the brain: fragments of beta-amyloid clump together in 'plaques' between nerve cells, and twisted strands of tau form 'tangles' within the nerve cells. These plaques and tangles lead to the death of nerve cells, causing the brain to shrink.

Clinical trials of Alzheimer's drugs are always going to be difficult, in part because trial participants are patients with advanced stage disease, who have already lost a significant number of nerve cells. But Professor Chris Dobson, who recently helped secure £17 million from the Higher Education Funding Council for England for a new Chemistry of Health Building, including the Centre for Misfolding Diseases, believes that most of the trials to date were destined to fail from the start because of a fundamental lack of understanding of the mechanisms that lead to Alzheimer's.

Understandably, most of the researchers tackling Alzheimer's approach the disease as a clinical – or at least a biological – problem. Dobson instead sees it as also being about chemistry and physics. He argues that the protein tangles and plaques – collectively known as aggregates – are demonstrating a physical property similar to the way in which crystals precipitate out of, say, salty water: all they need is a 'seed' to kick off the precipitation and the process runs away with itself. "In essence," he says, "biology is trying to suppress molecules behaving in a physical way." For his contributions, Dobson has been awarded the 2014 Heineken Prize for Biochemistry and Biophysics.

In 2009, Dobson, together with colleagues Professors Tuomas Knowles and Michele Vendruscolo, published a study that broke down the aggregation process into a combination of smaller steps, each of which could be tested experimentally. It became apparent to the team that drugs were failing in trials because they were targeting the wrong steps. "And this is still happening," says Vendruscolo. "Companies are still putting small molecules into clinical trials that, when we test them using our methods, we find stand no chance."

They believe there may be a role to play for 'neurostatins', which could do for Alzheimer's what statins already do to reduce cholesterol levels and prevent heart attacks and strokes. In fact, they may have already identified compounds that might fit the bill.

Professor Michel Goedert from the Medical Research Council Laboratory of Molecular Biology admits that there is a gap between our understanding of Alzheimer's and our ability to turn this into effective therapies.

"We know much about the causes of inherited forms of Alzheimer's disease, but this knowledge has so far not led to any therapies," he says. "It's clear now that abnormal protein aggregation is central to Alzheimer's disease, but we don't know the mechanisms by which this aggregation leads to neurodegeneration." Goedert himself played an instrumental part in studies that implicated the aggregation of tau protein in Alzheimer's disease and other neurodegenerative diseases, work that led to him being awarded the 2014 European Grand Prix from the Paris-based Foundation for Research on Alzheimer's Disease.

"I don't think we should talk of a cure," says Goedert. "At best, we will be able to halt the disease. Prevention will be much more important." Part of the problem, he says, lies in the fact that there is no absolute way of identifying those at risk of developing Alzheimer's disease.

The market for an Alzheimer's drug is massive, which is why pharmaceutical companies are racing to develop new drugs. Goedert doesn't believe we will ever find a single 'magic bullet', but will need to use combination therapies – in the same way that we treat other diseases, such as HIV – with each drug targeting a particular aspect of the disease.

Professor David Rubinsztein from the Cambridge Institute for Medical Research agrees with Goedert that we need to look at preventing Alzheimer's rather than just focusing on treating the disease. He, too, believes in the concept of neurostatins. "These compounds would be safe, well tolerated by most people and generally good for you; you could take them for many years before the onset of disease," he says. "Then we wouldn't need to worry about identifying people at highest risk of the disease – everyone could take them."

Rubinsztein is the academic lead for Cambridge's new Alzheimer's Research UK Drug Discovery Institute, part of a £30 million Drug Discovery Alliance that also includes the University of Oxford and University College London. This state-of-the-art institute will fast-track the development of new treatments for Alzheimer's disease and other neurodegenerative diseases. In particular, the Alliance will look at promising drug targets, assess their validity and develop small molecules that target them. These could then be taken up by pharmaceutical companies for clinical trials, removing some of the risk that results in most 'promising' drug candidates failing early on.

Rubinsztein is optimistic about our chances of fighting Alzheimer's. "If you could delay the onset of Alzheimer's, even by three to five years, that discovery would be transformative and massively reduce the number of people getting the disease," he says. "We're not asking to stop the disease, just to delay it. It's really not such a big ask."

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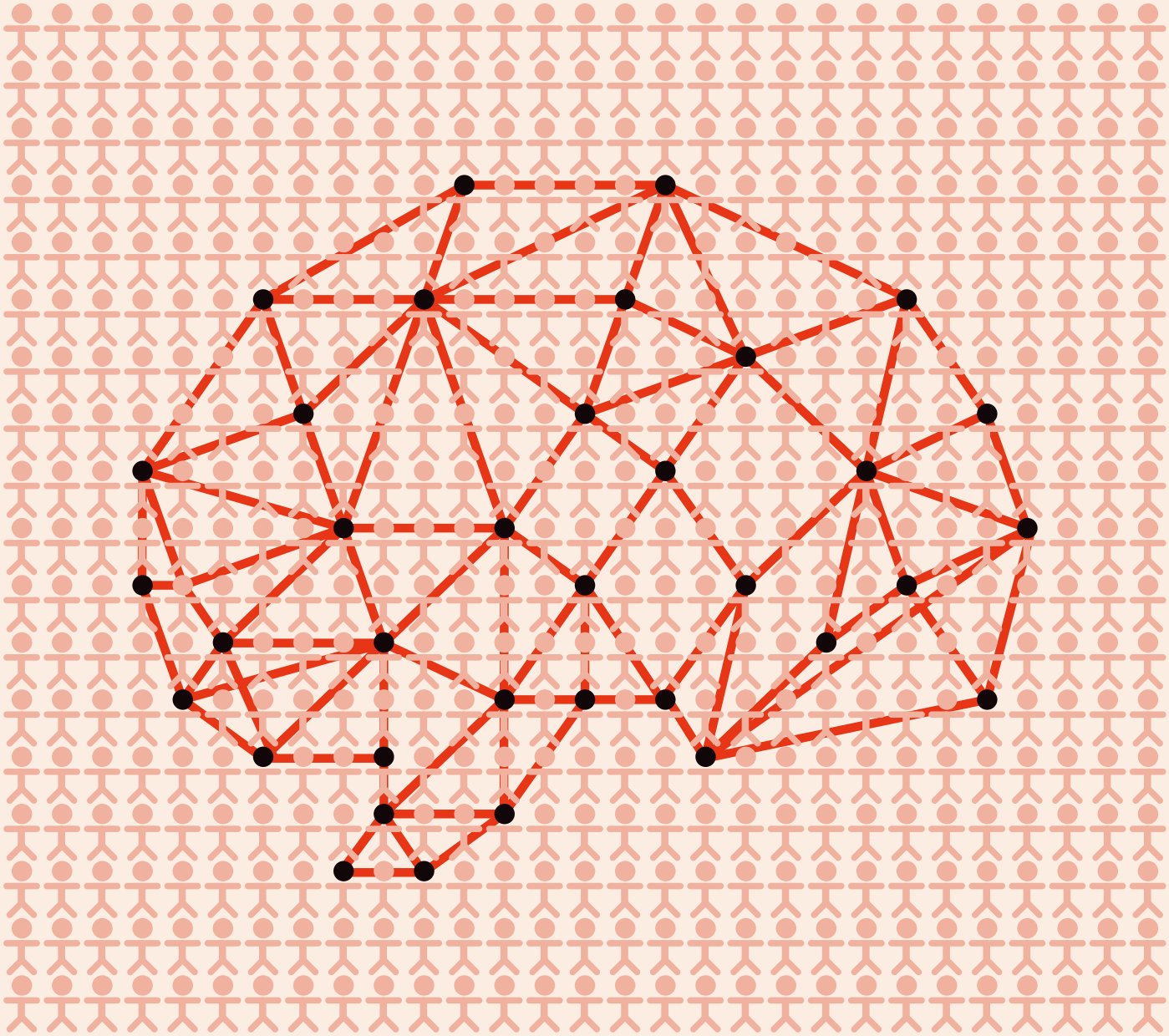

Mental health: *the bigger picture*

Adolescence is a dangerous time for the onset of mental health problems. Advances in brain imaging are helping to picture how neural changes in these crucial years can lead to chronic debilitating mental illness.

Restless, disordered, uncertain, impulsive, emotional – the teenage brain can be a confused fury of neural firings and misfirings.

For most 14- to 24-year-olds – the "risky age" as Professor Ed Bullmore describes it – the maelstrom eventually subsides. For some, episodes of depression, low self-esteem, self-harm or paranoia may intensify and become more frequent. For around 1 in 100, the change in mental state is so marked that it will become difficult for them to distinguish their delusions and hallucinations from reality – one of the hallmarks of schizophrenia.

"Schizophrenia is a particularly feared diagnosis," says Bullmore. "People tend to think it means a chronic lifelong dependency on medication and therapy. It can mean this, but it can also last only a few years. The main thing that patients and their families want to know is what does the future hold – am I likely to be able to resume my life, get a job, and so on?"

Bullmore is co-chair of Cambridge Neuroscience, an initiative to enhance multidisciplinary research across the University, and leads the Department of Psychiatry, where he and colleagues have been developing imaging techniques that are revealing where and over what timescale abnormalities in the brain develop in people with mental health problems.

This is no easy task. Even being able to show a neural abnormality has been a major and relatively recent

advance for understanding a condition that, Bullmore says, has in the past been regarded with prejudice and assumptions. “Demonstrating neural change moves us away from what might be regarded as a blaming approach where someone is made to feel personally responsible for the fact these symptoms exist. Imaging shows you that’s not the case – there is a biological basis.”

The task is made difficult because there is no single event or area of the brain that underlies schizophrenia. It has only been from the collation of results from imaging studies worldwide that it has become apparent that when it comes to mental health disorders the scientists need to look at the big picture – the changes happening in wiring circuits across the whole brain.

Imaging techniques such as magnetic resonance imaging (MRI) are helping to map the brain in unprecedented detail. Structural MRI follows the movement of water as it diffuses along the pathways forged by neurons – showing the network of connections spread across the brain. Functional MRI measures slow rhythmic activity in the brain; if two areas of the brain show activity at the same time the chances are they are functionally connected. Bullmore and colleagues have developed mathematical methods to calculate the probability of there being such a connection.

“Neuroscience is no longer just about neurons,” he explains. “We can also now talk in terms of hubs, networks and connectomes. If the brain is thought of as a computer, with ‘processors’ in the outer grey matter and ‘wires’ that connect them in the inner white matter, some hub regions are more highly connected than others.”

In schizophrenia, connectivity in the wiring diagram goes awry and highly connected hubs are especially affected – “you could call it a hubopathy,” says Bullmore. His team’s research has demonstrated that those who have suffered decades of schizophrenia have large-scale network abnormalities compared with a healthy brain, which goes some way to explaining the diversity and severity of symptoms experienced in schizophrenia. The question is: can imaging be used to chart this progression?

Bullmore and his colleagues believe so: “Roughly a third of patients recover, a third have intermittent symptoms and a third will be affected for decades by schizophrenia. At diagnosis we can’t currently tell which of these outcomes lies in store. But we think one day we will be able to correlate the pattern of network activity with future outcome.”

It’s not only what happens to patients post-diagnosis that interests Bullmore, but also what has happened neurologically in the years before diagnosis.

“For me, one of the most exciting aspects of psychiatry is that we can use imaging to study the ‘risky age’ of brain development to understand how the connectome grows or matures in healthy brains. We can then start to pinpoint which genetic and environmental factors might favour healthy adolescent brain network development and which factors might predispose to abnormal network development, leading to chronic disability or distress.”

In 2012, Bullmore and colleagues Professor Ian Goodyer and Professor Peter Jones in Cambridge’s Department of Psychiatry (in collaboration with Professor Ray Dolan and Professor Peter Fonagy from University College London) launched the NeuroScience in Psychiatry Network, funded by the Wellcome Trust. They have been recruiting a panel of 2,000 healthy volunteers aged 14–24 years, 300 of whom have had brain scans to contribute to one of the most comprehensive ‘circuit diagrams’ of the teenage brain ever attempted.

“Remarkably little is known about how brain networks grow during the crucial transition from childhood dependence to life as independent adults,” adds Bullmore. “The adolescent brain is still a bit of a black box. But it is a big step forward that we can now see healthy human brain development much more clearly, especially with the next-generation brain scanners coming to Cambridge soon [see panel]. It’s very exciting to think that we should then be able to understand and predict the pathways of brain network development that lead to schizophrenia.”

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Opening the black box

The arrival of two state-of-the-art MRI machines in Cambridge, thanks to funding from the Medical Research Council (MRC), will revolutionise the study of the brain.

“A brain scan is much more than an image,” contends Ed Bullmore. “It’s really a very large collection of numbers. With the best scanners and some high-performance computing, you can start to think not only about disease mechanisms but also about identifying early risk factors and preventative action.”

Two of the newest scanners in the UK will arrive at the Cambridge Biomedical Campus in 2016, and a new high-speed secure link will be created through to the recently opened £20 million West Cambridge Data Centre, which will analyse the data.

One scanner, a new 7-Tesla ‘ultrahigh-field’ MRI machine, will help researchers see how the human brain works as a whole, yet also with the precision of a grain of sand a fraction of a millimetre across. It will further the study of dementia, brain injury, obesity, addiction, mental health disorders, pain and stroke.

‘7T’ is a collaboration between the University and the MRC’s Cognition and Brain Sciences Unit (CBSU). Professor James Rowe, from the Department of Clinical Neurosciences and the CBSU, explains: “The new scanner is a major advance to study the details of the human brain not only in health but also the effects of age and the origins of brain diseases. The unprecedented detail and sensitivity at 7T is essential in the national effort towards a cure for dementia and mental illness.”

Joining the 7T scanner will be a positron emission tomography (PET)–MRI machine, which shows changes in the brain down to the level of individual molecules. Until now only two PET–MRI scanners existed in the UK, but MRC Dementias Platform UK has invested in five more nationally, creating what is thought to be the first nationally coordinated MRI–PET network anywhere in the world.

“Beating dementia is a long-term goal,” adds Rowe. “These scanners will make a very significant contribution to this eventual success and to the lives of patients and their families.”

A bedside device that measures 'brain signatures' could help diagnose patients who have consciousness disorders – such as a vegetative state – to work out the best course of treatment and to support family counselling.

In 10 minutes, Srivas Chennu can work out what's going on inside your head.

With the help of an electrode-studded hairnet wired up to a box that measures patterns of electrical activity, he can monitor the firing of millions of neurons deep within the brain. A few minutes later, wheeling his trolley-held device away, he has enough information to tell how conscious you really are.

What Chennu is looking for with his electroencephalogram (EEG) is the brain's electrical 'signature'. At any one moment in the body's most complex organ, networks of neurons are firing up and creating 'brain waves' of electrical activity that can be detected through the scalp net.

This isn't new technology – the first animal EEG was published a century ago – but computational neuroscientist Chennu has come up with a way of combining its output with a branch of maths called graph theory to measure the level of a person's consciousness. What's more, he's developing the technology as a bedside device for doctors to diagnose patients suffering from consciousness disorders (such as a vegetative state caused by injury or stroke) to work out the best course of action and to support family counselling.

"Being conscious not only means being awake, but also being able to notice and experience," he explains. "When someone is conscious, there are patterns of synchronised neural activity arcing across the brain that can be detected using EEG and quantified with our software."

So for a healthy brain, the brain's signature might look like a raging scrawl of lines sweeping back and forth, as integrated groups of neurons perceive, process, understand and sort information. When we sleep, this diminishes to a squiggle of the faintest strokes as we lose consciousness, flaring occasionally if we dream.

"Understanding how consciousness arises from neural interactions is an elusive and fascinating question. But for patients diagnosed as vegetative and minimally conscious, and their families, this is far more than just an academic question – it takes on a very real significance.

"The patient might be awake, but to what extent are they aware? Can they hear, see, feel? And if they are aware, does their level of awareness equate to their long-term prognosis?"

Chennu points to charts showing the brain signature of two vegetative patients. On one chart, just a few lines appear above the skull. In the other, the lines are so many they resemble, as Chennu describes, a multi-coloured mohican, almost indistinguishable from the signature one would see from a healthy person.

Did either of the patients wake up? "Yes, the second patient did, a year after this trace was taken. The point is, if you think that a patient will wake up, what would you do differently as a clinician, or as a family member?"

The research is based on the finding that a patient in a vegetative state could respond to yes or no questions, as measured by distinct patterns of brain activity using functional magnetic resonance imaging. It was discovered by Chennu's colleagues in the Department of Clinical Neurosciences and the Medical Research Council Cognition and Brain Sciences Unit (MRC CBSU), led by Dr Adrian Owen.

In 2011, the group found the same attention to commands could be measured using EEG – a less expensive and more widely available technology. Three years later, Chennu and Dr Tristan Bekinschtein from the CBSU, and now in the Department of Psychology, showed that their mathematical analysis of the EEG outputs was enough to measure the ambient amount of connectivity in a patient's brain.

Chennu hopes that the machine will fill a technology gap: "Misdiagnosis of true levels of consciousness in vegetative patients continues to be around 40% and depends on behavioural examination. In part this is because there is no gold standard for the assessment of a patient's awareness at the bedside."

With funding from the Evelyn Trust, he will assess and follow the treatment and rehabilitation trajectory of 50 patients over a three-year period. This will be the first time that a study has linked diagnosis, treatment and outcome to regular real-time assessment of the activity of a patient's brain.

Meanwhile he is continuing to develop the medical device with industry as part of the National Institute for Health Research Healthcare Technology Co-operative for Brain Injury, which is hosted within the Department of Clinical Neurosciences.

"Medical advances mean that we are identifying subtypes of brain injury and moving away from 'one size fits all' to more-targeted treatment specific for an individual's needs," adds Chennu, who is also funded by the James S. McDonnell Foundation and works as part of a team led by Professors John Pickard and David Menon.

At any one moment in the body's most complex organ, networks of neurons are firing up and creating 'brain waves'

Intriguingly the device could even offer a channel of communication, as Chennu speculates: "The question that fascinates us is what type of consciousness do patients have? Perhaps we can create systems to translate neural activity into commands for simple communication – interfaces that could provide a basic but reliable communication channel from the 'inbetween place' in which some patients exist.

"Moreover, we think that the measurement of brain networks will provide clinically useful information that could help with therapeutics for a larger majority of patients, irrespective of whether they are able to demonstrate hidden consciousness."

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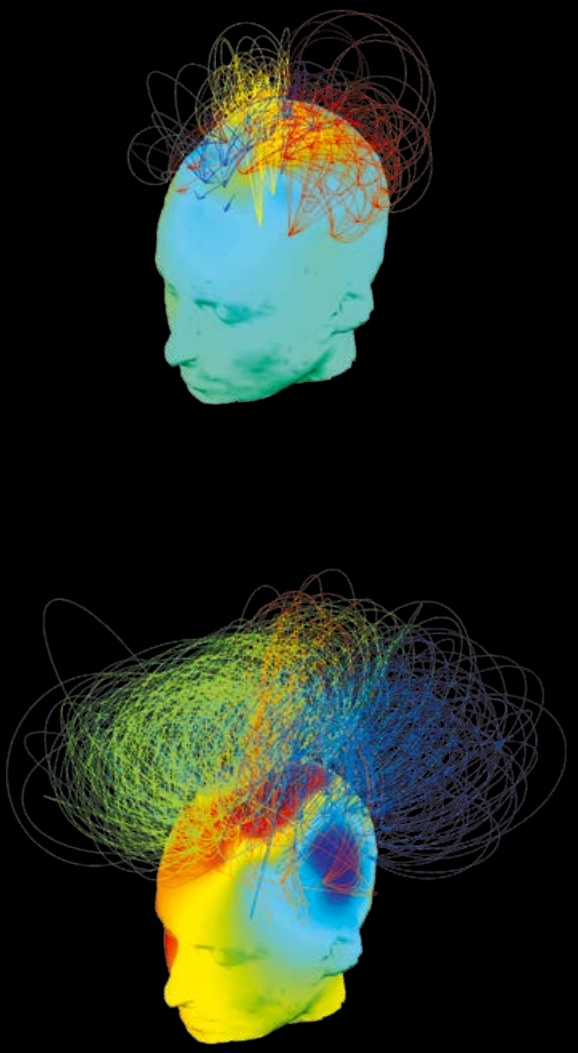
Image
The patient at the top is in a vegetative state; the patient in the middle is also in a vegetative state but their brain appears as conscious as the brain of the healthy individual at the bottom



Credit: Srivas Chennu

Brain signatures

New directions in the study of the mind

We know a great deal about the brain but what does it actually mean to be conscious, asks a new research programme in the Faculty of Philosophy.

In what way are newborn babies, or animals, conscious? Why do some experiences become part of one's consciousness yet others do not?

"It's sometimes assumed that it's obvious what consciousness is, and the only question is how it is embodied in the brain," says Professor Tim Crane. "But many people now recognise that it's not clear what it means to say that something has a mind, or is capable of thought or conscious experience. My view is that there are lots of assumptions that are being made in order to get to that conclusion and not all of the assumptions are correct."

Crane leads a new research initiative in the Faculty of Philosophy supported by the John Templeton Foundation that aims to tackle the broad question of the essence of the mind. And to do this they are moving beyond the reductionist view that everything can be explained in terms of the nuts and bolts of neuroscience.

"That doesn't mean we are interested in proving the existence of the immortal soul, or defending any religious doctrine – we are interested in the idea that the brain's-eye view isn't everything when it comes to understanding the mind.

"The nervous system clearly provides the mechanism for thought and consciousness but learning about it doesn't tell us everything we need to know about phenomena like the emotion of parental love, or ambition or desire. The mere fact that something goes on in your brain when you think does not explain what thinking essentially is."

The team in Cambridge are also distributing funds for smaller projects elsewhere in the world, each of which is tackling similar questions of consciousness in philosophy, neuroscience and psychology.

"Collectively we want to recognise 'the reality of the psychological' without saying that it's really just brain chemicals," adds Crane. "It's important to face up to the fact that we are not just our neurons."

www.newdirectionsproject.com

Think Small

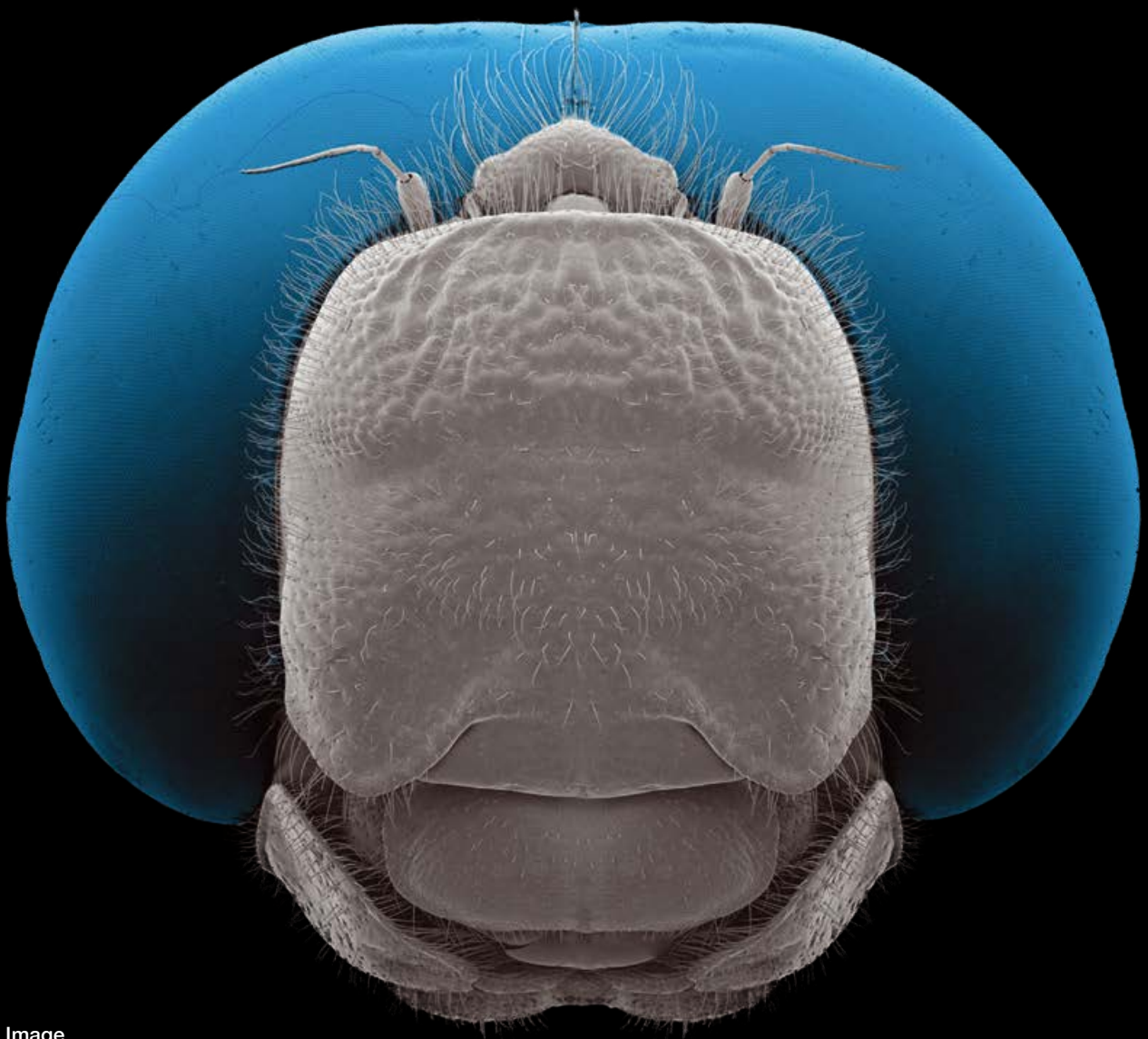


Image
A dragonfly (shown here in blue) has a larger brain than a robber fly (green) or a killer fly (yellow), but what are the trade-offs?

Credit: Sam Fabian

Cambridge researchers are studying what makes a brain efficient and how that affects behaviour in insects – including in the aptly named killer fly.

As in economics, there is a law of diminishing returns in neuroscience – doubling the investment going in doesn't equal double the performance coming out. With a bigger brain comes more available resources that can be allocated to certain tasks, but everything has a cost, and evolution weighs the costs against the benefits in order to make the most efficient system.

"Larger brains are specialised for high performance, so there's a definite advantage to being bigger and better," says Professor Simon Laughlin of the Department of Zoology, whose research looks at the cellular costs associated with various neural tasks. "But since most animals actually have very small brains, there must also be advantages to being small." Indeed, there is strong selection pressure to have the minimum performance required in order to survive and it's not biologically necessary to be the best, only to be better than the nearest competitor.

So does size matter? Do small insects with relatively few neurons have the same capabilities as much larger animals? "When an animal is limited, is it because their neural system just can't cope? Or is it because they're actually optimised for their particular environment?" asks Dr Paloma Gonzalez-Bellido from Cambridge's Department of Physiology, Development and Neuroscience.

With funding from the US Air Force, Gonzalez-Bellido is studying the hunting behaviours of various flying insects – from tiny killer flies, slightly larger robber flies to large dragonflies – to determine how their visual systems influence their attack strategy, and what sorts of trade-offs they have to make in order to be successful.

Dragonflies are among the largest flying insects, and hunt smaller insects such as mosquitoes while patrolling their territories. They have changed remarkably little in the 300 million years since they evolved – most likely because they are so well optimised for their particular environmental niche.

"Other researchers have found that dragonflies are capable of doing complex things like internally predicting what their body is going to do and compensating for that – for instance, if they're chasing a target and turn their wings, another signal will be sent to turn their head, so that the target stays in the same spot in their visual field," says Gonzalez-Bellido. "But are smaller animals, such as tiny flies, capable of achieving similarly complex and accurate feats?"

Gonzalez-Bellido also studies the killer fly, or *Coenosia attenuata*. These quick and ruthless flies are about four millimetres long, and will go after anything they think they can catch – picky eaters they are not. However, the decision to go after their next meal is not as simple as taking off after whatever tasty-looking morsels happen to fly by. As soon as a killer fly takes off after its potential prey, it exposes itself and runs the risk of becoming a meal for another killer fly.

To help these predacious and cannibalistic flies eat (and prevent them from being eaten), they need to fly fast and to see fast. Insects see at speeds much higher than most other animals, but even for insects, killer flies and dragonflies see incredibly fast, at rates as high as 360 hertz (Hz) – as a comparison, humans see at around 60 Hz.

"For prey animals, the most important thing is to get out of the way quickly – it doesn't matter whether they know exactly what's coming, just that it doesn't catch them," says Gonzalez-Bellido. "Predators need to be both fast and accurate in their movements if they're going to be successful – but for very small predators such as insects, there are trade-offs that need to be made."

By making the 'pixels' on their photoreceptors (the light-sensitive cells in the retina) as narrow as possible, killer flies trade sensitivity for resolution. In bright light, they see better than their similar-sized prey, the common fruit fly. However, the cap on sensitivity and resolution imposed upon killer flies by their tiny eyes means that they can only see and attack things that fly close by.

While dragonflies, with their larger eyes and better resolution, can take their time and use their brain power to calculate whether a prey is suitable for an attack, killer flies attack before they've had a chance to determine whether it's something they can actually catch, subdue or eat – or they risk missing their prey altogether. Once a killer fly gets relatively close to its potential prey, it has to decide whether to keep going or turn back – this is one of the trade-offs resulting from evolving such a tiny visual system.

In the early 2000s, Laughlin determined the energy efficiency of single neurons, by estimating the numbers of ATP molecules – the molecules that deliver energy in cells – used per bit of information coded. To do this he compared photoreceptors in various insects. Laughlin and his colleagues found that photoreceptors are like cars – the higher the performance, the more energy they require, and costs rise out of proportion with performance. "For any system, whether it's in a tiny insect or a large mammal, you don't want something which is over-engineered, because it's going to cost more," says Laughlin. "So what's the root of inefficiency, and how did nature evolve efficient nerve cells from the bottom up?"

Researchers in the Department of Engineering are taking the reverse approach to answer questions about how the brain works so efficiently by looking at systems from the top down. "If you reverse engineer an animal's behavioural strategy by asking how an animal would solve a task under specific constraints and then work out the optimal solution, you'll find it's often the case that animals are pretty close to optimal," says Dr Guillaume Hennequin, who looks at how neurons work together to produce behaviour.

Hennequin studies how brain circuits are wired in such a way that they become optimised for a task: how primates such as monkeys are able to estimate the direction of a moving object, for example. "How brain circuits generate optimal interpretations of ambiguous information received from imperfect sensors is still not known," he says. "Coping with uncertainty is one of the core challenges that brains must confront."

Different animals come up with their own solutions. Both dragonflies and killer flies have systems that are optimal, but optimal in their own ways. It's beneficial for killer flies to be so small, since this gives them high manoeuvrability, enabling them to catch prey that turns at speed. Dragonflies are much bigger, and can do things that killer flies can't, but their size means they can't turn or stop on a dime, like a killer fly can.

"By answering some of the questions around efficiency in brain circuits, large or small, we may be able to understand fundamental principles about how brains work and how they evolved," says Laughlin.

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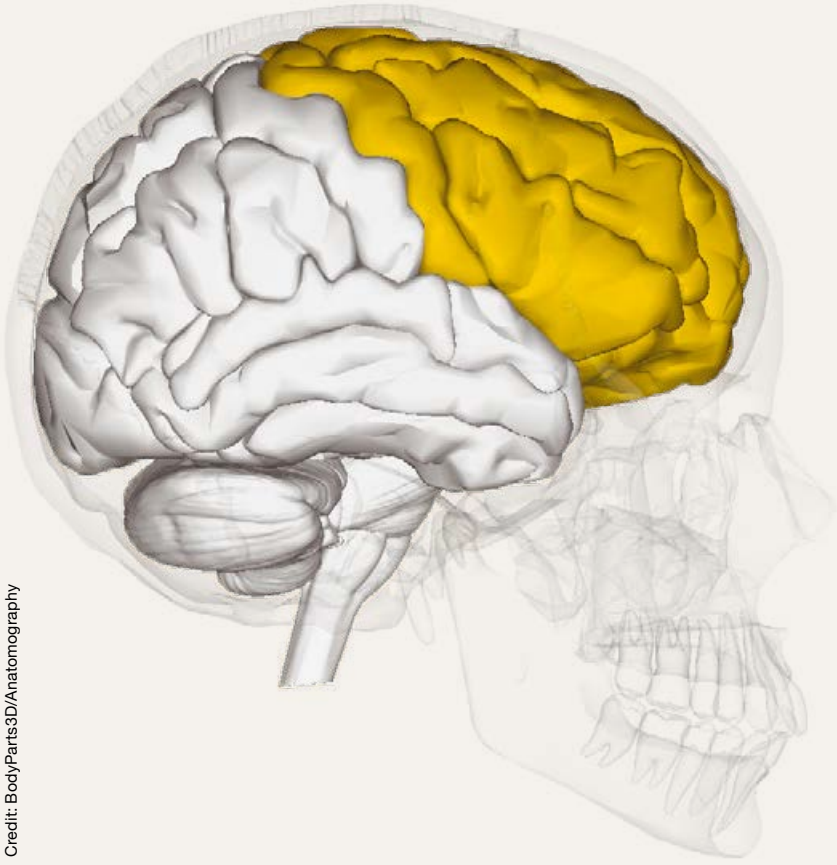
VITAL TO LEARNING



Credit: BodyParts3D/Anatomography

The wonderful world of the frontal lobe

Have you lost your house keys recently? If so, you probably applied a spot of logical thinking. You looked first in the most obvious places – bags and pockets – and then mentally retraced your steps to the point when you last used them.

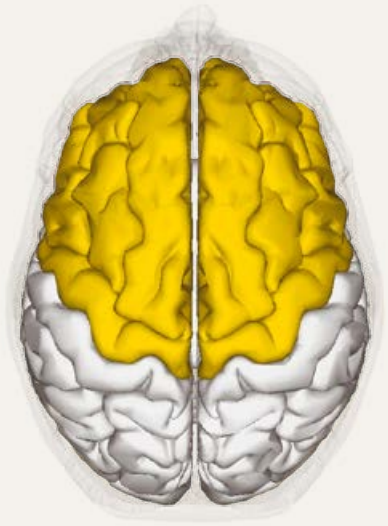
Researchers looking at child development often use search-and-find tasks to look at the ways in which children apply what they are learning about the physical world. Tests carried out on toddlers reveal that something quite remarkable happens in child development between the ages of two and five – a stage identified by both educationalists and neuroscientists as critical to the capacity for learning.

Dr Sara Baker is a researcher into early childhood at the Faculty of Education. She is interested in the role of the brain's prefrontal lobe in how young children learn to adapt their understanding to an ever-shifting environment. Many of her studies chart changes in children's ways of thinking about the world. She uses longitudinal designs to examine the shape of individual children's learning curves month by month.

Research by Baker and colleagues is contributing to an understanding of the acquisition of skills essential to learning. She explains: "The brain's frontal lobe is one of the four major divisions of the cerebral cortex. It regulates decision-making, problem-solving and behaviour. We call these functions executive skills – they are at the root of the cognitive differences between humans and other animals. My executive functions enable me to resist a slice of cake when I know I'm soon having dinner."

In an experiment designed to identify the age at which executive skills develop, Baker and colleagues used a row of four interconnected boxes to test children's ability to apply their knowledge of basic physics. A ball rolled down an incline entered the first box and disappeared. A barrier (its top visible) was slotted in between two of the boxes to stop the ball rolling any further. The children were asked to open the door of the box in which the ball was hidden.

Aged 29–31 months, only 32% of the children correctly identified the location of the ball by working out that the barrier would have stopped it. Aged 32–36 months, 66% of children were successful. Toddlers under the age of three appear to understand the principles of solidity and continuity, but have trouble acting on this knowledge. A single month in a child's age affected their ability to carry out the task correctly.



"The brain's frontal lobe is one of the four major divisions of the cerebral cortex. It regulates decision-making, problem-solving and behaviour. We call these functions executive skills – they are at the root of the cognitive differences between humans and other animals"

Baker's interest in children's development of executive skills dates from the moment a decade ago when she picked up a picture book while sitting in the foyer of a nursery school; the narrative focused on opposites: big/small, light/dark, hot/cold. How would children respond if they were asked to point to the opposite picture to the one depicting the word they heard spoken? This question became the topic for her PhD. Her findings confirmed that the huge variability of children's executive skills could explain the range of social and cognitive behaviours we see emerging in the early years. What we learn at this stage, and what we learn to apply, sets us on course for life.

Most three-year-olds find the 'opposites' task hard. Given two pictures of bears, one big, one small, they automatically point to the big bear when they hear the word 'big' spoken aloud. They point to the big bear even when they have been asked (and appear to have understood) to point to the image that is the opposite of the word they hear.

Five-year-olds are much more successful in carrying out the task explained to them. "By age five, most children have acquired the ability to override their impulses, and put them on hold, in order to follow a request," says Baker. "The ability to control impulses is vital to children's socialisation, their ability to share and work in groups – and ultimately to be adaptable and well adjusted."

What happens in children's brains and minds to enable them to make these important leaps in understanding? The answer involves an understanding of neuroscience as well as child development. Baker and colleagues are engaged in multidisciplinary projects including examining how individuals with autism may perceive and learn about the physical world differently from those without a diagnosis. Her team is also developing a pedagogical, play-based approach in collaboration with teachers.

"Executive function is a hot topic in education. When we talk to teachers about the psychology behind frontal lobe development, they immediately recognise how important self-regulation is, and will tell you about the child who can't concentrate. It might be the case that this child is struggling with their executive functions: their working memory or inhibitory control might be flagging," says Baker.

"The tricky part is to grasp the processes developing in the child's brain and come up with ways to encourage that development. In early years' education, playful learning and giving children freedom to explore could help to encourage independence as well as the ability to know when to ask for help, both of which depend on self-regulatory skills. If we want to encourage adaptability and self-reliance, we have to look beyond the formal curriculum."

Baker's research into children's ability to apply knowledge to successfully predict the location of an object hidden from view revealed much more than simply which age group was successful. She says: "In looking at the data from tasks, it's not enough to focus only on children's failures. We need to look at why they search for an object in a particular place. Often they're applying something else that they've learnt."

When younger children opened the same door twice in the boxes experiment, despite the barrier having been moved, they were applying logic: an object may be precisely where it was found before. After all, it's always worth looking for the house keys first where they should be.

In another experiment (involving dropping balls into opaque tubes that crossed each other), the younger children applied their knowledge of gravity (the ball would fall down the tube) but failed to take into account that the tubes were not straight. Baker says: "When children repeat a mistake, they reveal something about their view of the world and, as researchers, we learn how their brain is developing. As teachers and parents, our role is to help children to overcome that strong, but wrong, impulse."

During the course of a day, your frontal lobe will have enabled you to do far more than find your keys. The synaptic firing of millions of cells in your brain may have guided you through a tricky situation with colleagues or prompted you to make a split-second decision as you crossed a busy road. "The development of this vital area of your brain happened well before you started formal education and will continue throughout your lifetime," says Baker.

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Credit: Hanno Svoboda

Image
Growth cones of retinal axons (purple) growing among cells in the brain (green)

The amazing axon adventure

How does the brain make connections, and how does it maintain them? Cambridge neuroscientists and mathematicians are using a variety of techniques to understand how the brain 'wires up', and what it might be able to tell us about degeneration in later life.

To read these words, light is first refracted by the cornea, through the pupil in the iris and onto the lens, which focuses images onto the retina. The images are received by light-sensitive cells in the retina, which transmit impulses to the brain. These impulses are carried by a set of neurons called the retinal ganglion cells. Once the impulses reach the brain, the brain then has to piece together the information it receives into an understandable image. All of this happens in a fraction of a second.

Information travels from the retina to the brain via axons – the long, threadlike parts of neurons – sent out by the retinal ganglion cells. During embryonic development, axons are sent out to find their specific targets in the brain, so that images can be processed.

For an axon in a growing embryo, the journey from retina to brain is not a straightforward one. It's a very long way for a tiny axon, through a constantly changing series of environments that it has never encountered before. So how do axons know where to go, and what can it tell us about how the brain is made and maintained?

Two University of Cambridge researchers, Professor Christine Holt of the Department of Physiology, Development and Neuroscience, and Dr Stephen Eglen of the Department of Applied Mathematics and Theoretical Physics, are taking two different, but complementary, approaches to these questions.

With funding from the European Research Council and the Wellcome Trust, Holt's research group is aiming to better understand the molecular and cellular mechanisms that guide and maintain axon growth, which in turn will aid better understanding of how nerve connections are first established.

"It's an impressive navigational feat," says Holt. "The pathway between the retina and the brain may look homogeneous, but in reality it's like a patchwork quilt of different molecular domains."

On the pathway through this patchwork quilt, there is a set of distinct beacons, breaking the axon's journey down into separate steps. Every time the growing axon reaches a new beacon, it has to make a decision about which way to go. At the tip of the axon is a growth cone, which 'sniffs out' certain chemical signals emitted from the beacons, helping it to steer in the right direction.

The growth cones are receptive to certain signals and blind to others, so depending on what the axon encounters when it reaches a particular beacon, it will behave in a certain way. Holt's research group uses a variety of techniques to determine what the signals are at the steering points where axons alter their direction of growth or their behaviour, such as the optic chiasm where certain axons cross to the opposite side of the brain, or at the point where they first leave the eye.

While Holt uses experiments to understand the development of the visual system, Eglen uses mathematical models as a complementary technique to try to answer the same questions.

"You've got much more freedom in a theoretical model than you do in an experiment," he says. "A common experimental approach is to remove something genetically and see what happens. I think of that a little like taking the battery out of your car. Doing that will tell you that the battery is necessary for the car to function, but it doesn't really tell you why."

Theoretical models allow researchers to approach the questions around neural development from a different angle. To capture the essence of the neural system, they try to represent the building blocks of development and see what kind of behaviour would result.

But no model yet can fully capture the complexities of how the visual system develops, which Eglen views not only as a challenge for him as a mathematician, but also as a challenge back to the experimental community.

"It had been thought that if we built a model and took out all of the guidance molecules, there would be no topographic order whatsoever," says Eglen. "But instead we found that there is still residual order in how the neurons are wired up, so there must be extra molecules or mechanisms that we don't know about. What we're trying to do is to take biology and put it into computers so that we can really test it."

"In the past 15–20 years, there's been a revolution in terms of being able to identify the specific molecules that act as guidance receptors or signals, but there's still so much we don't yet know, which is why we're using both theoretical and experimental techniques to answer these questions," says Holt. "And in addition to this question of wiring, we're also looking at the problem of mapping – how do the terminal ends of the axons find their ultimate destination in the brain?"

Holt's group has found that the same guidance molecule can have different roles depending on what aspect of growth is going on – but the question then becomes how do you wire the brain with so few molecules?

Adding to the complexity was another puzzling discovery – that the growth cones of axons can make proteins. Previous knowledge held that new proteins could be synthesised only within the main cellular part of each neuron, the cell body (where the nucleus is located), and then transported into axons. However, Holt's group found that the growth cones of axons are also capable of synthesising proteins 'on demand' when they encounter new guidance beacons, suggesting that messenger RNA (mRNA) molecules play a role in helping axons to navigate to their correct destinations. mRNAs are the molecules from which new proteins are synthesised, and further experiments found that axons contain hundreds or even thousands of different types of this nuclear material.

In addition to their role in axon growth when the brain is wiring itself up during development, certain types of mRNA are also important in maintaining the connections in the adult brain, by keeping mitochondria – the energy-producing 'batteries' of cells – healthy, which, in turn, keeps axons healthy.

"It is a whole new view to the idea of degeneration in later life – a lot of different components have to work together to get local protein synthesis to work, so if just one of those components fails, degeneration can occur," says Holt. "We've also found that many of the types of mRNA that are being translated in axons are the same ones that you see in diseases like Huntingdon's and Parkinson's, so basic knowledge of this sort is essential for the development of clinical therapies in nerve repair and for understanding these and other neurodegenerative disorders."

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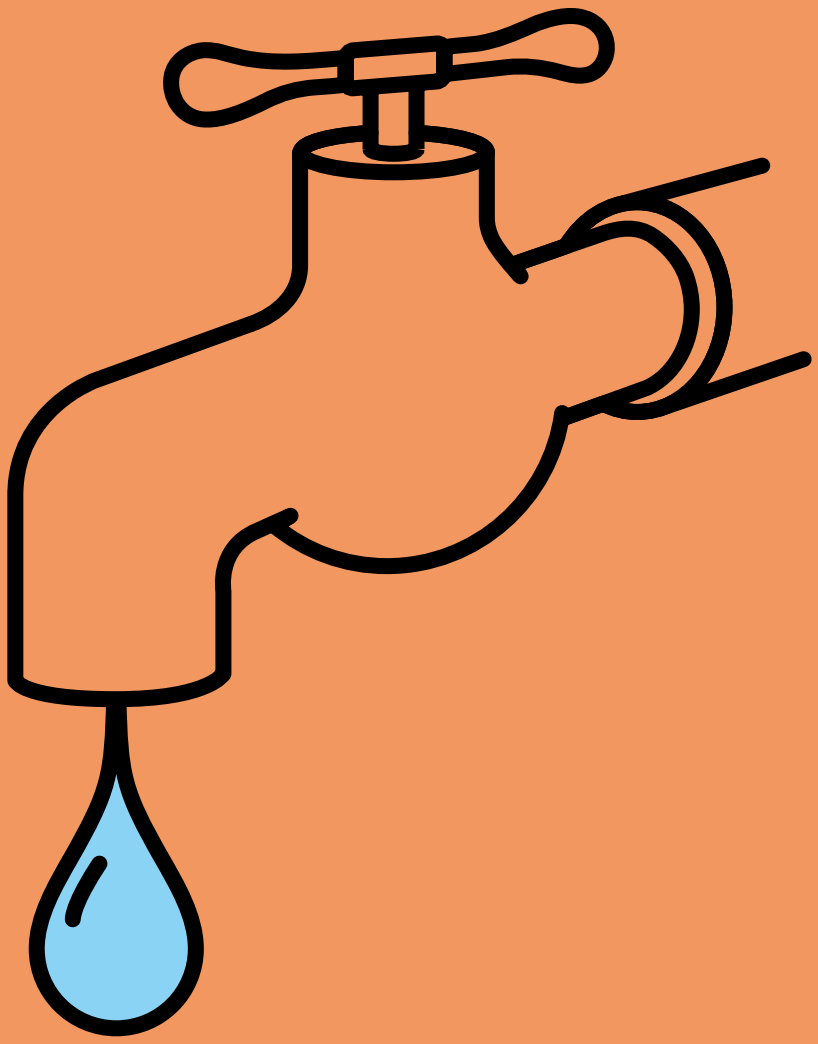
Once more with feeling



There are many challenges facing people with spinal cord injury – and walking again is often the least of their problems. Cambridge research could help patients take control of their lives once more

Spinal cord injury is, in many respects, a testosterone disease, says Professor James Fawcett.

What he means by this is that four out of five spinal cord injuries happen to men, and the most common age group is early adulthood. “Men are not good at assessing risk at that age,” he says. “Females are much more sensible.”

It is perhaps not surprising, then, that when asked about their priorities, most quadriplegic people will select a return of sexual function as second after the use of arms and hands. Third on the list, above being able to walk, is a return of bladder and bowel control. “Way down the list is walking, because wheelchairs work reasonably well and patients can get used to using them,” says Fawcett, who heads the John van Geest Centre for Brain Repair at Cambridge.

Restoring bladder and bowel control is a particular challenge, however. Currently, patients have to fill their bladder with botulinum toxin (botox) to paralyse it and catheterise themselves several times a day. This may be the simplest method, but catheterisation can cause infection and scarring in the urethra.

Instead, Fawcett is developing a device based on the ‘Brindley device’, named after physiologist Giles Brindley, who trained at Cambridge after the Second World War. The Brindley device is an implant to which an external stimulator is applied manually, causing the bladder to contract and empty itself. It has been used in thousands of patients, but it, too, is not without problems: it necessitates severing sensory nerves from the pelvis into the spinal cord, causing weakening of the pelvic muscles – and loss of sexual function. (For most male patients, Viagra can at least help them maintain an erection, but this is only half the problem. ‘Well OK, doc,’ they say, ‘you’ve given me an erection, but what’s the use if I can’t feel it?’”)

Fawcett and colleagues are developing a ‘biorobotic’ version of the Brindley device that can read signals from the sensory nerves in the pelvis, rather than requiring them to be cut. These signals would stop the bladder emptying itself at embarrassing times, tell the patient how full the bladder is, and allow them to use the electronics to empty it.

The ability to record signals from individual nerves has applications beyond just bladder control: Fawcett envisioned the technology as enabling patients who had lost a limb – such as soldiers losing arms or legs – to control robotic limbs. “The limbs themselves are quite sophisticated,” he says, “but what doesn’t work at all well is their interface with the nervous system.” The technology required for recording signals for a whole limb has proven to be extremely complicated, so the team is looking at the bladder-control device as a simpler demonstration of a proof of concept.

Biorobotics will be one focus of a proposed new Spinal Injury Research Centre to be based at Addenbrooke’s Hospital. Although still at the very early planning stages, the Centre will capitalise on Cambridge’s position as the regional trauma centre for the East of England (even though a lack of facilities means spinal injury patients have to be sent to Stoke Mandeville near Oxford for rehabilitation).

A simplified version of the adapted Brindley device has so far been trialled in around 50 dogs, in whom spinal cord injury is surprisingly common, particularly in dogs with longer spines, such as dachshunds. Many owners of injured dogs want to keep their pets but, as Fawcett explains, “the dogs are perfectly happy to paddle around with wheels under their back legs, but they do so dribbling urine around your house.”

Restoring bladder and bowel control is a particular challenge. Currently, patients have to fill their bladder with botulinum toxin (botox) to paralyse it and catheterise themselves several times a day

In fact, a randomised controlled trial in 2013 showed that injured dogs may even be able to do away with their wheels. Professor Robin Franklin from the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute showed that transplanting cells found in the nasal cavity, known as olfactory ensheathing cells, into the injured spine could help restore movement to the previously paralysed limbs. Although the cell transplant did not restore bowel or bladder control, it was, says Franklin, “a landmark study” that offers the promise of translation into humans. Franklin’s colleague Dr Mark Kotter is currently seeking funding to carry out a trial in humans.

But as Fawcett says, the priority among injured patients is to recover use of their upper limbs. Spinal cord injury causes damage to motor nerve fibres travelling from the brain and to sensory nerve fibres travelling to the brain. Both are structurally different and need to be coaxed to regenerate across the site of the injury – but even getting the nerve fibres to span these couple of centimetres is a challenge.

“The problem is scar tissue,” says Fawcett. “It’s very difficult for nerve fibres to grow through this tissue.” He has identified an enzyme, chondroitinase, which can dissolve scar tissue. The enzyme works in rats and is in preclinical development for use in humans by the US biotech company Acorda Therapeutics.

Once the scar tissue has been dissolved, the nerve fibres need to regenerate and make new connections. Although restoring motor nerve fibres is proving a challenge, Fawcett has managed to restore sensory nerve fibres in rats, which is an important start. “Patients need to be able to feel what they’re doing and to sense pain. If they turn on a hot tap, they can easily scald themselves if they can’t feel the heat. And of course, they want sensation back in their genitalia.”

In most spinal cord injuries, some nerve fibres will always survive, and Fawcett believes we may be able to harness these to bypass nerve damage if we can harness a remarkable property of the young brain known as plasticity, which enables new connections to be made as we learn new skills. If a young child receives a spinal injury, their chances of recovery are much better than for an adult as their brain can adapt, but as we age, a cartilage-like coating wraps around nerve fibres, cementing the connections in place. These molecules make it difficult for the brain of an injured adult to find a way to bypass the injury.

“Interestingly,” explains Fawcett, “one of the main constituents of this cartilage is the same as that which blocks nerve growth in scar tissue – and we know we can dissolve this using chondroitinase. This should make rehabilitation – teaching the brain to do useful things again – dramatically more successful.”

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THE HIGHWAY TO ADDICTION

The discovery of a brain circuit 'shortcut' could explain why some addicts unintentionally relapse, and suggests that a shift in focus for therapies might help those who want to stay off drugs.

There is a road down which those with substance addiction travel. Its beginnings are influenced by circumstances and genetics; it becomes well trodden, habitual, initially reinforced by pleasurable effects and then by cues; and, for some, it will become a road they can never leave.

Addiction is a chronic, relapsing psychiatric disease, with complex behavioural processes and equally complex changes to brain circuits. The brain of a person who has drunk alcohol or taken drugs is different to the brain of one who has not, as pharmacologist Dr David Belin describes: "I like whisky. I started drinking whisky when I was 20 and I have only a small amount now and then. But if I were to scan my brain, it changed that very first time, and it continues to be changed."

And because drugs change the brain in ways that foster compulsive drug and alcohol abuse, quitting is difficult, even for those who want to. Belin and Professor Barry Everitt, from the Department of Pharmacology, have shown that some are more vulnerable than others to developing addiction – and to relapsing.

Their recent research, published in *Nature Communications*, uncovers a new neural 'short cut', or 'back door', in rat brains that could explain why some cocaine addicts relapse without intending to. The results, they believe, could suggest new forms of behavioural and pharmacological therapies.

A decade ago, both Belin and Everitt, independently, were the first to show that addiction manifests itself differently in different individuals and that, for some, compulsive cocaine-seeking behaviour would continue despite adverse circumstances. In a rat model, around 20% of animals addicted to cocaine still sought the drug despite the risk of receiving mild electric shocks on doing so.

"This was the first time in the field of addiction that the idea of inter-individual differences in vulnerability to compulsive drug seeking was raised," explains Belin, who is funded by the Wellcome Trust. "With regard to psychiatric disorders, we are not equally vulnerable."

Drug addiction had largely been regarded as the end point of a progressive loss of control over drug seeking resulting from a failure of part of the brain – the prefrontal cortex – that deals with decision making.

"Certainly, chronic exposure to drugs alters the prefrontal cortex, which governs motivation, inhibitory control and choice. But it also alters an area of the brain called the basolateral amygdala, which is associated with the link between a stimulus and an emotion," explains Belin.

To explain further he gives the example of choosing to eat a cake or an apple. "The basolateral amygdala stores the pleasurable memories associated with eating the cake, but the prefrontal cortex manipulates this information, helping you to weigh up whether or not you should eat another slice or choose the apple instead. If you eat the slice, regions of the ventral striatum, the structure that processes reward and links emotions to actions, are activated."

However, Belin and Everitt's latest research has shown that this is not the only neuronal circuit that underlies cocaine-seeking behaviour.

Using their rat model, they identified a completely new highway that links impulses with habits. This brain circuit links the basolateral amygdala indirectly with the dorsolateral striatum, which is the neural locus of habits.

"Because it doesn't recruit the prefrontal cortex it doesn't involve choice," explains Belin. "It's a short cut or back door directly to habit. It means that addicts can have internal urges they are not aware of that drive drug seeking. It's a newly recognised function of this brain circuitry.

"It would explain situations in which individuals who have been abstinent for five years suddenly relapse, telling their counsellor 'I was walking in the street and I found myself with a glass of wine – and I promise you I didn't want it.' This has often been dismissed as 'weakness of the will' and then denial. This may also happen, but what our results in rats suggest is that there are occasions in which the stimuli go via motivation straight to the habit part of the brain without an individual even being aware of it."

The researchers believe that this is a breakthrough in understanding how drugs like cocaine can hijack the brain with such devastating consequences. "We can speculate that the subset of individuals currently using drugs who are especially vulnerable to addiction might have a stronger pathway – a 'superhighway' to habit formation."

The finding could explain the puzzling feature of why substance abusers repeatedly do something they know is bad for them. This is an area that interests Dr Valerie Voon in the Department of Psychiatry. “There appears to be a form of impulsivity called ‘waiting impulsivity’ that doesn’t involve choice and that predisposes to drug addiction.”

Waiting impulsivity is seen when a runner takes off before the starter pistol, or when someone interrupts inappropriately. Voon has devised a way of measuring it in humans based on tasks studied in rats. She also uses another task that teases apart decisions that are made through choices that are goal directed (i.e. taking into account the goal or outcome) from those that are habitual (i.e. relying rather automatically on past rewarding choices).

“We find that alcohol addiction correlates with waiting impulsivity. Once you’re abstinent, the compulsivity or habits also improve. Now that we have this test we can start to cut across other addictions – is there an underlying neural process shared by all? Can we ascribe causality? Can we suggest new treatments?”

Belin suggests that a combination of behavioural and pharmacological treatments might be the answer to helping addicts quit.

Treatments such as cognitive behavioural therapy aim to restore the function of the prefrontal cortex so that emotions don’t automatically elicit habits. “But if people are not aware of their impulses then they can’t subjectively or cognitively apprehend the motivation and the impulse to take drugs or drink,” says Belin. “It’s possible that mindfulness might be beneficial in helping them identify the impulses.”

Although there is currently no effective pharmacological treatment for cocaine addiction, his team has recently shown that N-acetylcysteine might be a possibility, but only if used early enough on the road to addiction when the individual still has the motivation to stop.

The researchers now plan to extend their study of cocaine addiction to compulsive alcohol- and heroin-seeking behaviour. They and Voon would like to understand to what degree behavioural traits such as impulsivity, novelty preference and anxiety – using brain imaging to identify neural correlates – can be used as a predictor of compulsive drug seeking.

“Drug taking is always volitional to begin with – you take drugs because you want to experience something,” adds Belin. “Unfortunately they hijack the learning mechanisms in your brain so that you don’t really take them because you want them but because stimuli in your environment tell you to do so. We want to work out how we can help people become aware that their impulses are wrongly triggering their habits.”

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Extreme sleepover: Going underground in search of zombies

Lucy Wrapson reports on her fieldwork analysing the curious cave paintings found on Isla de Mona, in the Caribbean, and their equally enigmatic artists.

Isla de Mona has been many things: a source of melons and cotton hammocks for conquistadors in the 16th century; a pirate haunt in the 17th and 18th centuries; an industrial island fertilising the fields of the Western world with the fossilised guano of giant fish-eating bats in the 19th; a US air base in the 20th; and now, both a nature reserve and a destination for migrants seeking a better life in the USA.

This tiny island, just seven miles by four, with no permanent settlement, lies in the dangerous Mona Passage between Puerto Rico and the Dominican Republic, and it is the prehistory that brings us here.

The plateau of limestone and dolomite is riddled with caves filled with signs of human activity. Much of this is pre-Columbian (i.e. before the Spanish arrived in the late 15th century) and consists of painted images, finger-drawn designs and extensive extractive finger scratches, which are sometimes deep within the 'dark zones', where no natural light falls.

I am with archaeologists Dr Alice Samson from Cambridge's McDonald Institute for Archaeological Research and Dr Jago Cooper from the British Museum for their summer fieldwork. As a conservator with specialism in the materials and techniques of painting, I am here to analyse the pigments used to make pre-Columbian markings and with the team look at the layer structures of engravings and painted images.

I'm using an X-ray fluorescence spectrometer to examine the elemental composition of the pictographs, and will later take tiny samples away for further analysis. I want to find out whether the people who made these images used materials that were at hand in the caves, or transported them in from elsewhere.

Mona's prehistoric peoples appear to have lived on the island from at least 2800 BCE, surviving a century after the arrival of the Spanish at the end of the 15th century. The inhabitants at the time of the conquest, commonly referred to as Taínos, brought us the words hurricane, barbeque, hammock, canoe, potato and cannibal.

Caves feature prominently in Taíno mythology and it is likely that many of the anthropogenic images in the caves are zemís (considered by some the origin of the word 'zombie'). Zemí refers to any object, animal, vegetable or mineral, which was animate and could be called upon to intervene in human affairs. Zemís were found, constructed or painted in 3D and 2D form. Although the presence of human-like figurative designs is common in Caribbean rock-art, Alice and Jago's work is bringing to light a staggering amount of physical modification to the caves from the pre-Columbian era, particularly the extraction of soft white lime from the walls and ceilings. The purpose of this extraction and what the material was used for are not yet known.

Each morning I wake at 5.30am to the sounds of subtropical birds. It's the only time of day cool enough to go for a run. The coastguards and rangers all eat early; for them, life on Mona is a cycle of week-on-week-off at work, with a small aircraft bringing them to and from the Puerto Rican mainland to Mona via a bumpy grass airstrip.

At the camp, there's a small study centre (happily, with solar-powered Wi-Fi) as well as basic accommodation where the workers live, and where migrants can rest before they are moved from the island. Mona throws together strange combinations of people: border police, rangers, military personnel, scientists, cavers, immigrants and boy scouts.

We set off early in the morning. Some of the caves are nearby, but others involve more effort to carry our equipment, as they are some distance from our camp. Mona's environment can be inhospitable and it has a fearsome reputation. There is little natural water, except sometimes deep in the caves. It is dry, hot and thorny, and the rocks are sharp. As we walk to the caves, we often disturb one of Mona's endemic and therefore incredibly rare iguanas. They typically scuttle away from us into a hidden cave mouth.

Credit: All images, Alice Samson, El Corazón del Caribe research project

Finger-drawn designs are sometimes deep within the ‘dark zones’, where no natural light falls

Our team also includes Masters’ students from the Centro de Estudios Avanzados in Puerto Rico, and we work together analysing, documenting and photographing the evidence in the caves. Colonists, buccaneers, guano-miners and boy scouts have all left their mark, often with dated graffiti. On several days, we join a team of cavers who year on year visit this most cavernous location on earth to map the island’s 200-plus caves. It’s a great opportunity to learn about cave mapping and geology from experts.

If possible, lunch is taken in a cliff-side cave mouth, with a view out over the sea. On occasion, two nosy Red-Footed boobies wheel round and round to get a better look at us. The caves themselves are extremely hot, humid and dirty. At the end of the day we walk into the Caribbean sea, fully dressed in our ‘cave clothes’.

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Cover
A dragonfly (shown here in blue) has a larger brain than a robber fly (green) or a killer fly (yellow), but how does that affect their behaviour? Find out more on p. 24 this issue.

Credit: Sam Fabian