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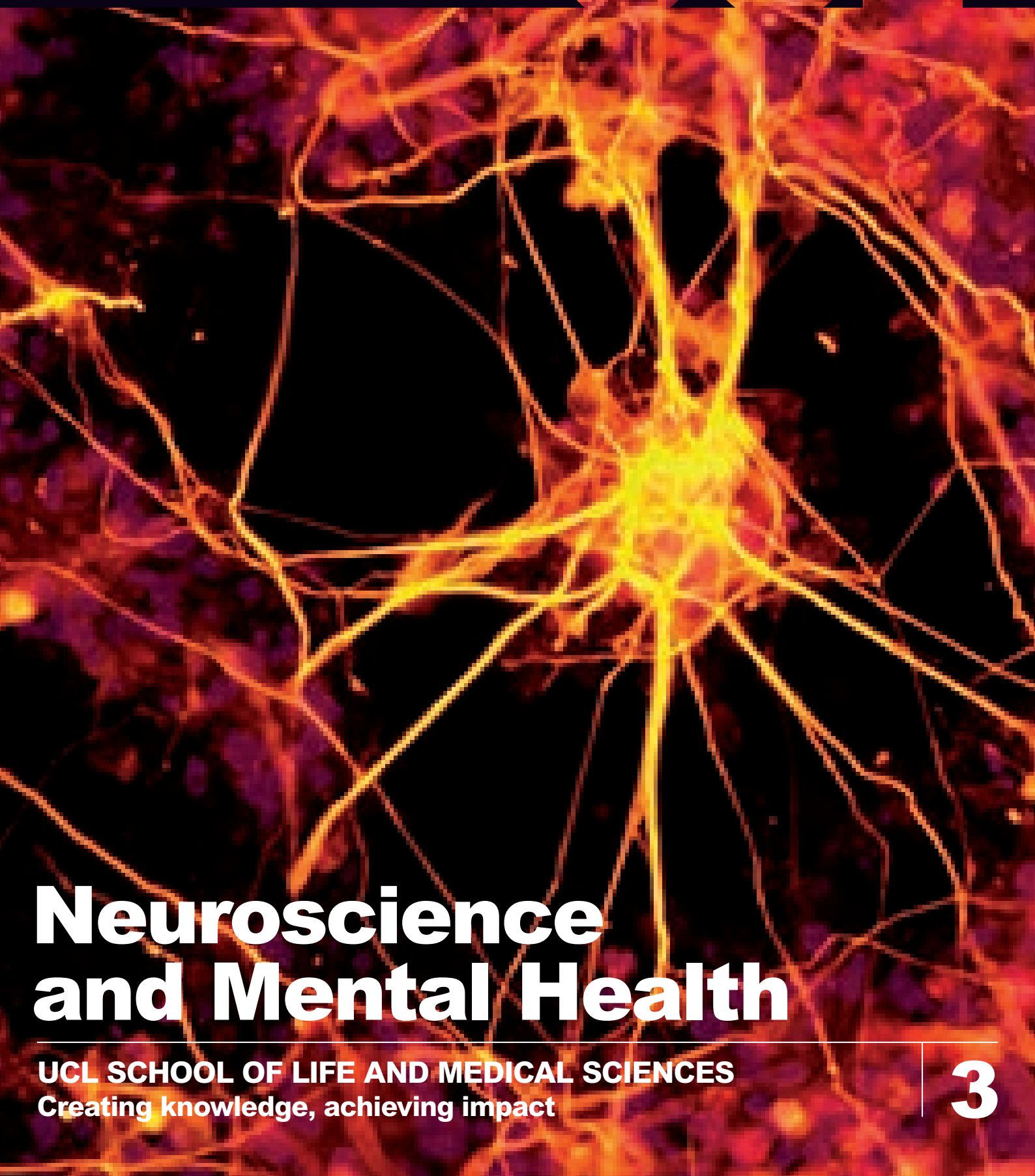

Neuroscience and Mental Health

UCL SCHOOL OF LIFE AND MEDICAL SCIENCES
Creating knowledge, achieving impact

3

PREFACE

UCL's School of Life and Medical Sciences encompasses arguably the greatest concentration of biomedical science and population health expertise in Europe. Our performance in the UK's last Research Assessment Exercise was outstanding, and for most key measures the School comfortably tops UK league tables.

In part because of UCL's size and organisational complexity, the scale of the School's achievements is not always apparent. This publication, one of four, seeks to address this. Our recent reorganisation, with the creation of four new Faculties, has been designed to create a more coherent structure, of which the Faculty of Life Sciences, headed by the Dean, Professor Mary Collins, is a clear example. But the School's restructuring has also placed great emphasis on cross-Faculty interactions and interdisciplinary research – and indeed on interactions with UCL departments outside the School. Such interdisciplinary endeavour is promoted through 'Domains', inclusive strategically led fluid networks. This approach allows us to connect all our activities related to fundamental research, promoting collaboration and the sharing of expertise, platforms and resources. Professor Michael Duchen and Dr Paola Oliveri are chairs of the Basic Life Sciences Domain.

UCL is acutely aware that scientific advance of real relevance to society is not only aided by an interdisciplinary approach but also through collaborative strategic alliances with other research-intensive institutions with complementary strengths. Our founding partner status in the new Francis Crick Institute engages us in what will be the European powerhouse of biomedical research expertise. Our links with our London Academic Health Science Centre partners also include our joint engagement together with the Medical Research Council in a new imaging company, Imanova, and our commitment to the London Life Sciences Concordat. Wider linkage to the London and South East super-cluster is secured by our involvement in the Global Medical Excellence Cluster (GMEC) for which we lead in the field of rare diseases. Our growing collaboration with our Bloomsbury neighbours, the London School of Hygiene and Tropical Medicine, is fuelling exciting developments in genetic epidemiology and pathogen research.

The breadth and quality of our research creates almost unique opportunities. Our recent merger with the London School of Pharmacy adds to our capacity in drug development, formulation and adoption. Our highly productive links to the health service, through UCL Partners, provides access to unmatched clinical expertise and large patient groups. We are fortunate to be partners in three National Institute for Health Research (NIHR) Biomedical Research Centres and a new NIHR Biomedical Research Unit in dementia.

The School's academic environment is one in which intellectual curiosity can prosper, while a high priority is also given to the practical application of knowledge to improve health and quality of life. This can take many forms, including commercialisation of new products as well as developing and informing health and social policy, and engaging with important stakeholders, including the public.

This publication, one of four (see right), showcases some of the outstanding research in translation and experimental medicine being carried out within the School and with collaborators across UCL and our NHS partners, in London, nationally and internationally. It is impossible to be comprehensive, but the stories give a flavour of the breadth, quality and impact of the School's research in this area. Looking forward, our aims are to enhance and expand our research to ensure we remain a global leader, and to see more people benefit from the groundbreaking research being carried out across the School.

Sir John Tooke

Vice-Provost (Health) and
Head of the UCL School of Life
and Medical Sciences.

1 **Basic Life Sciences:** 'Discovery' research, from molecules to ecosystems.

2 **Translation and Experimental Medicine:** Driving translation to benefit patients' health and well-being.

3 **Neuroscience and Mental Health:** The science of the brain and nervous system, from synapse to social interactions.

4 **Population Health:** Protecting and improving the health of populations, UK and globally.

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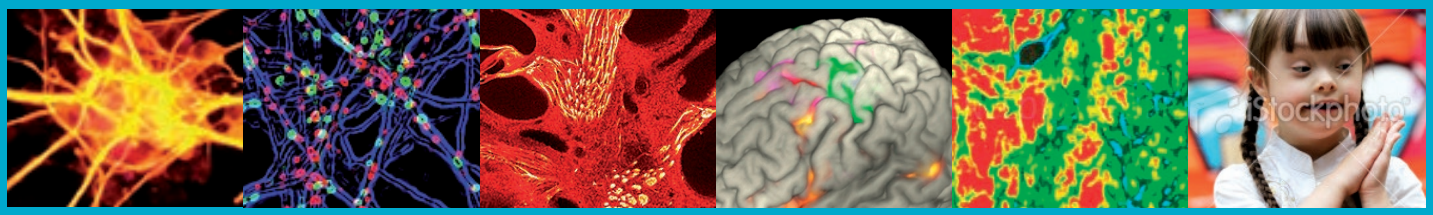

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THE GRANDEST CHALLENGE: NEUROSCIENCE AND MENTAL HEALTH

Understanding the brain and nervous system is perhaps the most challenging problem in the whole of biology – but the rewards could be substantial.

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The brain has been described as the most complex structure in the known Universe, and understanding how it works is one of the greatest challenges facing science. Even simple numerical descriptions boggle the mind: 100 billion neurons; 1000 trillion synapses; 1000 km of wiring connections. From the mundane matter of moving from A to B to the most profound philosophical questions – 'who am I?' – the brain lies at the heart of human existence and consciousness.

Neuroscientists are chipping away at the function of the brain, approaching the challenge from multiple directions. Some are studying the molecular properties of key nervous system proteins, particularly the receptors of neurotransmitters. This work is leading to a greatly increased understanding of how neurons operate and signal transmission is controlled. Other teams are examining how the activities of neurons are integrated in microcircuits and larger neural networks.

Others favour a 'top down' perspective, examining regional brain structure and function through imaging techniques such as magnetic resonance imaging (MRI) and functional MRI, alongside 'tractography' – mapping the connections between regions. Furthermore, there is growing interest in the 'social brain', recognition of the fact that humans are uniquely social animals and much brain activity is devoted to managing relationships with others.

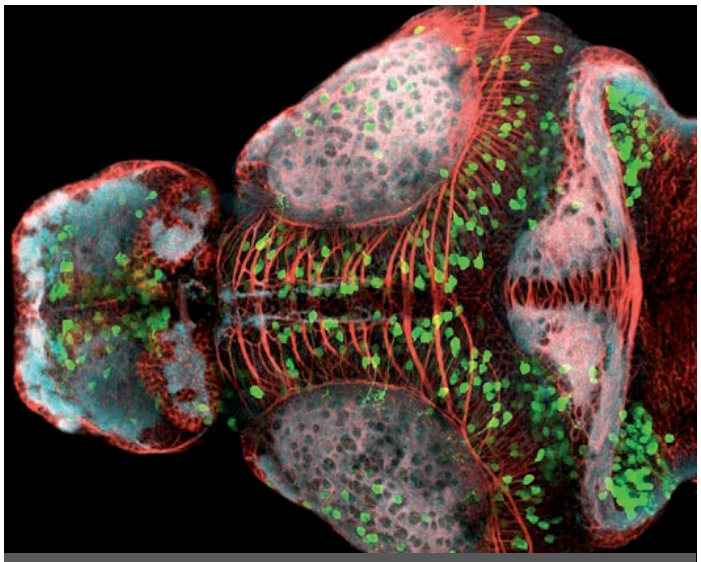
As well as the intellectual challenge of understanding nervous system function, neuroscience has the potential to make a profound impact on health. Diseases affecting the nervous system already impose an enormous burden on individuals, society and our health infrastructure, and their impact is likely to increase still further. Mental health conditions are predicted to have the greatest health burden globally by 2020. As populations age, neurodegenerative conditions such as Alzheimer's disease will become increasingly common – their economic costs presenting an enormous challenge to already hard-pressed families and healthcare systems.

Mental health conditions are predicted to have the greatest health burden globally by 2020.

Many conditions remain poorly served by modern medicine. Chronic pain is poorly controlled, regain of function after nerve injury is rarely successful, and pharmacological treatments for psychiatric conditions, despite some successes, are far from perfect. Treatment options are similarly limited for neurodegenerative diseases, and other conditions linked to damage to brain tissue such as stroke and multiple sclerosis.

On the other hand, there are reasons to be optimistic. Advances in a wide range of areas are providing new insight into disease processes and novel leads for new interventions. Genetic studies are revealing new contributory factors for numerous conditions, while imaging techniques are providing a more refined view of the nervous system damage associated with neurodegenerative conditions.

Neuroscience may also be able to provide a deeper understanding of neuropsychiatric conditions. Psychiatry, unlike most disease areas, continues to depend primarily on categorisation by symptoms. The diagnostic criteria for many conditions remain opaque and controversial, and generally bear little relationship to objective pathological measures or reflective of genetic causes. There is thus a great need to develop a better understanding of disease mechanisms – a challenge likely to require insight at multiple levels of organisation, genetic, molecular, cellular, neurological and neuropsychological.



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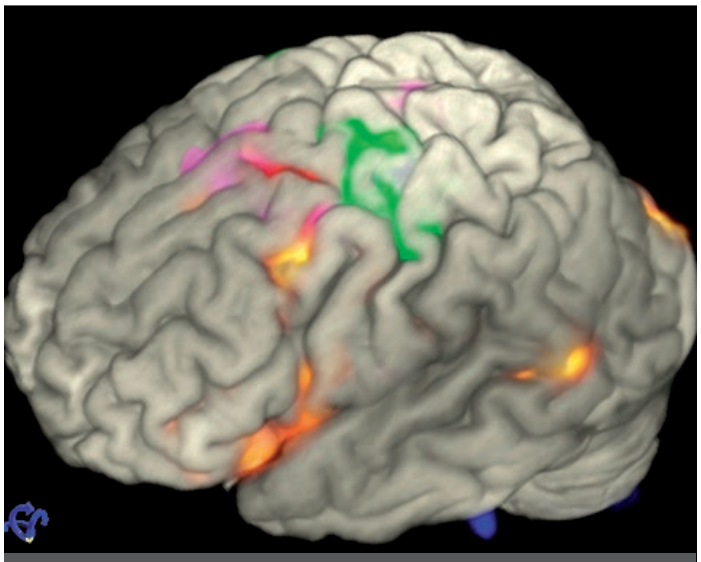

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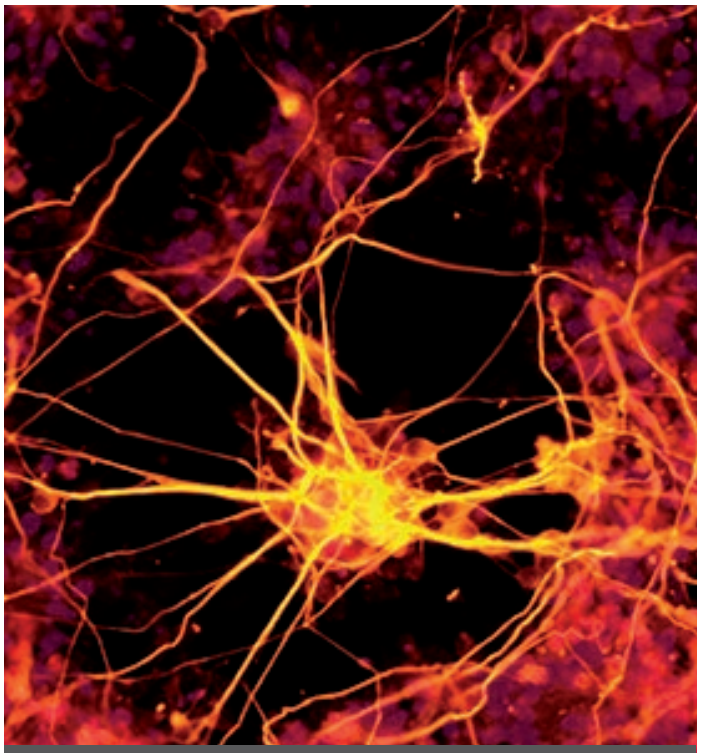

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Translation is an important aim of UCL's neuroscience research. Also covered in the companion volume on Translation and Experimental Medicine, UCL researchers are making important contributions across multiple conditions and types of treatment – drug development, gene therapy, stem cell therapy, psychotherapy and biomarker development. Implementation is also an important priority; key work in health services research and policy development is covered in the companion volume on Population Health.

UCL has housed some of the world's leading neuroscientists, including Nobel laureates Andrew Huxley and Bernard Katz. Today's researchers are maintaining and building on the foundations laid by these luminaries, collectively creating a community of expertise matched by few other institutions anywhere in the world. Their work is revealing fundamental insight into the brain and nervous system, and leading to new approaches to treatment for diseases of critical importance to physical and mental health.

REACHING OUT

UCL's neuroscience community is at the forefront in engaging lay audiences.

UCL has a strong commitment to communicate its work to audiences outside the research community, and its neuroscience researchers are among the most active contributors to these efforts. Projects are highly varied, spanning work with the media, including national TV and radio, patient-focused events, science festivals, school visits and public lectures, discussions and conferences, and innovative partnerships with bodies such as the British Library and Tate Liverpool.

Some events are geared towards patients and their families, such as the Retina Patient Day organised by Professor Robin Ali and Dr Mike Michaelides in the UCL Institute of Ophthalmology. Similarly, the Deafness, Cognition and Language Research Centre (DCAL) maintains exceptionally strong links with the deaf community.

UCL neuroscientists are frequent contributors to TV and radio shows. In a notable recent case, Dr Joe Devlin and Professor Cathy Price scanned Stephen Fry's brain for his 'Fry's Planet Word' series.

Numerous Events are held at UCL and partner venues, while UCL's Professor Mark Lythgoe has a key role as co-director of the highly successful Cheltenham Science Festival. UCL has also organised innovative interdisciplinary public events with the British Library, 'Do you Hear What I Hear?' in 2010 and 'The Performing Brain – A moving story' in 2012, each involving more than 20 UCL neuroscientists.

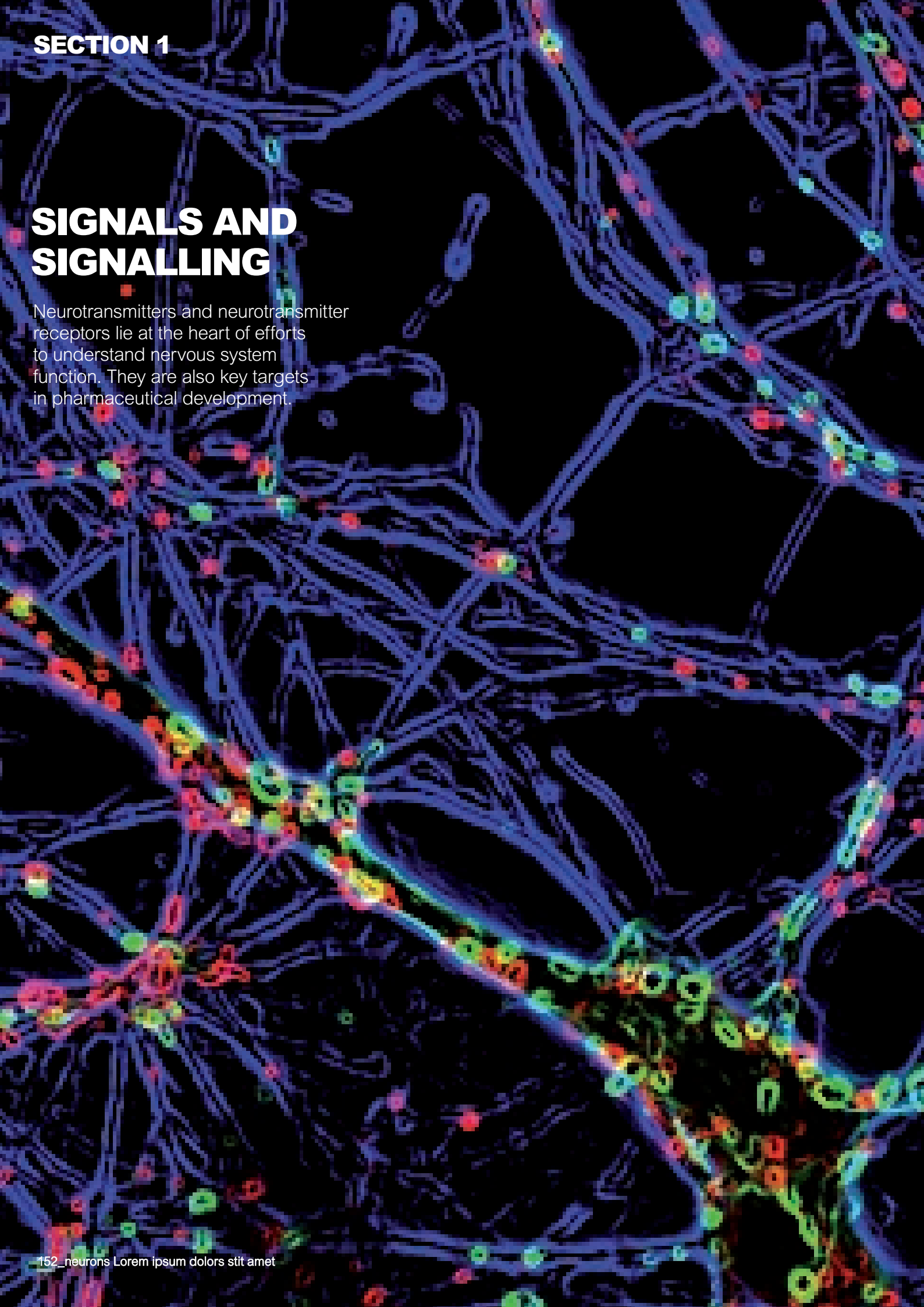
Policy-makers and politicians are an important audience, with UCL researchers such as Professors Geraint Rees, Uta Frith and Sarah-Jayne Blakemore contributing to the Royal Society's Brain Waves project, identifying key issues for society arising from neuroscience research.

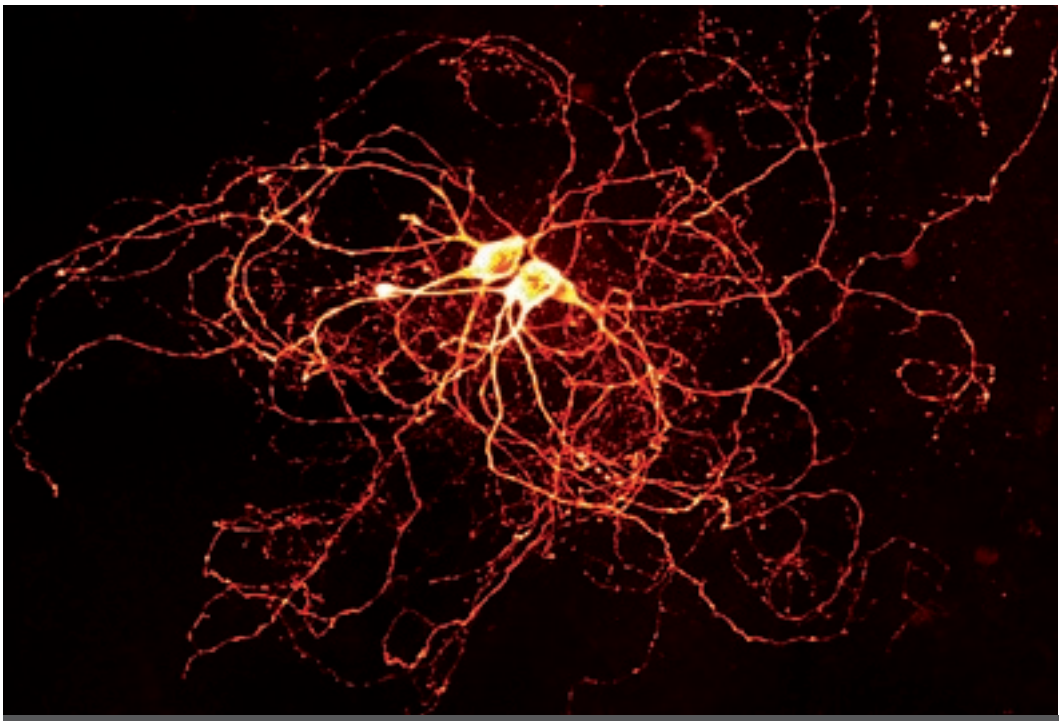
More unusually, the Institute of Cognitive Neuroscience appointed James Wilkes as a poet-in-residence, working with Professor Sophie Scott and others, while Dr Michelle de Haan collaborated with Tate Liverpool on an art–science project, 'Wondermind', linked to Alice in Wonderland.

Details of these and many other projects can be found at www.ucl.ac.uk/neuroscience.

SIGNALS AND SIGNALLING

Neurotransmitters and neurotransmitter receptors lie at the heart of efforts to understand nervous system function. They are also key targets in pharmaceutical development.





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In 1936, Otto Loewi and Henry Dale (who spent an early part of his career at UCL) received a Nobel Prize for demonstrating that neurotransmission was a chemical rather than electrical phenomenon. This profound discovery established that the extraordinary functions on the nervous system could be traced to the action of small chemicals transmitting signals across the synapse. Since then, neurotransmitters and the receptors they act upon have been subject to intense scrutiny. The aims have been both practical – to develop new therapeutics – but also intellectual: to understand the function of the nervous system in terms of its constituent parts.

The principal excitatory neurotransmitter in the CNS is glutamate, which binds to several classes of receptor, including NMDA, AMPA and kainate receptors. As well as characterising NMDA and kainate receptors, **Professor Stuart Cull-Candy** has unravelled many key aspects of AMPA receptor function. His early studies revealed that glutamate binding to receptors generated several distinct conductance levels, representing transitions of the same channel[1]. He also discovered that certain astrocytes (glial cells), express similar AMPA receptors[2], enabling them to respond rapidly to glutamate[3].

Neurotransmitters and the receptors they act upon have been subject to intense scrutiny. The aims have been both practical – to develop new therapeutics – but also intellectual: to understand the function of the nervous system in terms of its constituent parts.

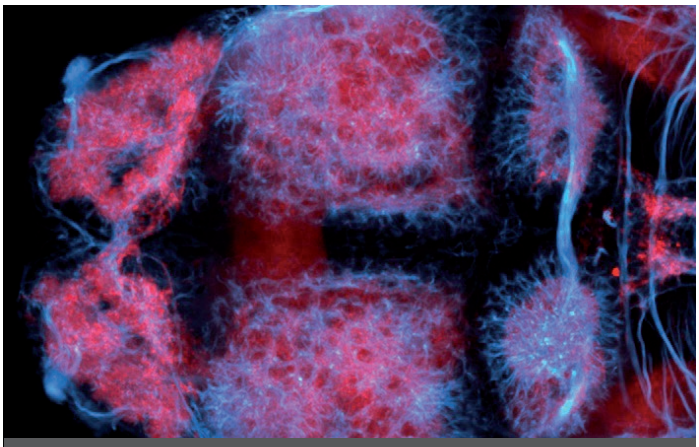
AMPA receptors play a critical role in synaptic 'plasticity' – changes in the properties of the synapse after a signal has been transmitted. In effect, the synapse 'remembers' past activity and subsequently responds more (or less) vigorously. This effect can be mediated by changes in AMPA receptor numbers or the conductance of single AMPA receptor channels. Various forms of such plasticity are thought to underlie learning and memory.

Professor Cull-Candy and **Professor Mark Farrant** have been particularly interested in calcium-permeable forms of AMPA receptors, which have been implicated in several neurological diseases. Calcium permeability depends critically on the presence of the GluA2 subunit. After high-frequency synaptic activity, calcium-permeable AMPA receptors are rapidly replaced by calcium-impermeable receptors – a change triggered by calcium entry through the receptors

1 Cull-Candy SG, Usowicz MM. Multiple-conductance channels activated by excitatory amino acids in cerebellar neurons. *Nature.* 1987;325(6104):525–8.

2 Usowicz MM, Gallo V, Cull-Candy SG. Multiple conductance channels in type-2 cerebellar astrocytes activated by excitatory amino acids. *Nature.* 1989;339(6223):380–3.

3 Silver RA, Traynelis SF, Cull-Candy SG. Rapid-time-course miniature and evoked excitatory currents at cerebellar synapses in situ. *Nature.* 1992;355(6356):163–6.



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channels, creating a form of negative feedback[4]. More recent work has focused on the influence of newly identified accessory transmembrane proteins, the 'TARPs', on calcium-permeable AMPA receptors (see page xx).

Another researcher with an interest in glutamate neurotransmission is **Dr Alasdair Gibb**. His focus, however, is the NMDA receptor, and in particular its potential involvement in Parkinson's disease (see page xx). His expertise in recording neural activity, mainly in rodent brain slices, also leads to numerous collaborations – for example with **Professor Patricia Salinas**, on the impact of Wnt signalling on the strength of synaptic connections[5].

Dr Gibb is also heavily involved in teaching at UCL, and has also helped to organise workshops to transfer skills and promote interactions between researchers in academia and industry. Funded by the Medical Research Council and industry, and organised through the British Pharmacological Society, the workshop aims to encourage a two-way flow of information between the two sectors. With industry increasingly reluctant to invest in brain-related conditions, academia has a vital role to play in generating a deeper understanding of disease processes and new therapeutic leads.

While glutamate and other excitatory neurotransmitters spark the nervous system into life, GABA (γ -aminobutyric acid) acts to keep it in check. The balance between excitatory and inhibitory neurotransmitters keeps the CNS responsive but not overexcitable, and any distortions to this balance can have a major impact on health.

Professor Trevor Smart's group is exploring the structural basis for the neurophysiological effects of GABA, focusing on its receptors and their modulation by chemicals such as neurosteroids. This work has led to a new mouse model of anxiety and depression, and a growing focus on translational work on new agents targeting GABA receptors (see page xx).

Similarly, Professor Smart's colleague **Dr Clare Stanford** is characterising a potential animal model of attention-deficit hyperactivity disorder (ADHD). The model was a serendipitous discovery when Dr Stanford and **Professor Stephen Hunt** noticed that the symptoms of a substance P (tachykinin-1) receptor knockout mouse were strikingly similar to those of ADHD[6]. Supporting its relevance to human disease, variation in the human tachykinin-1 receptor gene has been linked to susceptibility to ADHD[7].

As well as GABA receptor–ligand interactions, Professor Smart has also examined the mechanisms of receptor trafficking and mobility in the plasma membrane (areas also being studied by **Dr Josef Kittler** and, for calcium channels, **Professor Annette Dolphin**; see companion volume on Basic Life Sciences). Control of receptor numbers at the synapse, through intracellular trafficking and membrane translocation, are clearly important mechanisms of regulation. In mice, interfering with phosphorylation of $GABA_A$ receptors, for example, affects intracellular trafficking and ultimately leads to abnormalities in spatial memory[8].

A critical aspect of these studies is the ability to visualise the location of receptors in the cell. Professor Smart's group has pioneered new methods of labelling, introducing binding sites for quantum dots and fluorescently labelled snake toxins – significantly smaller than conventional methods such as antibody labelling. Receptors can now be tracked at single molecule level in living cells. In collaboration with **Dr Guy Moss**, his group has also been working on ultra-high-resolution systems, such as 'hopping mode' scanning ion conductance microscopy, to image the three-dimensional surface of living cells. Developed with collaborators at Imperial College and in industry, the technique provides structural detail at nanoscale resolution[9].

Professor Neil Millar's focus is on nicotinic acetylcholine receptors, one of the two major classes of acetylcholine receptor. As well as being present at the neuromuscular junction, they are widely distributed throughout the nervous system.

Until recently, nicotinic acetylcholine receptors received less pharmacological attention than glutamate receptors. But there is a growing interest in acetylcholine receptors, which have now been implicated in several neurological conditions and in cognitive processes.

Much of Professor Millar's research involves collaboration with Eli Lilly, which maintains an active programme of research on modulators of acetylcholine receptor function. The partnership is mutually beneficial. The academic research generates insight into the basic biology of receptors that may inform drug development, while the UCL lab gains access to industrial resources such as chemical libraries. It also enables junior researchers to experience work in a commercial lab.

Professor Millar also works closely with UCL's Department of Chemistry, where researchers generate new agents to test the properties of receptors.

4 Liu SQ, Cull-Candy SG. Synaptic activity at calcium-permeable AMPA receptors induces a switch in receptor subtype. *Nature.* 2000;405(6785):454–8.

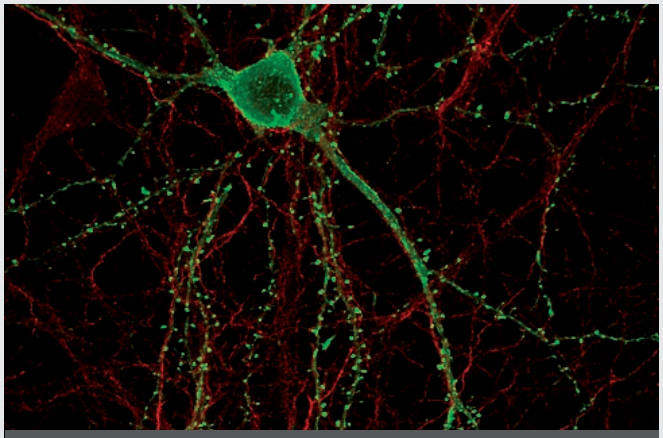
5 Ciani L *et al.* Wnt7a signaling promotes dendritic spine growth and synaptic strength through Ca^{2+}/Calmodulin-dependent protein kinase II. *Proc Natl Acad Sci USA.* 2011;108(26):10732–7.

6 Yan TC, Hunt SP, Stanford SC. Behavioural and neurochemical abnormalities in mice lacking functional tachykinin-1 (NK1) receptors: a model of attention deficit hyperactivity disorder. *Neuropharmacology.* 2009;57(7-8):627–35.

7 Yan TC *et al.* NK1 (TACR1) receptor gene 'knockout' mouse phenotype predicts genetic association with ADHD. *J Psychopharmacol.* 2010;24(1):27–38.

8 Tretter V *et al.* Deficits in spatial memory correlate with modified {gamma}-aminobutyric acid type A receptor tyrosine phosphorylation in the hippocampus. *Proc Natl Acad Sci USA.* 2009;106(47):20039–44.

9 Novak P *et al.* Nanoscale live-cell imaging using hopping probe ion conductance microscopy. *Nature Methods.* 2009;6(4):279–81



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AGAINST THE FLOW

Key insights are being gained into AMPA receptors, critical players in neuronal function.

AMPA receptors, one of the two main ion channel receptors activated by glutamate, the nervous system's principal excitatory neurotransmitter, are fundamental to nervous system function. Of particular significance is their role in 'plasticity', changes that affect how strongly a signal is transmitted. **Professors Stuart Cull-Candy** and **Mark Farrant** have spent many years investigating these critical membrane proteins, most recently shedding important light on a family of newly discovered accessory proteins, the so called 'stargazin' family of TARPs (transmembrane AMPA receptor regulatory proteins).

Of particular interest has been the AMPA receptor's permeability to calcium. Most AMPA receptors are not permeable to calcium, because of the presence of a specific component of the receptor – the GluA2 subunit. Professor Cull-Candy and Professor Farrant have shown that the absence of GluA2 renders receptors sensitive to 'plugging' by large positively charged polyamines that occur naturally within nerve cells, restricting ion flow to specific situations.

Work on AMPA receptors was transformed by the discovery in 2005 of a family of proteins that associate with the receptors and regulate their activity. The first of these proteins, stargazin, was identified in the *stargazer* mutant mouse (so named because of its distinctive head movements). Stargazin is now known to be part of a family of six TARPs that are differentially distributed throughout the brain – and which differ in their influence on AMPA receptor properties, and thus in their effects on neuronal signalling.

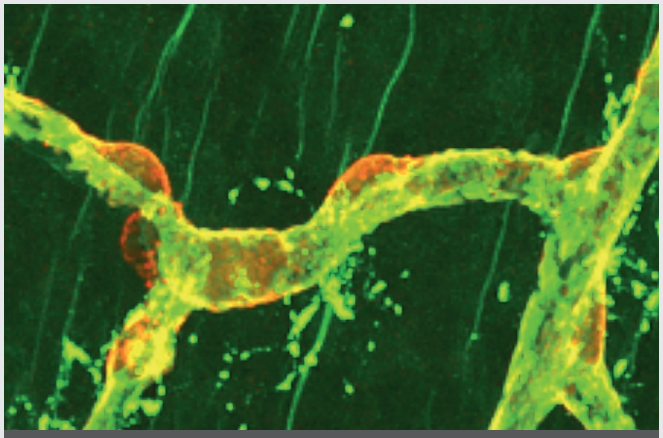
Professors Cull-Candy and Farrant have found that TARPs such as stargazin significantly reduce the ability of polyamines to plug the channel. Furthermore, their research has revealed that a supposedly non-functional member of the TARP family (known as γ-5) has specific effects at calcium-permeable AMPA receptors in glial cells. Unlike other TARPs, these effects are partly inhibitory, reducing ion flow and restricting AMPA receptor expression.

Abnormal AMPA receptor regulation has been implicated in several serious neurological and psychiatric disorders. During development, calcium-permeable AMPA receptors are present in oligodendrocyte precursor cells (which give rise to myelin-producing glial cells). Unfortunately, this renders the cells vulnerable to damage linked to low oxygen levels, which can ultimately lead to conditions such as cerebral palsy. Professors Cull-Candy and Farrant have found that TARPs play a key role in AMPA receptor regulation in oligodendrocyte precursor cells. Ultimately, a fuller understanding of the dynamics of AMPA receptors, and the influence of TARPs, could inform new efforts in drug discovery and treatment.

Soto D *et al.* Stargazin attenuates intracellular polyamine block of calcium-permeable AMPA receptors. *Nature Neurosci.* 2007;10(10):1260–7.

Soto D *et al.* Selective regulation of long-form calcium-permeable AMPA receptors by an atypical TARP, gamma-5. *Nature Neurosci.* 2009;12(3):277–85.

Zonouzi M, Renzi M, Farrant M, Cull-Candy SG. Bidirectional plasticity of calcium-permeable AMPA receptors in oligodendrocyte lineage cells. *Nature Neurosci.* 2011;14(11):1430–8.



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GLIAL CELLS – ESSENTIAL SUPPORT FOR LIFE

The oligodendrocytes that form the insulating myelin sheath around CNS neurons play a key role in cognitive function and control of muscle contraction.

Efficient transmission of signals along axons in the CNS depends on a fatty insulating sheath of myelin, produced by a class of glial cells known as oligodendrocytes. As the work of **Professor David Attwell** and colleagues has revealed, oligodendrocytes and their precursor cells also respond to neurotransmitters and some are electrically excitable. These properties remain enigmatic, but they may have important consequences for health.

Oligodendrocytes are typically characterised as 'support' cells for neurons, wrapping axons in myelin sheaths that help to maintain action potential propagation along an axon. Their importance is illustrated by conditions such as multiple sclerosis, cerebral palsy and spinal cord injury, which are associated with loss of the myelin sheath.

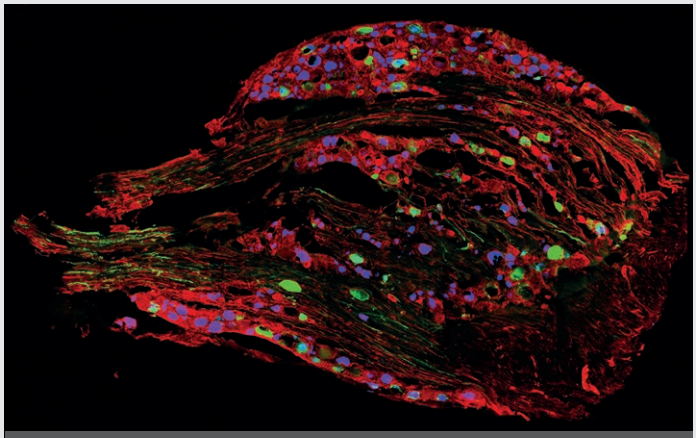
Central to these conditions is the response of oligodendrocytes, and their precursor cells, to neurotransmitters, particularly the excitatory transmitter glutamate. In low-energy conditions, a transporter that normally imports glutamate into neurons and oligodendrocytes begins to run in reverse, expelling glutamate. This excess glutamate was known to act on one class of glutamate receptor on oligodendrocyte lineage cells (AMPA receptors). However, Professor Attwell and colleagues found that white matter oligodendrocytes and their precursors also express NMDA receptors responsive to external glutamate which, unlike NMDA receptors in neurons, are active even at resting potentials.

Furthermore, contrary to received wisdom, it turns out that some oligodendrocyte precursor cells actually generate an action potential after neurotransmitter binding. The significance of this electrical signalling remains to be elucidated, but it may play a role in controlling the development of the cells.

Further research on the neurotransmitter receptors involved in controlling myelination during nervous system development, and in triggering demyelination in pathological conditions, will provide potential leads for the development of new agents for conditions such as multiple sclerosis, cerebral palsy and spinal cord injury.

Káradóttir R, Cavelier P, Bergersen LH, Attwell D. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. *Nature.* 2005;438(7071):1162–6.

Káradóttir R, Hamilton NB, Bakiri Y, Attwell D. Spiking and nonspiking classes of oligodendrocyte precursor glia in CNS white matter. *Nature Neurosci.* 2008;11(4):450–6.



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A CHANNEL TO BETTER PAIN RELIEF

Rare individuals who lack the ability to feel pain could hold the key to better treatments for chronic pain.

On occasion, pain may persist long after tissues have recovered. Such chronic pain is difficult to treat. By taking advantage of advances in human genetics, **Professor John Wood** and colleagues are generating important insights into the cellular mechanisms of pain, and providing crucial leads for the development of new pain-relieving therapies.

In 2006, Professor Geoffrey Woods and Dr James Cox in Cambridge with Professor Wood described six members of a family from Pakistan who were completely unable to experience pain. The family came to light through the 'street theatre' performances of one young boy, who would stab himself with knives and walk on hot coals for a captive audience; sadly, he died after throwing himself off a house roof.

Although affected family members showed normal responses to heat and cold, pressure, tickle and so on, they were completely unresponsive to painful stimuli. A classical gene-mapping strategy pinpointed a region of chromosome 2 as critical to the condition, and within this region the SCN9 gene – encoding a sodium channel, Nav1.7, already being studied by Professor Wood – stood out as a strong candidate. Sure enough, mutations affecting SCN9 were found in all affected family members.

Curiously, although Nav1.7 is highly specific to pain detection, it has one other critical role. People with SCN9 mutations have no sense of smell, and mice engineered to lack the Nav1.7 channel are similarly unable to detect odours. An unexpected spin off from this work on pain may therefore be a better understanding of the sense of smell.

Recent years have seen dramatic progress in human genetics, with sequencing-based methods increasingly being used to identify mutations affecting pain detection – either loss of pain sensation or unusual pain sensitivity. Professor Wood, Dr Cox, who has now moved to UCL and colleagues have identified genes underlying such conditions and use sophisticated mouse engineering techniques to eliminate the corresponding genes just in pain-sensing neurons, to characterise their role in the cellular processes underlying pain.

A collaboration with UCL's Professor Andres Ruiz-Linares, for example, has identified a mutation affecting the TRPA1 ion channel in a South American family affected by periods of debilitating pain. Agents already exist that act on this protein, offering the immediate prospect of a potential therapy. Similarly, the other key proteins identified are important targets for the development of much-needed new agents for pain control.

Cox JJ *et al.* An SCN9A channelopathy causes congenital inability to experience pain. *Nature.* 2006;444(7121):894–8.

Nassar MA *et al.* Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc Natl Acad Sci U S A.* 2004;101(34):12706–11.

Weiss J *et al.* Loss-of-function mutations in sodium channel Nav1.7 cause anosmia. *Nature.* 2011;472(7342):186–90.

Kremeyer B *et al.* . A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. *Neuron.* 2010;66(5):671–80.

Pic to come

Factors compete for binding to RNA polymerase.

TWO'S COMPANY

Identification of two binding sites for endogenous neurosteroids on GABAA receptors is offering the prospect of new treatments for anxiety and depression.

GABA is the critical inhibitory neurotransmitter in the CNS. It acts on two main classes of receptor, $GABA_A$ and $GABA_B$. In the brain, binding to the former is modulated by several 'neurosteroids', which are released in a range of circumstances including stress, pregnancy and after alcohol consumption. Abnormalities in their interactions with GABA receptors have been implicated in numerous conditions, including anxiety, depression and alcoholism. By identifying how and where neurosteroids bind to $GABA_A$ receptors, **Professor Trevor Smart** and colleagues have laid the foundations for targeted agents to tackle these debilitating conditions.

To identify the regions of the receptor critical to interactions with neurosteroids, Professor Smart's group made use of a form of the fruit fly GABA receptor that shows little response to neurosteroids. A comparison of these fruit fly receptors with those in the human brain suggested that neurosteroids associated with the receptor's transmembrane domains. By introducing single amino acids from these domains of the fly protein into the human receptor, Professor Smart's team identified one transmembrane domain in a single GABA receptor subunit as critical to neurosteroid action.

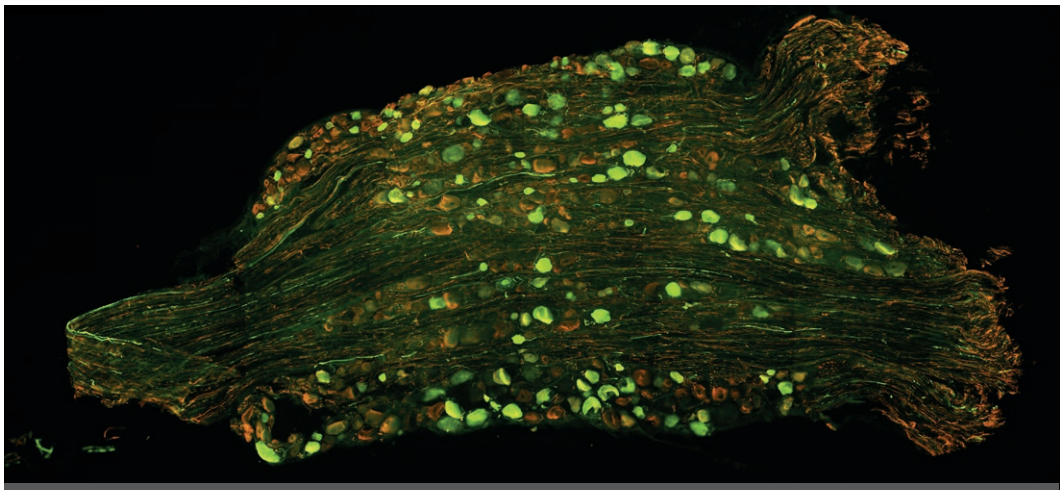
Neurosteroid activity is known to depend on particular chemical features that promote the formation of hydrogen bonds. By systematically altering residues in the transmembrane region able to form hydrogen bonds, Professor Smart's group was able to narrow down the points of interaction to two specific residues.

The location of these residues suggested that neurosteroids were binding at two distinct sites on the receptor. This was consistent with the fact that neurosteroids have two effects on GABAA receptors – at very low concentrations they are modulators of GABA action but at high concentrations they are direct activators of the receptor. Further analysis confirmed that binding at one site was responsible for modulation, while binding at both sites drove full activation.

By structurally mapping GABAA receptor sequence onto the structure of a related protein, Professor Smart and colleagues could visualise likely neurosteroid-binding sites. As predicted, amino acid changes affecting such binding sites significantly affected neurosteroid action.

An understanding of the precise molecular interactions responsible for neurosteroid modulation has opened the door to rational design of neurosteroid analogues able to bind GABAA receptors. Professor Smart is working with colleagues in UCL's Department of Chemistry to construct such modulators. His group has also developed an animal model that shows signs of heightened anxiety, and will be an important tool for testing potential new therapeutic agents.

Hosie AM, Wilkins ME, da Silva HM, Smart TG. Endogenous neurosteroids regulate GABAA receptors through two discrete transmembrane sites. *Nature.* 2006;444(7118):486–9.



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A three-way interaction between electrophysiology, molecular modelling and synthetic chemistry provides a way to probe connections between ligand binding, receptor structure and modulation of receptor function.

Energy demands

Neurons are naturally the main focus of CNS research, but an important support role is played by a type of glial cell, oligodendrocytes, which form the insulating myelin sheath around axons. Loss of this sheath is a significant factor in conditions such as multiple sclerosis, cerebral palsy and spinal cord damage. This may be partly caused by harmful effects of glutamate on oligodendrocytes which, as **Professor David Attwell** and colleagues have discovered, express NMDA receptors with unusual properties (see page xx).

A second major area of interest for Professor Attwell's group is energy use by the brain. Although just 2 per cent of body mass, the brain accounts for 20 per cent of its energy use. Largely this reflects the energy demands of the pumps that reverse the ion flows generating synaptic and action potentials.

It turns out that several systems exist to match the brain's energy supply (provided in the form of oxygen and glucose in the blood) to its fluctuating energy needs. At a tissue level, blood supply is increased to active brain areas. Professor Attwell and colleagues discovered that cells known as pericytes, which wrap around capillaries in the brain, may play an important role in controlling brain energy supply[10] by dilating during neural activity and thus increasing local blood flow. Poor recovery of capillary blood flow after stroke may also reflect abnormal pericyte function.

Even within neurons, surprisingly sophisticated mechanisms exist to meet localised energy demands. **Dr Josef Kittler** and Professor Attwell have shown that neurons use intracellular transport systems to move mitochondria to sites of high synaptic activity, where energy needs are highest[11] (see companion volume on Basic Life Sciences).

Blood supply and energy metabolism are of fundamental importance to the brain. Widely used functional imaging techniques actually measure changes in blood flow, which is assumed to reflect local brain activity. Furthermore, impaired blood supply might be a factor in Alzheimer's disease and in the aftermath of cerebral ischaemia, when blood flow fails to return to normal levels even after initial vessel blockages are cleared. Hence, understanding the mechanisms that control brain energy supply is important both to research and to treatment of major clinical conditions[12].

The origins of pain

Pain may be unpleasant, but it helps to keep us alive. Specific sensory neurons detect when tissue has been damaged, sending signals to the brain that are perceived as pain. By combining work on inherited human conditions affecting pain perception with experimental studies in mice, **Professor John Wood**'s group has identified critical players in pain detection – targets now being energetically pursued by the pharmaceutical industry.

Although rare, inherited pain syndromes are invaluable in revealing important molecular components of pain sensing. The genes affected clearly play a critical role in pain and, once identified, their function can be studied in more detail in mice. Professor Wood's group has developed highly efficient methods to knock out genes specifically in damage-sensing neurons in adult animals, revealing much about their function.

Pain detection is heavily dependent on sodium channels, including Nav1.7 (see page xx) and Nav1.8. Work on the latter revealed an important difference between mechanical, cold-induced and inflammatory pain – all of which require Nav1.8 – and neuropathic pain and heat sensing, which are independent of Nav1.8[13].

Cold pain is particularly interesting as, unlike other types of neural activity, pain signalling increases as temperatures fall. With Professor Peter Reeh from Erlangen, Germany, and colleagues, Professor Wood has shown that this effect depends on the presence of Nav1.8, the function of which is unaffected by low temperatures[14].

Professor Wood's group continues to pursue other critical components of damage-sensing neurons, including those responsible for detection of mechanical pressure and pain. As well as his group in UCL, he has also established a satellite lab in South Korea. With high-throughput sequencing technologies enabling mutations underlying human pain syndromes to be identified ever more rapidly, the number of leads available for functional studies is enough to keep both labs fully occupied.

10 Peppiatt CM, Howarth C, Mobbs P, Attwell D. Bidirectional control of CNS capillary diameter by pericytes. *Nature.* 2006;443(7112):700–4.

11 Macaskill AF *et al.* Miro1 is a calcium sensor for glutamate receptor-dependent localization of mitochondria at synapses. *Neuron.* 2009;61(4):541–55.

12 Attwell D *et al.* Glial and neuronal control of brain blood flow. *Nature.* 2010;468(7321):232–43. Review.

13 Abrahamsen B *et al.* The cell and molecular basis of mechanical, cold, and inflammatory pain. *Science.* 2008;321(5889):702-5.

14 Zimmermann K *et al.* Sensory neuron sodium channel Nav1.8 is essential for pain at low temperatures. *Nature.* 2007;447(7146):855–8.

SECTION 2

ALL JOIN TOGETHER

The complex functions of the nervous system reflect the activities of individual cells but also how the coordinated behaviour of networks of neurons.

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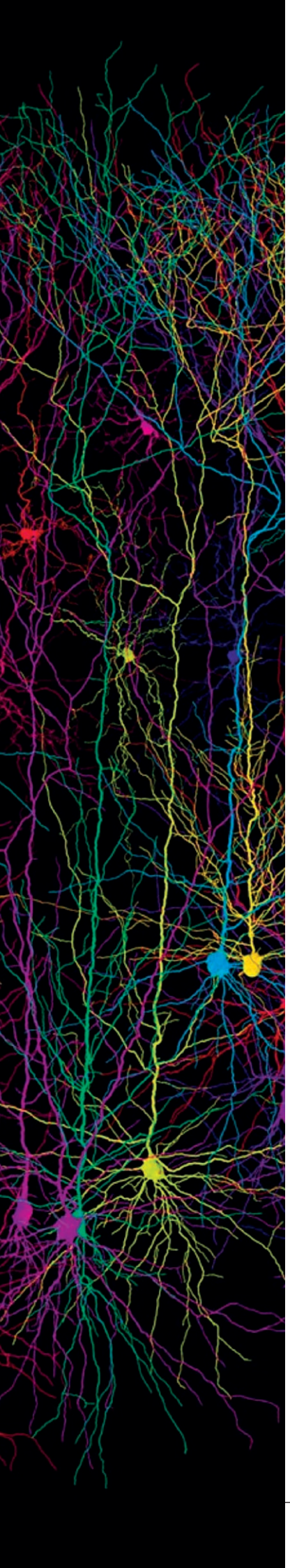

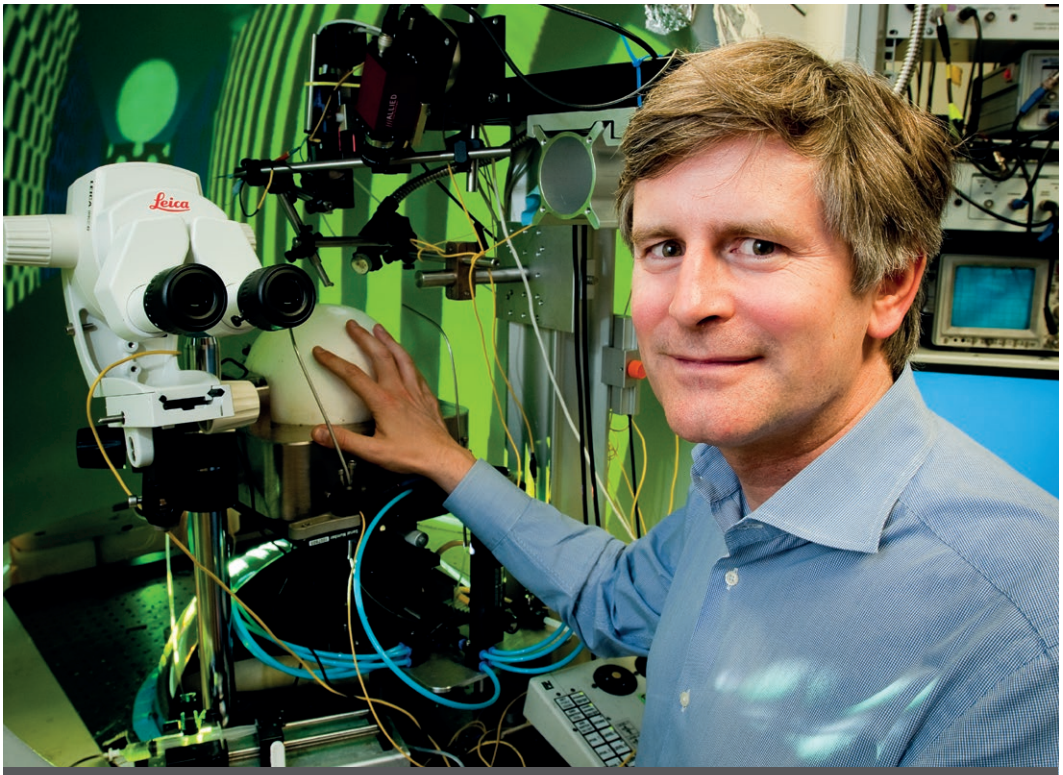

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One of the most striking properties of neurons is their organisation into three-dimensional networks of often staggering complexity. This arrangement is generally thought to be critical to the computational capacities of neural systems. However, it is becoming apparent that individual neurons are capable of surprisingly complex computations – and even subcompartments of neurons, dendrites, possess computational abilities.

Cells and circuits

Professor Michael Häusser's ambitious aim is to work out how the activities of single neurons and cellular circuits are integrated in specific behaviours. Computational processes have generally been conceived in terms of circuits, but Professor Häusser is drawing attention to the unexpectedly sophisticated roles that single cells – or even parts of cells – can play in these processes.

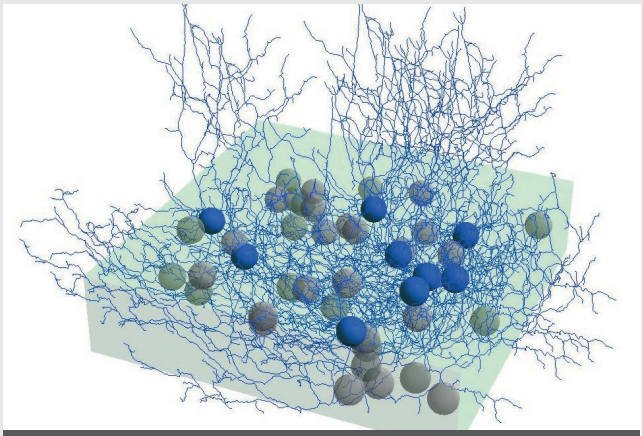
Computational processes have generally been conceived in terms of circuits, but research is drawing attention to the unexpectedly sophisticated roles that single cells – or even parts of cells – can play in these processes.

Signals are received by neurons through protrusions known as dendrites. A neuron may have anything from one to several thousand dendrites, each one branching repeatedly to create a characteristic dendritic tree. One of the most striking examples is the cerebellar Purkinje cell, where, from one 'trunk', some 200,000 parallel dendrites branch off.

The sheer numbers of dendrites contribute to the great complexity of neural networks. However, recent work is leading to a reappraisal of their role. In particular, rather than just passively transmitting signals, they also seem able to perform neural computations (see page xx).

For this work, **Dr Tiago Branco**, a postdoctoral fellow in Professor Häusser's lab, was awarded the 2011 Eppendorf and *Science* Prize for Neurobiology. He has gone on to uncover other interesting features of input signal processing along the dendrite. Close to the cell body, signals sum linearly, but only during short time windows. Signals further down the dendrite, by contrast, are amplified and are combined over longer time windows. As a result, inputs distant from the axon are surprisingly effective at triggering action potentials. Different positions on the dendrite thus appear to perform different functions,

15 Branco T, Häusser M. Synaptic integration gradients in single cortical pyramidal cell dendrites. *Neuron.* 2011;69(5):885–92.



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GAIN OF FUNCTION

Neurons do not simply add together the inputs they receive – they also perform more complex computations.

A neuron receives multiple synaptic inputs which collectively govern its response – typically by modulating firing rate. Simplistically, a neuron's output could reflect the sum of its inputs but to perform complex computations more nuanced responses are required. **Professor Angus Silver** and colleagues have used a combination of experimental manipulation and modelling to demonstrate how neurons can achieve 'gain control' – where inputs combine multiplicatively rather than additively..

Neurons can be considered as 'input–output' devices, and it is of fundamental importance to understand how outputs, particularly firing rates, are shaped by different patterns of input. Do neurons simply sense the difference between two input signals (an additive function) or are they capable of multiplying them together, thereby achieving an amplifying effect or gain control?

Early theories suggested that inhibitory inputs into neurons could form the basis of gain control. These ideas fell out of favour as experimental studies found little evidence for mechanisms to support them. However, Professor Silver pointed out, this might reflect the fact the methods being used to generate synaptic input signals were not sufficiently similar to those occurring in real life. With more realistic inputs, he was able to show that inhibition was indeed able to modulate gain in cerebellar granule cells.

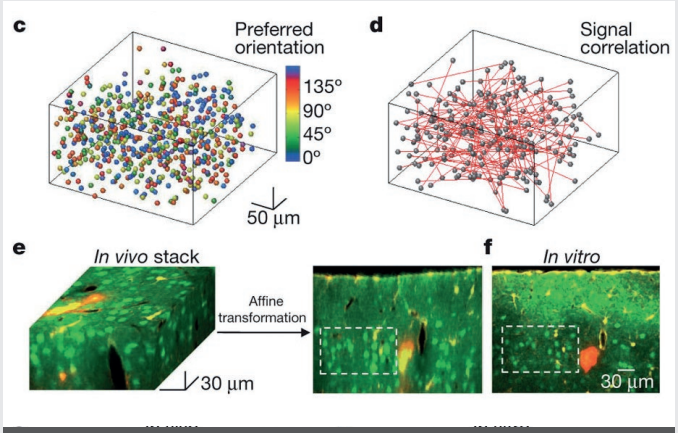
Recently, Professor Silver has extended these findings, by examining the role of short-term activity-dependent changes in synaptic strength in neuronal computation. Synapses between the two cells show 'frequency-dependent short-term depression' – reduced activation on multiple stimulation, because supplies of neurotransmitter are depleted or a depression in the responsiveness of the postsynaptic neuron.

Notably, variation in the degree of short-term depression had a non-linear impact on cell outputs. This too has the effect of enabling inhibition to powerfully control the gain of cells. Moreover, simulations suggested that similar effects were possible within the dendritic trees of more complex neurons.

The results point to the importance of short-term depression and inhibition in this neuronal computation. Since short-term depression and inhibition are widespread phenomena, and the effect seems to be robust to potential disruptors such as noise, it could be a common mechanism for controlling neuronal gain within the nervous system.

Mitchell SJ, Silver RA. Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron.* 2003;38(3):433–45.

Rothman JS, Cathala L, Steuber V, Silver RA. Synaptic depression enables neuronal gain control. *Nature.* 2009;457(7232):1015–8.



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MAKING CONNECTIONS

An innovative combination of *in vitro* and *in vivo* techniques is revealing the brain's microcircuitry.

Study of brain function has typically been either 'top down' – such as functional imaging – or 'bottom up', focused on individual neurons. The middle ground, how collections of neurons operate together, has been more difficult to dissect experimentally. By combining innovative in vivo imaging and *in vitro* recording, **Dr Tom Mrsic-Flogel** and colleagues have taken important steps towards understanding how neural networks are organised in the brain.

The staggering complexity of the brain, with its billions of neurons and trillions of synapses, may seem to confound attempts to discern fundamental principles of its operation. Yet a great deal is now understood about individual neurons and their responses to external stimuli. What is much less clear is how the activities of individual neurons are integrated and operate collectively.

Neuroanatomically, the issue is a challenge because of the sheer number of neurons and the complexity of their connections. Although areas of the brain specialise in particular functions, such as vision or motor control, the role of neighbouring neurons may be quite distinct, while neurons some distant apart may share a common function.

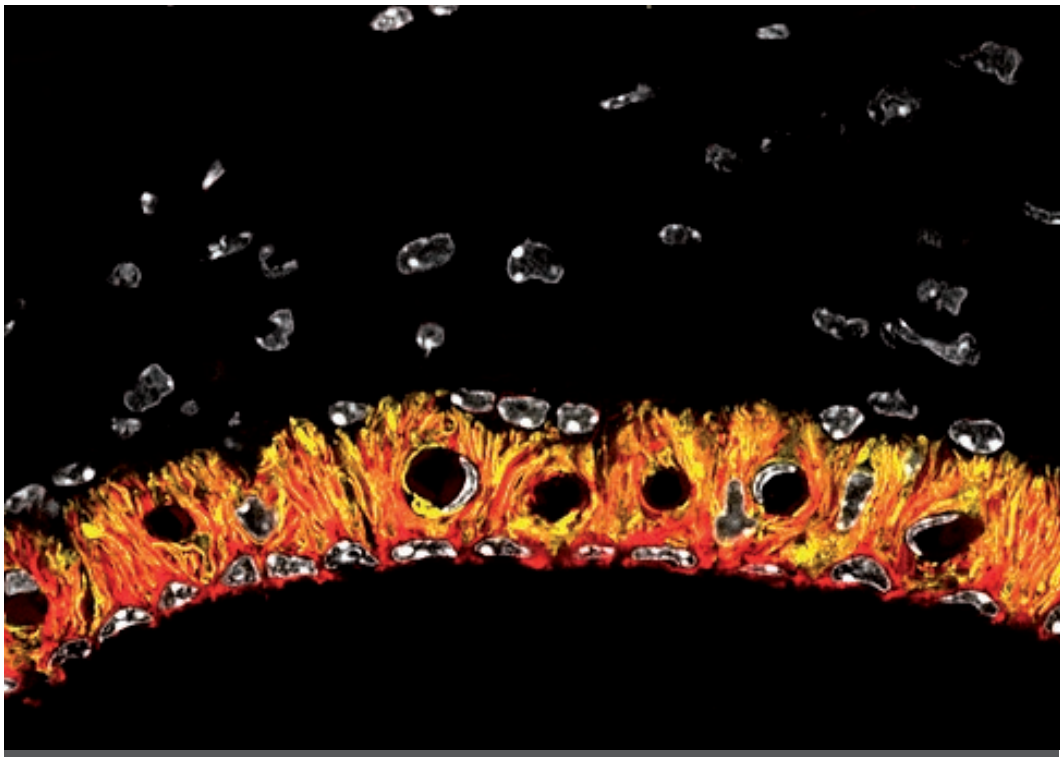
To dissect functional connectivity, Dr Mrsic-Flogel's group is combining two techniques, using an area of the rodent visual system as an experimental model. In vivo, two-photon imaging is being used to detect calcium signals and identify neurons that show similar responses to experimental stimuli (simple artificial visual stimuli or more naturalistic movies). These findings are then superimposed on the results of electrical recordings from neurons, which reveal pathways of signalling between individual neurons.

The total volume of cortex imaged amounted to about xx mm3 (around xx cells), while electrical signals were recorded from more than 100 cells.

The findings suggested that there is a correlation between the shared functions of neurons and connections between them. Interestingly, this relationship was strongest when the naturalistic movies were being viewed. Hence neurons appear to be organised into networks that link cells showing similar responses to external stimuli, collating information before transmitting it to other areas of the brain. Synaptic plasticity may help to strengthen connections between neurons that respond to similar stimuli.

Dr Mrsic-Flogel's work provides one of the first glimpses of how neuronal function is integrated in fine-scale neural circuits. The method offers promise for further dissection of this critical but currently poorly understood aspect of brain architecture.

Ko H *et al.* Functional specificity of local synaptic connections in neocortical networks. *Nature.* 2011;473(7345):87–91.



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16 Mathy A *et al.* Encoding of oscillations by axonal bursts in inferior olive neurons. *Neuron.* 2009;62(3):388–99.

17 Kitamura K, Häusser M. Dendritic calcium signaling triggered by spontaneous and sensory-evoked climbing fiber input to cerebellar Purkinje cells in vivo. *J Neurosci.* 2011;31(30):10847–58.

18 Rancz EA, Häusser M. Dendritic spikes mediate negative synaptic gain control in cerebellar Purkinje cells. *Proc Natl Acad Sci U S A.* 2010;107(51):22284–9.

19 Saviane C, Silver RA. Fast vesicle reloading and a large pool sustain high bandwidth transmission at a central synapse. *Nature.* 2006;439(7079):983–7.

20 Hallermann S et al. Bassoon speeds vesicle reloading at a central excitatory synapse. *Neuron.* 2010;68(4):710–23.

21 Kanichay RT, Silver RA. Synaptic and cellular properties of the feedforward inhibitory circuit within the input layer of the cerebellar cortex. *J Neurosci.* 2008;28(36):8955–67.

22 Vervaeke K *et al.* Rapid desynchronization of an electrically coupled interneuron network with sparse excitatory synaptic input. *Neuron.* 2010;67(3):435–51.

evaluating either the precise timing or the intensity of inputs[15].

Such work is possible because of key technological innovations, particularly the ability to stimulate and record electrical signals from highly localised parts of a neuron. For the former, neurotransmitters are applied in molecular 'cages' which are broken open by targeted pulses of light. Electrical signals can be detected by patch clamping, while calcium signals are visualised using calcium-sensitive dyes and two-photon microscopy. Furthermore, new 'optogenetic' tools (see page xx) are providing additional opportunities to manipulate the behaviour of individual neurons. Experimental results feed into computational models, often developed in collaboration with the Gatsby Computational Neuroscience Unit (see page xx).

The latest techniques visualise neural activity in living brains, now possible while animals engage in specific activities. Professor Häusser is using a 'mouse virtual reality' set up, in which animals are held stationary, so continuous recordings can be made, but navigate virtual reality environments by running on a rollerball.

As well as dendrites, Professor Häusser's group is also looking at how the activities of multiple neurons are coordinated in networks. Working primarily with cerebellar Purkinje cells and inputs from 'climbing fibres', which provide the main sensory input to the cerebellar cortex, such studies are shedding light on how multiple signals are processed through an archetypal neural network[16,17,18].

The function of individual neurons and networks is also the focus of **Professor Angus Silver**. His group combines experimental studies and computational modelling to understand how neurons signal, how they integrate multiple signals to perform computations, and how the behaviour of neural networks is coordinated.

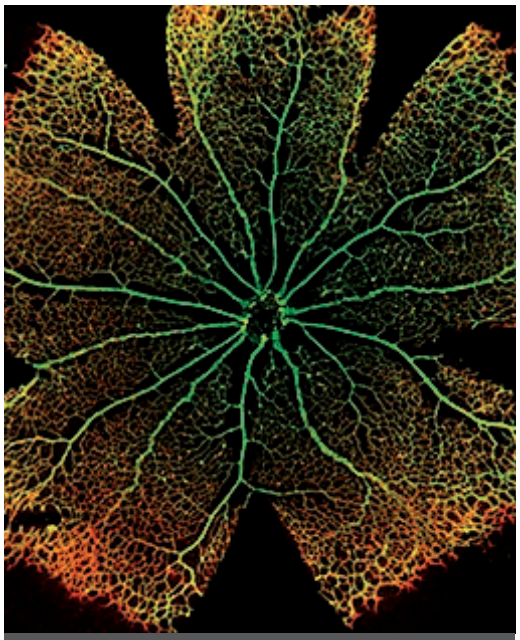
Work at the synapse has revealed that nerve terminals have a larger number of synaptic vesicles than previously thought, around 300, and that they can be mobilised and recycled at great speed[19]. Studies with Dr Stephan Hallemann and colleagues in Leipzig, Germany, and colleagues have implicated the cytoskeletal protein Bassoon in this rapid reloading[20].

The computational capacity of individual neurons is of great interest. Neurons do not simply add together the inputs they receive, but can amplify (or scale down) signal rates – gain control. Professor Silver's group has identified several key features of this critical property (see page xx).

In terms of circuitry, Professor Silver has identified a feedforward inhibitory circuit in the cerebellum, involving cerebellar mossy fibre cells, Golgi cells and granule cells, which is likely to be important in coding the timing of responses[21]. Other studies have explored synchronisation of activity in a network of inhibitory interneurons. Depending on the patterns of stimulation, inputs can either generate or destroy synchronisation. These network effects are mediated by the pacemaker currents in these interneurons and the gap junction-mediated electrical connections between them[22].

Work in Professor Silver's lab draws heavily on advanced imaging techniques. To examine rapid events, where conventional two-photon microscopy is too slow, his group has developed high-speed acousto-optic lens technology, which can follow events at millisecond resolution in tens of neurons in three-dimensional networks. This exciting technology may have wider application, in areas such as high-capacity data storage and 3D lithography.

Computational tools form a further aspect of the group's work. The NeuroMatic suite of applications is widely used to gather and analyse electrophysiological data. The neuroConstruct software application provides a way



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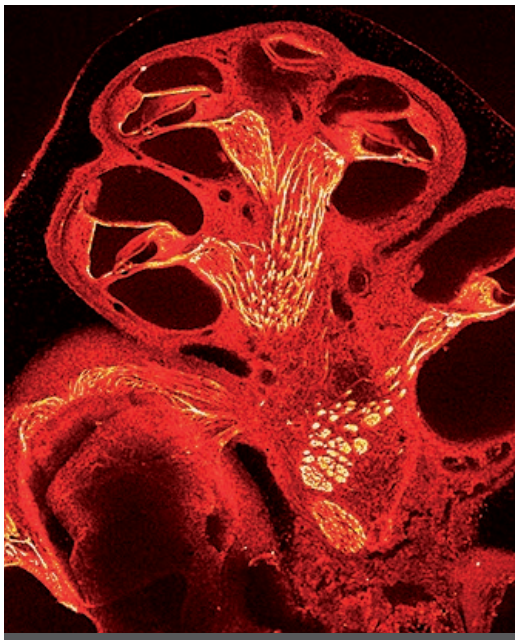

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23 Gleeson P, Steuber V, Silver RA. neuroConstruct: a tool for modeling networks of neurons in 3D space. *Neuron.* 2007;54(2):219–35.

24 Gleeson P *et al.*NeuroML: a language for describing data driven models of neurons and networks with a high degree of biological detail.*PLoSComput Biol.* 2010;6(6):e1000815.

25 Benucci A, Frazor RA, Carandini M. Standing waves and traveling waves distinguish two circuits in visual cortex. *Neuron.* 2007;55(1):103–17.

26 Benucci A, Ringach DL, Carandini M. Coding of stimulus sequences by population responses in visual cortex. *Nature Neurosci.* 2009;12(10):1317–24.

27 Nauhaus I, Busse L, Carandini M, Ringach DL. Stimulus contrast modulates functional connectivity in visual cortex. *Nature Neurosci.* 2009;12(1):70–6.

28 Kanichay RT, Silver RA. Synaptic and cellular properties of the feedforward inhibitory circuit within the input layer of the cerebellar cortex. *J Neurosci.* 2008;28(36):8955–67.

to build and visualise 3D neural network models in exceptional detail[23]. The lab is also leading an international project to develop a standardised XML-based computer language for exchanging models developed using a wide range of tools[24]. NeuroML is in global use, including by the Whole Brain Catalogue at the University of California San Diego.

From eye to brain...

Vision has long been used as a model system for understanding brain function. In particular, much research has flowed from Wiesel and Hubel's ground-breaking discovery that specific neurons are sensitive to the orientation at which simple stimuli are presented.

Professor Matteo Carandini's research has built on these foundations, exploring how populations of cells rather than individual neurons respond to visual stimuli. His ultimate goal is to understand the neural circuitry that integrates the complex visual stimuli received from the real world, and also handles the multiple inputs from other regions of the brain reflecting past experience, attention, current mood and so on.

In addition, Professor Carandini, with Professor Kenneth Harris, also aims to develop mathematical models that capture the properties of the system and enable predictions to be made about its responses to specific stimuli.

Using the cat model, Professor Carandini's group has examined responses of neural populations to a range of more complex visual stimuli. Such work has identified distinctive features of responses to alternating stimuli[25], sequences of stimuli[26] and variations in contrast[27] (see page xx). More recently, he has also begun to use virtual reality environments (see above) to explore navigation of three-dimensional space and responses to finely controlled visual stimuli.

As well as these connections to UCL's extensive neuroscience community, Professor Carandini's interest in vision also benefits his colleagues in the Institute of Ophthalmology. With **Professor Robin Ali**, for example, he has developed systems for assessing neural activity after experimental gene therapy and stem cell therapies in mice, to characterise restoration of vision after treatment.

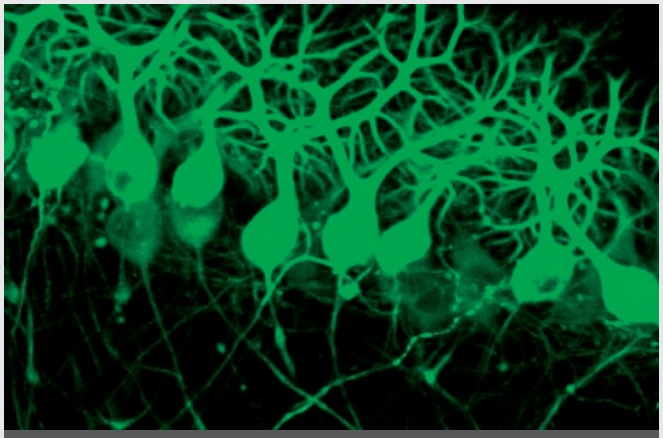
From ear to brain...

The auditory system has been extensively studied, to understand both the neurobiology of hearing and deafness. Historically, however, far more attention has been devoted to the initial transduction of sound signals in the cochlea than to the processing of sound signals in the brain.

Through experimental studies in mice and computational modelling, **Dr Jennifer Linden** is shedding light on complex sound processing in the auditory cortex (see page xx). In related work, her group is also using mouse models to improve understanding of hearing difficulties associated with abnormal sound processing.

One area of interest is specific language impairment, where young people struggle to acquire language skills while developing normally in other ways. In some cases, this may reflect an impaired ability to distinguish similar, rapidly occurring sounds. Dr Linden has been working on a strain of mice that show analogous hearing abnormalities, detected experimentally in their failure to spot gaps in otherwise continuous sounds. Interestingly, these deficits seem to originate in the auditory brain rather than the ear – neurons in parts of the auditory thalamus, a gateway for auditory information entering the cortex, seem to respond abnormally to rapidly changing sounds.

Dr Linden also has a growing interest in mouse models of human genetic conditions, including psychiatric disorders. With colleagues in Manchester and King's College London, she helped to identify structural abnormalities in the middle ear as the cause of hearing problems in a mouse model of Treacher–Collins syndrome[28]. She is now working on a model of Di George syndrome, an inherited condition associated with a greatly increased risk of schizophrenia as well as cardiac, facial and other



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NOISY NEIGHBOURS

How does the brain deal with the apparently random fluctuations of background 'noise'?

The brain is constantly carrying out almost impossibly complex computations. Like all complex dynamic systems, it has to contend with 'noise' – apparently random events that could potentially interfere with the fidelity of signalling. By combining theoretical modelling and experimental manipulation, **Professor Peter Latham** and **Professor Michael Häusser** have discovered possible strategies that the brain may use to deal with such fluctuations.

Noise is apparent in neural systems as variability in the response to identical stimuli, which could reflect two different effects. It could represent genuinely random noise, linked to chance molecular events (such as ion channel opening); in this case, variation carries no information. Or it could reflect different inputs from other neural systems (such as those signalling internal states); in this case, variation does carry meaning.

Professor Latham and Professor Häusser focused on the former, purely intrinsic noise. They examined the responses of a neural system to repeated identical stimuli, then looked to see what happened when a single additional spike was introduced. Does this single extra spike change the signals propagated through the network?

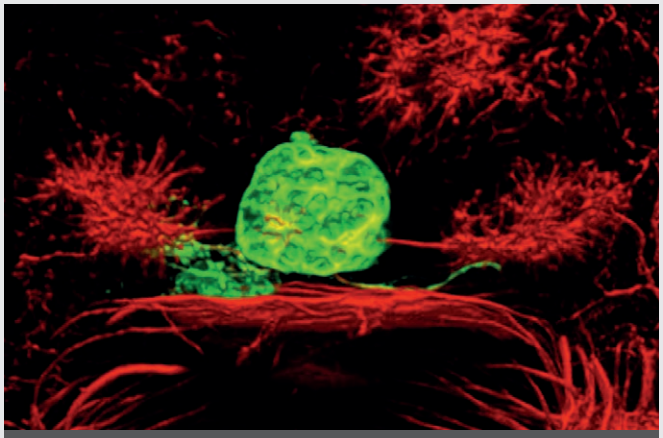
The extra number of spikes generated depends on the average number of connections made by a neuron (around 1500) and the average probability that an additional spike will be generated. The latter, determined experimentally, turned out to be 0.004. Modelling using these numbers suggested that one additional spike would trigger an average of 28 new spikes – implying that a small initial perturbation could rapidly escalate into a major change in neural activity. After just five steps, there would be around 17 million extra spikes in the system – a graphic example of the 'butterfly's wing' effect in the brain.

In fact, chaos is not the result in practice, partly because extra spikes are largely cancelled out by 'missed' spikes, eventually generating a steady state. Even so, modelling suggested that a rogue spike should have a small effect on local signalling, a prediction confirmed by experimental recording.

A key question is the extent to which the eventual steady state differs when a new spike is added. Theoretical analysis suggested that these fluctuations are proportional to the number of additional spikes generated – previously calculated at 28. Hence the amount of intrinsic noise in the system is large.

In terms of information coding, the results argue against mechanisms in which the precise timing of signals is important. Rather, to deal with noise, it is likely that information is coded by average firing rate in large numbers of neurons.

London M, Roth A, Beeren L, Häusser M, Latham PE. Sensitivity to perturbations in vivo implies high noise and suggests rate coding in cortex. *Nature*. 2010;466(7302):123–7.



Weibel–Palade bodies (blue).

I-SPY FRY EYE

Zebrafish use their eyes differently: an understanding of the genetic and neural basis of this peculiarity could help explain the widespread phenomenon of brain asymmetry.

When a zebrafish first sees a novel object, it will tend to appraise it with its right eye. As it becomes more familiar, it will be switch to its left. This odd behaviour reflects a common characteristic of vertebrate brains, lateralisation of function. In humans, for example, language is predominantly a left-hemisphere function. Over the past decade, **Professor Steve Wilson** and colleagues have gradually been unravelling the complex genetic, cellular and neural pathways that underlie the development of asymmetry in the zebrafish brain.

The fish brain is well-suited to such studies as it possesses a highly distinctive set of asymmetric brain structures. Most notably, part of its light-sensitive pineal gland, the parapineal, is always found on the left of the midline, while two nearby paired structures, known as habenulae, which relay signals from the front to the back of the brain, show striking asymmetries in morphology.

Of these structures, the parapineal seem to play the key role. During development, parapineal cells are initially found either side of the midline, but coalesce and migrate only on the left side. A decade ago, Professor Wilson showed that the Nodal signalling was critical to this process. Without it, embryos were still asymmetric, but the paripineal formed randomly on the left or right side.

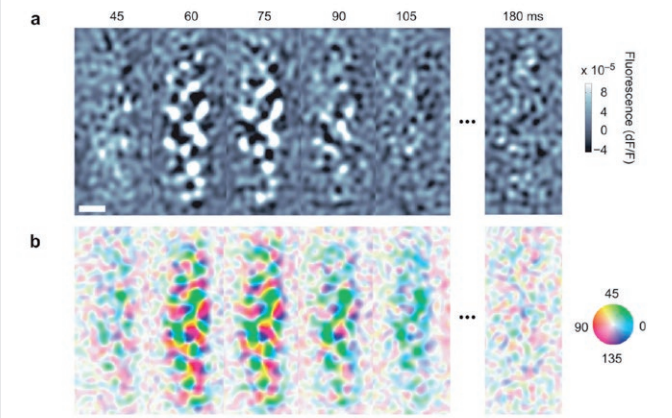
Work since has generated a more nuanced picture of a highly complex process. Recent work has identified FGF8 as a factor that can break the initial symmetry: without it, parapineal cells remain central. Once FGF8 has broken symmetry, Nodal is responsible for the leftwards bias in parapineal development. This still pushes back the question of how Nodal comes to be active asymmetrically. Indications are that a common signalling pathway, the Wnt pathway, is involved, relieving inhibition on Nodal on the left through the activity of an additional factor, Southpaw.

While many gaps remain to be filled, the work connects together gene activity, cell behaviour, developmental processes, neural connectivity and even behaviour. Remarkably, one strain of mutant fish, *fsi*, shows reversed brain asymmetry, and switch their eye use when viewing novel and familiar objects. Oddly, they also appear to be bolder, being less averse to novel stimuli. Development of additional behavioural assays will enable Professor Wilson to gain a better view of how alterations in symmetry affect what fish do.

Concha ML, Burdine RD, Russell C, Schier AF, Wilson SW. A nodal signaling pathway regulates the laterality of neuroanatomical asymmetries in the zebrafish forebrain. *Neuron*. 2000;28(2):399–409.

Regan JC, Concha ML, Roussigne M, Russell C, Wilson SW. An Fgf8-dependent bistable cell migratory event establishes CNS asymmetry. *Neuron*. 2009;61(1):27–34.

Carl M TD *et al.* Wnt/Axin1/beta-catenin signaling regulates asymmetric nodal activation, elaboration, and concordance of CNS asymmetries. *Neuron*. 2007;55(3):393–405



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GRATE EXPECTATIONS

How do populations of neurons deal with multiple stimuli arriving at the same time?

Much is now known about how individual neurons in the brain respond to specific experimental stimuli. In the case of the visual system, these stimuli are typically gratings of particular orientation. The real world is more complex, of course, requiring responses to multiple stimuli and coordinated activity in populations of neurons. By analysing responses to two gratings in different orientations, generating a plaid pattern, **Professor Matteo Carandini** and colleagues have uncovered some intriguing features of how populations of cells in the visual cortex respond to mixed stimuli.

Using a multi-electrode detection system, Professor Carandini is able to record activity across populations of hundreds of neurons in response to specific visual stimuli. A simple suggestion might be that the response to two superimposed gratings would be the sum of individual responses. And, indeed, this was largely true.

However, when the contrasts of the gratings differed, something interesting happened: the grating with the higher contrast tended to dominate the responses. This tendency was strongest when overall contrast was high. In this case the cortex appeared to operate a 'winner takes all' competition. Even though it was perfectly able to drive the cortex when presented alone, the grating of lower contrast effectively became invisible when presented together with the grating of higher contrast.

Interestingly, these patterns of responses could be modelled by a surprisingly simple mathematical description, derived from a model originally developed for individual neurons. Furthermore, the model also correctly predicted responses seen in the visual cortex of human participants presented with similar images.

The results also tally with a well-known perceptual phenomenon, 'masking'. It has been known since the 1990s that adding a mask visual stimulus on top of a test visual stimulus can render the latter invisible, and that the interaction between the stimuli could be described by simple arithmetical division. The latest results provide a physiological basis for these observations, in terms of the activity of populations of neurons.

More generally, contrast provides a simple but powerful mechanism for studying the responses of neurons to variations in stimuli. Professor Carandini's group is now increasingly turning to the mouse to explore both neural and behavioural responses. Such work has identified subtle additional factors affecting the animal's behaviour, including size of likely reward and recent successes and failures – emphasising the power of cross-talk from other neural systems to affect responses in the visual cortex.

Busse L, Wade AR, Carandini M. Representation of concurrent stimuli by population activity in visual cortex. *Neuron.* 2009;64(6):931–42.

Busse L *et al.* The detection of visual contrast in the behaving mouse. *J Neurosci.* 2011;31(31):11351–61.

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THE NEURONAL DECODER

An individual dendrite can discriminate the order in which it receives activation signals.

Brain function depends on the ability to detect and discriminate between a series of input signals. Neural systems need to know that one stimulus was received before another, as this may carry important information. It has been conjectured that networks of neurons would be able to capture information on the timing of stimulation, but **Professor Michael Häusser** and colleagues have shown that the timing of signals can, remarkably, be detected by a single dendrite.

Assessing the responses of individual dendrites to individual stimuli in a series is technically challenging, requiring extreme sensitivity both spatially (sub-micrometre) and temporally (sub-millisecond). To solve this problem, Professor Häusser used short flashes of light to release tiny amounts of neurotransmitter from molecular 'cages' at highly localised points on a dendrite, and recorded the resulting currents and calcium signals with exquisite spatial sensitivity.

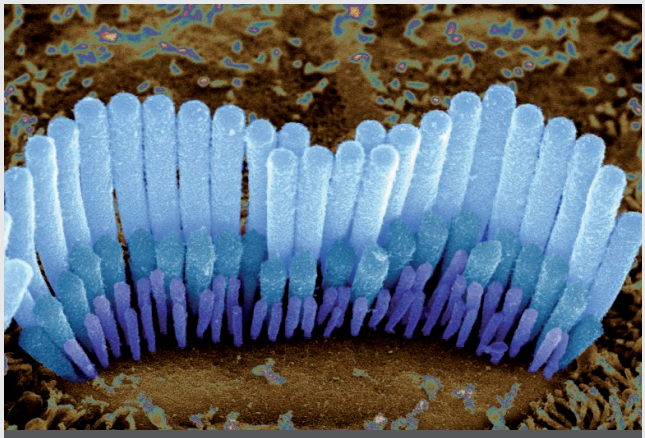
Through this approach, a series of stimuli were delivered at various points along a dendrite, either starting at the end and moving inwards, or starting close to the axon and moving outwards. Strikingly, although the dendrite received the same combination of stimuli, the order in which they were given made a big difference to the response of the axon. The likelihood that an action potential would be generated was significantly higher moving inwards than in the outwards direction.

This selectivity was dependent on NMDA receptors. In the presence of an NMDA receptor inhibitor, the dendrite's discriminatory abilities were lost. These findings enabled Professor Häusser and colleagues to develop a relatively simple model for the dendrite's behavior, based on an impedance gradient along the dendrite – a common characteristic of dendrites – and the NMDA receptor's sensitivity to resulting voltage differences.

Furthermore, varying the order in which stimuli were applied to different dendrites also generated differential responses in an axon. This effect was also captured in the model.

Detection of the order and timing of inputs has tended to be considered a property of networks of cells. This work suggests that it can actually be carried out by individual dendrites. Neural processing is characterised by waves of neural activity through networks, in which both the position and timing of activation conveys important information. It seems that even a structure as deceptively simple as a dendrite can detect the spatial and temporal characteristics of these signals.

Branco T, Clark BA, Häusser M. Dendritic discrimination of temporal input sequences in cortical neurons. *Science.* 2010;329(5999):1671–5



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FROM EAR TO HEAR

How does the brain convert a stream of impulses from the ear into a coherent auditory experience?

The ear contains remarkable machinery for converting sounds into electrical impulses which are relayed to the brain. Just as remarkable, and far less well understood, is how the brain processes and reconstructs these signals into the richly detailed soundscapes we experience. By combining experimental work on mice with computational modelling, **Dr Jennifer Linden** is generating new insights into higher-order processing of complex sounds in the brain.

Higher-order processing of sounds is thought to take place in a particular region of the temporal lobe, the auditory cortex. Yet surprisingly little is understood about the responses of neurons in this region and how these responses are integrated both with each other and with internal inputs – such as memory, physiological states or emotions, which can significantly affect neural processing of raw sound information.

In common with other areas of the cortex, the auditory cortex consists of several layers of cells with different morphologies and connectivity. It is generally assumed that these layers plays different roles in cortical processing, which should be apparent in characteristic responses to input stimuli. In practice, this has been surprisingly difficult to confirm experimentally.

Recently, however, Dr Linden has shown that cells in different layers of the mouse cortex vary in their responses to sound stimuli that are modulated at the slow rates typical of speech and music. This suggests that cortical circuitry may extract information about slow temporal modulations of auditory stimuli. The findings also suggest constraints on the possible patterns of connectivity between cortical layers.

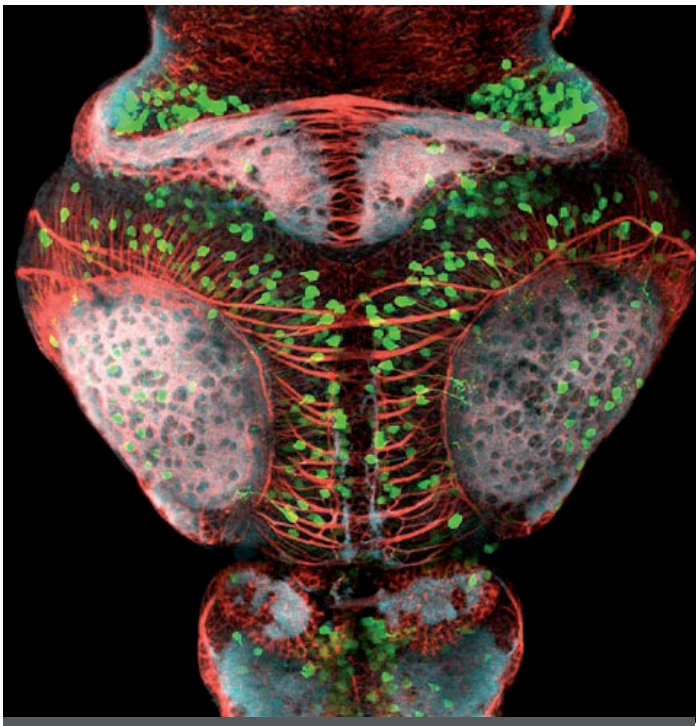
Complementing such experimental studies, Dr Linden also works with Dr Maneesh Sahani of the Gatsby Computational Neuroscience Unit on computational models of auditory cortical responses. The ultimate aim is to develop models that can reliably explain the responses of neurons to distinct aspects of complex auditory inputs, like the barrage of everyday sounds.

Much past work has been based on 'spectrotemporal receptive fields', which attempt to correlate the spectrogram of sounds to the responses they generate. However, Dr Linden and Dr Sahani have documented significant flaws in this model, as higher-order patterns in complex sound stimuli can generate misleading results. They have developed new models that more accurately predict neuronal responses to sound stimuli.

Christianson GB, Sahani M, Linden JF. Depth-dependent temporal response properties in core auditory cortex. *J Neurosci.* 2011;31(36): 12837–48.

Christianson GB, Sahani M, Linden JF. The consequences of response nonlinearities for interpretation of spectrotemporal receptive fields. *J Neurosci.* 2008;28(2):446–55.

Ahrens MB, Linden JF, Sahani M. Nonlinearities and contextual influences in auditory cortical responses modeled with multilinear spectrotemporal methods. *J Neurosci.* 2008;28(8):1929–42.



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abnormalities. Di George patients show a range of sensory abnormalities, and Dr Linden is now assessing auditory function in the mouse model to investigate the origins of these abnormalities. Ultimately, this may provide insight into the causes of perceptual and psychiatric problems in patients.

Building sites

Professor Steve Wilson runs one of Europe's largest zebrafish facilities. Banks of aquaria house thousands of the animals, popular with home fish keepers as well as developmental biologists. Zebrafish are an increasingly popular model organism, combining the advantages of being a vertebrate (like a mouse) with being easy to keep and breed (like a fly). Its embryo is transparent, making cellular studies easier.

Professor Wilson is interested in several key areas of neurobiology, particularly eye formation (see companion volume on Basic Life Sciences), the development of brain asymmetries (see page xx) and more recently the cellular environment in which stem cells develop[29]. However, as the house zebrafish aficionado, he also collaborates with numerous groups within UCL and internationally that are interested in using zebrafish to explore the function of their favourite genes in a vertebrate system. Professor Wilson has thus been involved in studies of multiple areas of zebrafish biology, from muscle function to brain development.

One notable feature of the lab's work is the spectacular imagery it generates. It is a regular winner in competitions such as the Wellcome Trust's Biomedical Image Awards, including two in 2011.

29 Cerveny KL *et al.* The zebrafish flotte lotte mutant reveals that the local retinal environment promotes the differentiation of proliferating precursors emerging from their stem cell niche. *Development.* 2010;137(13):2107-15.

There is much to be gained from fruitful dialogue between vision and hearing.

MAKING SENSE

Vision and hearing are the most critical of our senses. Loss of either can be highly disabling and a source of considerable distress. Much has been learned about the basic neuroscience of both vision and hearing, and this greater understanding offers the long-term prospect of improved treatments and ways to slow or prevent loss of these important sensory abilities.

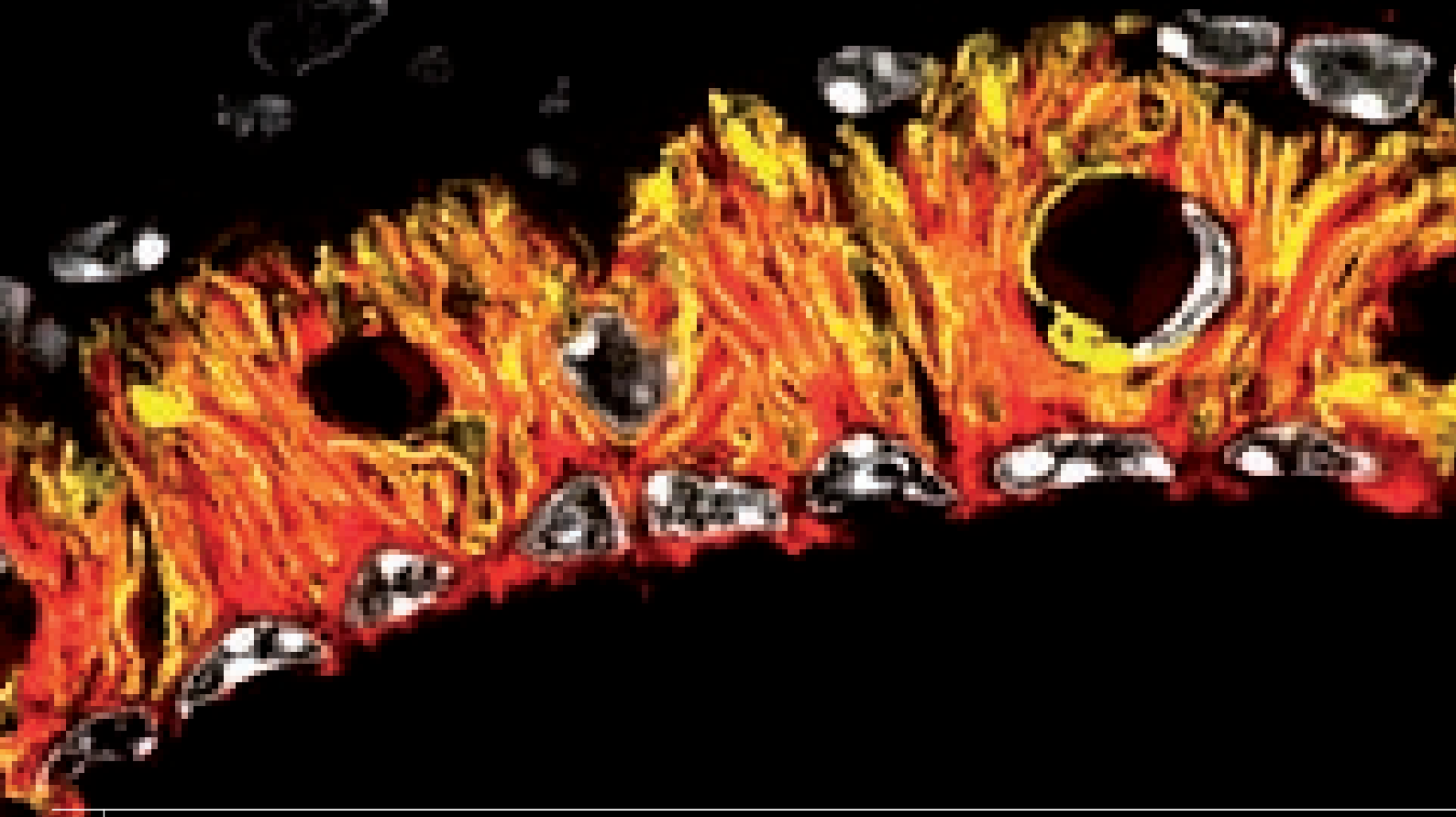
Vision and hearing show fundamental similarities. Both are based on the detection of external signals – light by the retina in the eye and sound waves in the inner ear. Neuronal signals are then transmitted to specialised regions of the brain for processing and analysis, generating visual and auditory perceptions of the outside world.

In both cases, perhaps most is understood about how inputs are detected. A great deal is now known about the retina and sight loss caused by abnormalities or degeneration in retinal cells. Similarly, much is now understood about how sound waves are converted into electrical impulses in the intricately constructed cochlea and how loss of hair cells leads to hearing loss.

Higher-order processing of visual and auditory information, by contrast, is less well understood. Even so, brain areas and networks associated with these senses have been well described and the neural mechanisms involved in sensory perception are gradually being unravelled.

Research in the UCL Institute of Ophthalmology and the UCL Ear Institute covers both basic understanding and practical intervention, and both signal transduction and higher-order processing. Ultimately the insights gained in one system may have relevance to the other. For example, the therapeutic advances in gene therapy and stem cell therapy, particularly advanced for eye disease, may yet have application in hearing disorders.

In partnership with Moorfields Eye Hospital, the UCL Institute of Ophthalmology has developed a strong focus in translational research. Professor Robin Ali and Professor James Bainbridge have developed a world-leading programme in gene therapy, establishing the world's first clinical trial of gene therapy for inherited blindness . It has also pioneered the use of embryonic stem cells to treat age-related macular degeneration, under the umbrella of the London Project to Cure Blindness (see companion volume on Translation and Experimental Medicine). The cornerstone of this work is provided by the National Institute for Health Research (NIHR) Biomedical Research Centre uniting hospital and research institute.



A further promising route to new therapies, being explored by **Professor Robin Ali** and **Dr Rachael Pearson**, with **Dr Jane Sowden** in the Institute of Child Health, is transplantation of photoreceptor precursor cells into the retina . Following encouraging work in animal models – most recently showing that, in mice, transplanted cells can integrate and restore visual function – efforts are underway to transplant photoreceptor precursors that have been derived from embryonic stem cells.

Research also covers the neuroscience of vision. **Professor Matteo Carandini**, for example, is examining how the brain deals with multiple visual stimuli arriving at the same time (see page xx). **Professor Steven Dakin** focuses on various aspects of visual perception, such as the special features of faces that underlie face recognition and the mechanisms used by the brain to estimate numbers and densities of objects . His work draws on visual illusions, an area in which **Dr Beau Lotto** combines research and extensive public outreach (alongside research into the vision of bees).

Similarly, much of the research in the UCL Ear Institute is of translational orientation. In particular, a major focus is on improving the function of assistive devices such as cochlear implants.

As in the eye, much research focuses on the loss of cells critical to sensory transduction, in this case the hair cells of the cochlea. A major cause of hearing loss, researchers such as **Dr Jonathan Gale** are hoping to develop methods to protect and maintain hair cells or to transplant new cells to replace those lost to degeneration. Underpinning such efforts is wide-ranging work to understand the mechanisms of degeneration, providing targets for intervention.

One of the most common hearing abnormalities, tinnitus, is surprisingly poorly understood. It is often assumed to result from cochlear damage but patients often show perfectly responses to hearing stimuli. **Dr Roland Schaette** has uncovered evidence that primary auditory signals in such patients are relatively small but then undergo a compensatory amplification in the midbrain – with the unfortunate effect of amplifying 'noise' in the system .

In terms of central auditory processing, **Dr Jennifer Linden** is studying how the organisation of the auditory cortex might be linked to its processing of complex sounds (see page xx). Similarly, **Professor David McAlpine** has studied how the brain locates the three-dimensional source of sound in the environment – an ability linked to the differing time taken for sound stimuli to reach the ears and thence the auditory cortex . His group is also interested in how the brain deals with different sound levels and how the context of a sound affects its neural representation.

1 Bainbridge JW *et al*. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med*. 2008;358(21):2231–9.

2 MacLaren RE *et al*. Retinal repair by transplantation of photoreceptor precursors. *Nature*. 2006;444(7116):203–7.

3 Pearson RA *et al*. Restoration of vision after transplantation of photoreceptors. *Nature*. 2012;485(7396):99–103.

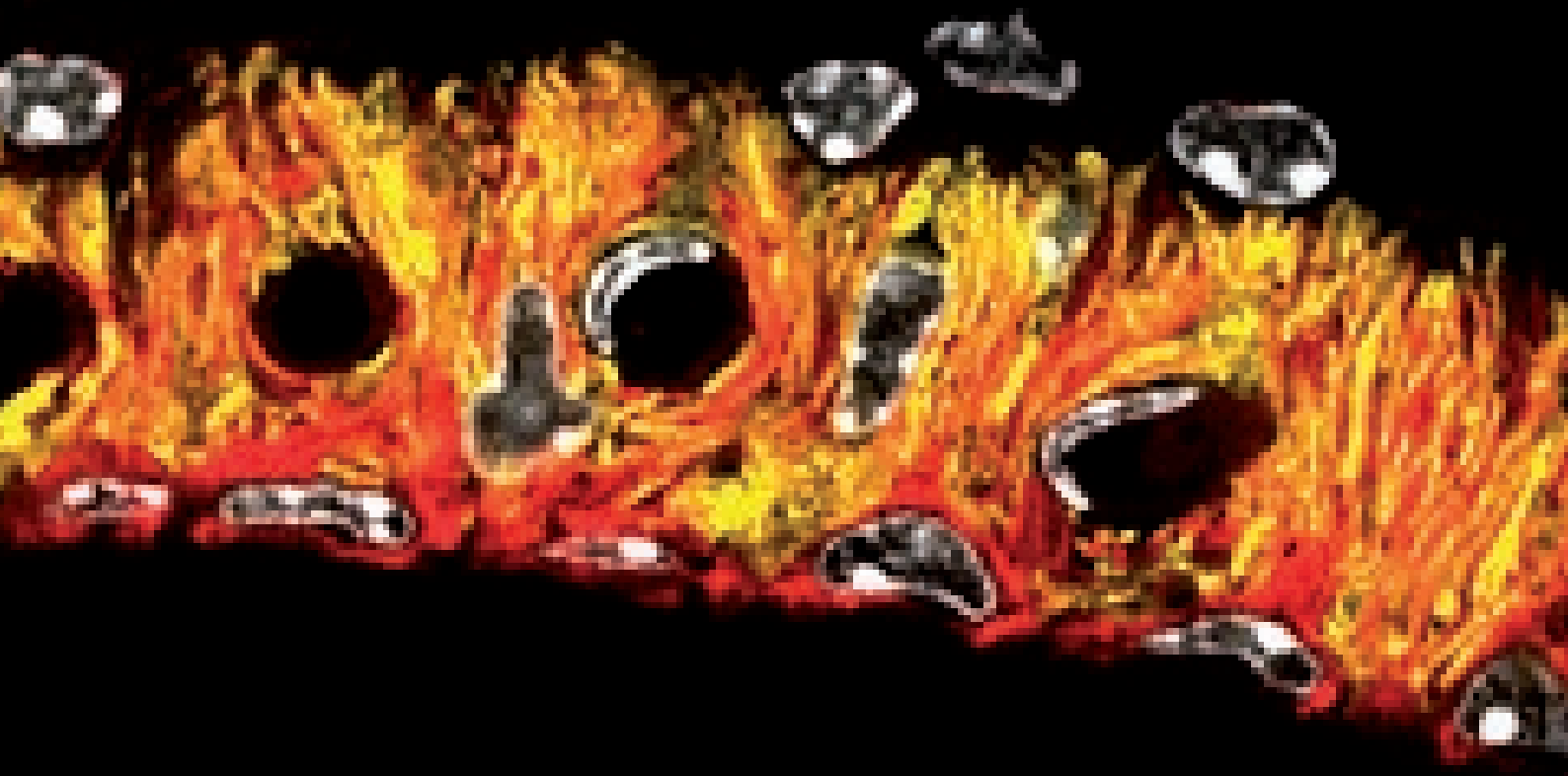
4 Dakin SC *et al*. A common visual metric for approximate number and density. *Proc Natl Acad Sci USA*. 2011;108(49):19552–7.

5 www.lottolab.org

6 Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *J Neurosci*. 2011;31(38):13452–7.

7 Harper NS, McAlpine D. Optimal neural population coding of an auditory spatial cue. *Nature*. 2004;430(7000):682–6.

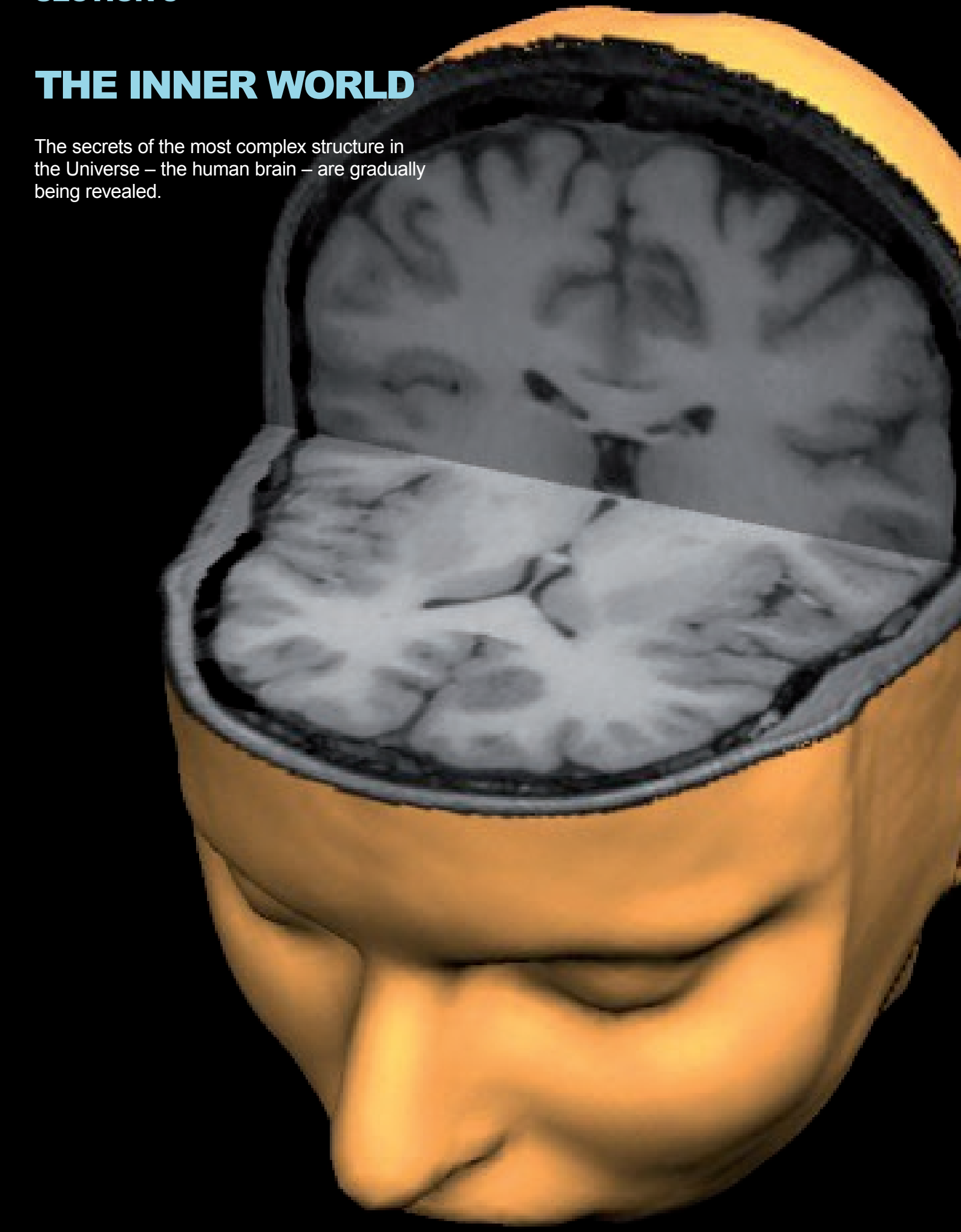
8 Dean I, Harper NS, McAlpine D. Neural population coding of sound level adapts to stimulus statistics. *Nature Neurosci*. 2005;8(12):1684–9.



SECTION 3

THE INNER WORLD

The secrets of the most complex structure in the Universe – the human brain – are gradually being revealed.



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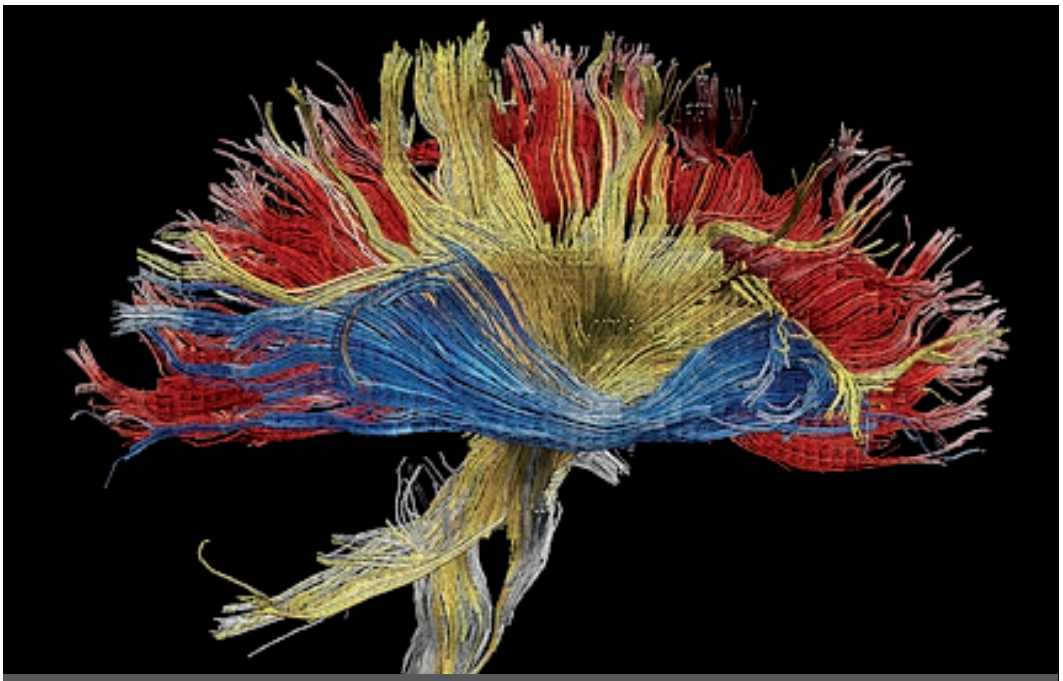

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The brain fascinates and beguiles. It generates an inner representation of the outside world and achieves astonishing feats of mental time travel. Our thoughts, our feelings, our learning; language, love and lust: all originate in 1.5 kg of wobbly jelly.

Recently, non-invasive imaging has thrown open a new window on the brain. Brain structure has been revealed by magnetic resonance imaging and neural connections by 'tractography' such as diffusion tensor imaging. Brain function has been visualised by functional MRI and magneto-encephalography (MEG).

Thanks to better hardware, software and experimental design, enormous advances have been made in understanding brain function. Equally important are the computational models that place experimental findings in a theoretical framework. Together, they are providing insight into how the brain accomplishes its remarkable feats.

Enormous advances have been made in understanding brain function. Equally important are the computational models that place experimental findings in a theoretical framework.

From description to function

The tools of brain imaging continue to advance, yet **Professor Ray Dolan** argues that technology is not the limiting factor. The key, he suggests, is to think carefully about what questions to ask.

Professor Dolan's colleague **Professor Karl Friston** and others have developed a widely used tool for managing imaging data, statistical parametric modelling (SPM). A powerful approach embedded within SPM is 'dynamic causal modelling'. While functional imaging provides a snapshot of brain activity, dynamic causal modelling infers the order and dependencies of activations – providing insight into mechanistic chains of events. Using this, and other approaches, Professor Dolan and colleagues are addressing a wide range of questions. An overarching aim is to understand the neurobiological basis of human behaviour – at scales ranging from neural pathways to the action of individual neurotransmitters.

Computational modelling is an integral part of this approach, providing a theoretical framework for linking behavioural observation to mechanistic understanding. A core focus has been the neurobiological basis of decision-making. An idealised decision-maker would maximise benefits ('rewards') and minimise harms ('punishment'). Notably, in experimental settings (as in real life), people show marked deviation from perfect decision-making. Professor Dolan is attempting to understand the core mechanisms of decision-making and the impact of factors ranging from nutritional status[30] to the way

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DECIDING FOR THE BETTER

Separate but interdependent brain systems may be involved in decision making.

One way decision-making can be conceptualised is in terms of 'habitual' mechanisms – repeating actions that have been beneficial in the past – versus more forward-looking processes: evaluating future possibilities and selecting the most profitable option. The recent work of **Professor Ray Dolan** and colleagues suggests that such mechanisms do indeed operate in the brain, but not in isolation.

Decision-making can be viewed as a mechanism to maximise positives ('rewards') and minimise negatives ('punishments'). For the brain to be able to choose actions optimally, it must be able to assess rewards – that is, assign a 'value' to them. The brain is also adept at predicting likely rewards, and actions delivering greater-than-anticipated rewards tend to be repeated.

Hence 'habits' are one important driver of decision-making. But the brain is also capable of 'goal-directed' actions, explicitly modelling future action–outcome contingencies so as to identify the best option. Distinct areas of the brain associated with these processes have been identified. Yet their relationship to one another has not been clear.

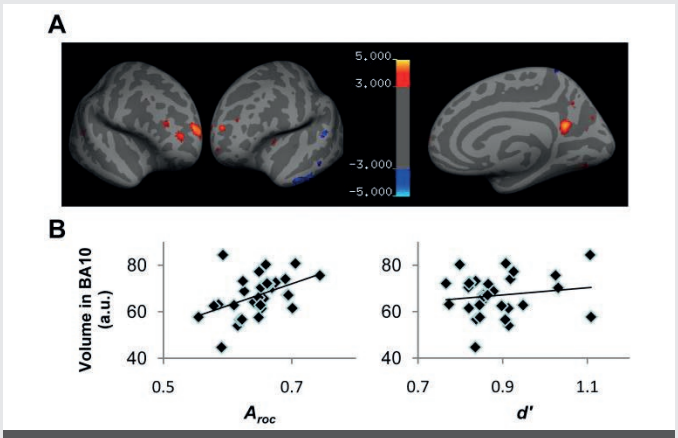
With Professor Nathanial Daw in New York and Professor Peter Dayan from the Gatsby Computational Neuroscience Unit, Professor Dolan developed a series of tasks to explore the contributions of these different systems to decision-making. Contrary to expectations, functional imaging suggested that decision-making typically depended not on either one system or the other on its own but on a sophisticated combination of both.

By refining the computational framework underpinning this analysis, Professor Dolan, Professor Dayan and Dr Klaus Wunderlich were able to distinguish precise areas associated with 'on the fly' modelling of future possibilities and with learning more associated with extensive training. Notably, while value calculations in these systems localised to distinct regions of the brain, signals from these areas converge on a region of prefrontal cortex, which processes the value assessments generated by the two decision-making systems and enacts a decision based on the more valuable option.

The studies suggest there are indeed separate value-based decision-making systems in the brain, but their activities are integrated within the prefrontal cortex (more specifically, the ventromedial prefrontal cortex. It is likely that real-life decision-making similarly involves weighing up the input from these different systems to guide choice of action. A better understanding how habitual choices are encoded, and overcome, could be of great significance to the many habit-based behaviours, from diet to addiction, that are not in our long-term interests.

Daw ND *et al.* Model-based influences on humans' choices and striatal prediction errors. *Neuron.* 2011;69(6):1204–15.

Wunderlich K, Dayan P, Dolan RJ. Mapping value based planning and extensively trained choice in the human brain. *Nature Neurosci.* 2012;15(5):786–91.



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I'M SURE I'M RIGHT...

Structural imaging has revealed regions of the brain associated with effective introspection about how well we make decisions.

Most decision making involves some level of uncertainty. We are often called upon to make rapid decisions in the face of incomplete information, and afterwards may have varying degrees of certainty about whether we made the right decision. A brain imaging study carried out by **Professor Geraint Rees** and colleagues has identified regions of the brain associated with accurate judgment of one's abilities – a neural fingerprint of introspective skills.

To assess introspective skills, participants undertook a tricky visual task. As well as monitoring how accurate people were in the task, Professor Rees and colleagues also asked them how confident they were in their answers. These do not necessarily correspond – someone may feel they are doing well when they are actually doing badly (or vice versa). For someone with good introspective abilities, however, confidence levels should correlate with actual performance. The difficulty of the task was adjusted so every participant got the same proportion of answers correct. But different participants showed very different abilities to introspect effectively about their performance.

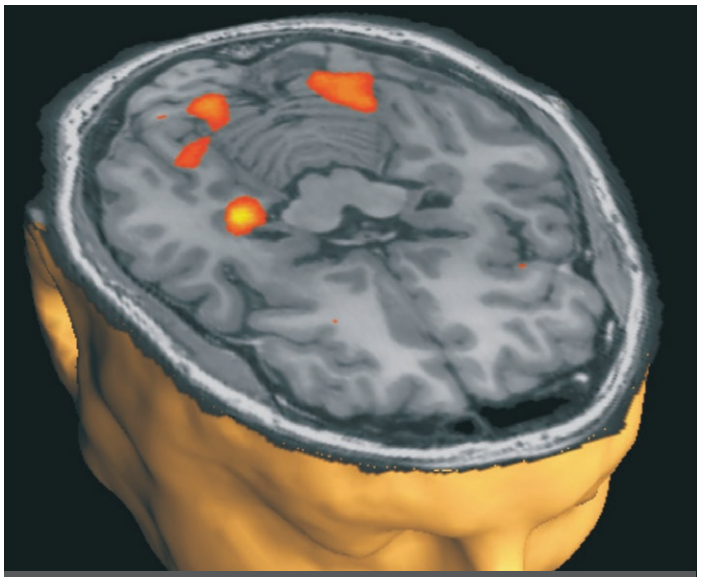
Furthermore, MRI scans revealed a part of the brain – regions of the prefrontal cortex – where the volume of gray matter correlated with accurate self-appraisal. Importantly, the volume of these regions did not correlate with actual performance or with confidence levels.

In follow-up studies using different types of perceptual test, the same regions were again linked to more accurate introspection. Hence, they are likely to be involved in generic introspection skills, not those specific to visual tasks.

Interestingly, the area of the prefrontal cortex identified has undergone extensive development during human evolution, suggesting that enhanced introspective or other 'meta-cognitive' skills have proven evolutionarily advantageous. The findings also raise the intriguing possibility that, given the plasticity of neural systems, it may be possible to 'train' people and enhance their introspective abilities.

Fleming SM, Weil RS, Nagy Z, Dolan RJ, Rees G. Relating introspective accuracy to individual differences in brain structure. *Science.* 2010;329(5998):1541–3.

Song C, Kanai R, Fleming SM, Weil RS, Schwarzkopf DS, Rees G. Relating inter-individual differences in metacognitive performance on different perceptual tasks. *Conscious Cogn.* 2011;20(4):1787–92.



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information is presented (the 'framing' effect)[31], as well as biases such as over-optimism[32] and a tendency to stick with the status quo when facing difficult choices[33].

The brain has a remarkable capacity to predict likely gains, and can compare these predictions with the rewards actually obtained. Registering this discrepancy underpins many forms of learning, by promoting actions that have proven especially fruitful in the past. A collection of deep brain nuclei collectively known as the striatum appears critical for this capacity[34]. The brain can therefore calculate the 'value' of possible actions, a computation that is then used to guide decision-making. Recent studies suggest there may be multiple neural mechanisms calculating value, which under certain circumstance may come into conflict (see page xx).

As well as choosing an option, the brain has to consider how energetically to pursue this option. A combination of modelling and experimental work, in collaboration with **Dr Marc Guitart-Masip** and **Professor Peter Dayan**, suggests that interplay between dopamine and serotonin systems could shape optimal choice and the 'vigour' with which they are pursued[35]. Alongside imaging studies, such work illustrates how decision-making can be dissected in terms of neural pathways and neurotransmitter action. Similarly, new computational approaches developed by Professor Friston, Professor Dolan and **Dr Rosalyn Moran** have been used to infer molecular events occurring at the synapse from relatively coarse imaging data – a hint of how imaging data might be exploited in the future (see page xx).

One good reason to characterise decision-making systems is the impact that 'poor' choices can have on individuals and those around them. Addiction, gambling, violence and other behaviours can be individually and socially devastating. Moreover, skewed decision-making characterises numerous psychiatric conditions of enormous individual and economic significance, from depression to schizophrenia. Currently, the neurobiology of these conditions is not well understood. In practice, psychiatric conditions are diagnosed purely on the basis of symptoms, with little consideration of underlying mechanistic causes. Hence classical diagnostic criteria systems are often problematic and endlessly debated.

Professor Dolan has therefore launched a radical crusade to provide a neurobiological understanding of mental and behavioural traits. With UCL's **Professor Peter Fonagy** and colleagues in Cambridge, he has been awarded £5.4 million funding from the Wellcome Trust to provide a baseline assessment of a cohort of young people who will be followed for five years and profiled for a wide range of behavioural and neurobiological traits.

Crucially, the study will not be constrained by existing diagnostic criteria, generating an entirely unbiased description of traits across a population. Equally importantly, the assessments are embedded in a coherent computational framework, providing powerful analytical tools for interpreting data. If successful, this study could be a first step towards a categorisation of psychiatric disorders based on underlying neurobiological mechanisms – a potentially far-reaching shift.

The focus on behaviour, neurobiological systems and computational models will synergise with the work of the Sainsbury Wellcome Centre (see page xx). In computational neuroscience, Professor Dolan has also established close links with the German Max Planck Society, including a joint Summer School in Computational Psychiatry and Aging and the possibility of a more extensive joint initiative.

Perception

Great progress has been made in understanding the neuroanatomical basis of perceptual and cognitive phenomena. Generally this has been based on pooling of data from groups of subjects. **Professor Geraint Rees**, however, is interested in a different question – how do these neural substrates vary between individuals?

One notable example had an unusual origin – the actor Colin Firth's guest editorship of BBC Radio 4's influential news programme *Today*. With the BBC's science and technology correspondent Tom Fielden, he worked with Professor Rees to test the idea that political affiliation might be reflected in the structure of the brain.

A sample of young people completed a standard five-point questionnaire on their political outlook, from very liberal to very conservative, and then underwent a structural MRI scan. Remarkably, significant differences were apparent: liberals had a relatively well-developed anterior cingulate cortex (ACC) and conservatives a proportionately larger amygdala.

The roles of these areas suggest a possible explanation. The ACC may provide greater capacity to tolerate novelty and uncertainty, typical of more liberal ways of thinking.

30 Symmonds M *et al.* Metabolic state alters economic decision making under risk in humans. *PLoS One.* 2010;5(6):e11090.

31 De Martino B, Kumaran D, Seymour B, Dolan RJ. Frames, biases, and rational decision-making in the human brain. *Science.* 2006;313(5787):684–7.

32 Sharot T, Korn CW, Dolan RJ. How unrealistic optimism is maintained in the face of reality. *Nat Neurosci.* 2011;14(11):1475–9.

33 Fleming SM, Thomas CL, Dolan RJ. Overcoming status quo bias in the human brain. *Proc Natl Acad Sci USA.* 2010;107(13):6005–9.

34 O'Doherty J *et al.* Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science.* 2004;304(5669):452–4.

35 Guitart-Masip M *et al.* Vigor in the face of fluctuating rates of reward: an experimental examination. *J Cogn Neurosci.* 2011;23(12):3933–8.

The amygdala has been implicated in fear and emotional responses, and perceptions of threat, psychological traits associated with more conservative attitudes. The correlations are consistent with known differences in physiological and neural responses between liberals and conservatives. But as they are only associations, it is impossible to assign cause and effect.

Notably, an algorithm trained to analyse scans ended up with a good ability to discriminate the very liberal from the conservative (71 per cent success rate). And the resulting academic paper may be the first to include both a journalist and an Oscar-winning actor as coauthors[36].

The space within us

Movement is integral to human existence. Furthermore, as well as being able to physically move from location to another, we also have the mental capacity to imagine ourselves somewhere else. The work of Professor John O'Keefe and Professor Neil Burgess has illuminated key aspects of these remarkable navigational and conceptualising abilities.

Navigation is a complex activity. It requires integration of visual information, internal proprioceptor and other data during locomotion, as well as memory and planning. A critical structure in these abilities is the hippocampus, acting in partnership with various regions of the cortex.

In the 1970s, in some of the first recordings from freely moving rats, Professor O'Keefe discovered that certain cells in the hippocampus preferentially fired when an animal was in a particular environmental location – the first description of 'place cells'[37]. This led Professor O'Keefe to make the initially controversial but ultimately influential suggestion that the hippocampus held some kind of 'cognitive map' of the outside world.

Subsequently, patterned activation of neurons was identified in the entorhinal cortex, which provides the major cortical input into the hippocampus. These 'grid cells' form a distinctive triangular lattice representing the external environment. First seen in rodents, Professor Burgess recently showed they were also present in the human brain (see page xx).

Professor Burgess has made much use of immersive virtual reality set-ups, creating artificial environments that participants navigate while undergoing functional imaging. Using this approach, his group has examined the role of the hippocampus and other brain areas during tasks such as route-finding in the dark, planning journeys and mentally imagining oneself in different locations. These experimental studies are also used to devise and test computational models.

Such studies have revealed the critical role played by boundaries in the formation of cognitive spatial maps. For example, when participants were imagining themselves in different parts of an artificial environment, increasing the numbers of boundaries was more helpful than adding extra landmarks or more detail[38].

Remarkably, imaging has also revealed a striking asymmetry in hippocampal function. The hippocampus is responsible for both spatial navigation and episodic memory (recall of events in one's own life).

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Patients with memory loss due to hippocampal damage also show a marked impairment in their ability to imagine fictitious or future experiences. The key problem seems to be an inability to create spatially coherent scenes in the mind's eye.

Imaging during various maze-navigation tests suggest that the left and right hippocampus specialise in these functions – the right primarily handling spatial information and the left temporal information[39].

Cognitive maps and the hippocampus are also the focus of **Professor Eleanor Maguire** and colleagues. Her group has developed a special interest in the changes the hippocampus undergoes as trainee taxi drivers learn 'the Knowledge' – memorising 25,000 streets and thousands of landmarks in central London. Such work provides a rare opportunity to study the plasticity of the adult brain longitudinally, comparing drivers before and after they have completed four years' training. Taxi drivers who successfully completed the course showed marked expansion of the posterior region of the hippocampus (unlike those who failed or dropped out). The downside, however, was a corresponding loss in some other aspects of memory[40].

Professor Maguire has also examined another aspect of hippocampal function – its role in imagining the future. Patients with memory loss due to hippocampal damage also show a marked impairment in their ability to imagine fictitious or future experiences. The key problem seems to be an inability to create spatially coherent scenes in the mind's eye.

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40 Woollett K, Maguire EA. Acquiring "the Knowledge" of London's layout drives structural brain changes. *Curr Biol.* 2011;21(24):2109–14.

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A NEW VIEW OF PAIN

Simply seeing the body can reduce sensations of pain.

The brain has remarkable abilities to integrate information from multiple sensory systems. These sensory systems are not independent, and inputs from one can have surprising effects on another – as **Professor Patrick Haggard** and colleagues have discovered in their studies on vision and pain.

In 2001, Professor Haggard found that participants could better discriminate tactile stimuli when they could see their arm, even if they could not see the stimuli themselves. Notably, this ability increased still further when the arm was magnified.

Follow up studies of this intriguing discovery examined whether a similar effect applied to pain perception. With a mirror box set-up, painful stimuli could be applied to participants' arms outside their field of vision, while maintaining an intact body image. Strikingly, when participants could see their arms, their subjective ratings of pain were reduced, as were the brain signals caused by painful stimulation.

Furthermore, as with touch, magnification further enhanced this analgesic effect (while making the hand look smaller actually reduced it). Vision alone increased heat-pain thresholds by, on average, 3.2°C. Sight of a stranger's hand or neutral object, by contrast, had no impact.

Recently, Professor Haggard has gone a step further, investigating what is happening within the brain that could explain these striking findings. Using an infrared laser, he subjected participants to a painful stimulus while scanning their brain activity. When participants could see their hand during painful stimulation, perceptions of pain were again reduced. This was found to correspond to enhanced connectivity between the brain's well-described 'pain matrix' and a network of regions in the posterior of the brain associated with visual perception of the body. Hence 'visually induced analgesia' does not simply reflect lower activity in pain networks but stems from modulation by networks associated with body perceptions.

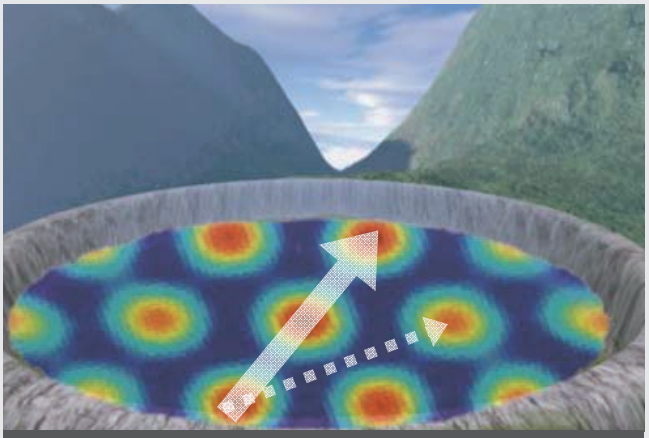
These intriguing studies suggest novel ways in which pain might be treated. Although pain control has traditionally addressed pain signalling, it may be possible to influence higher-level responses to control perceptions of pain.

Kennett S, Taylor-Clarke M, Haggard P. Noninformative vision improves the spatial resolution of touch in humans. *Curr Biol.* 2001;11(15):1188–91.

Longo MR, Betti V, Aglioti SM, Haggard P. Visually induced analgesia: seeing the body reduces pain. *J Neurosci.* 2009;29(39):12125–30.

Mancini F, Longo MR, Kammers MP, Haggard P. Visual distortion of body size modulates pain perception. *Psychol Sci.* 2011;22(3):325–30.

Longo MR *et al.* Linking pain and the body: neural correlates of visually induced analgesia. *J Neurosci.* 2012;32(8):2601–7.



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A MAP IN THE HEAD

The human brain contains 'grid cells' that provide an internal representation of external space.

How do animals know where they are? A critical role is played by 'grid cells', which appear to create an internal map of external space composed of equilateral triangular tiles. A grid cell fires whenever an animal passes over one of a series of locations arranged at the vertices of a triangular grid across the environment. Although well-characterised in rodents, only recently have indications of their presence been seen in humans, thanks to the work of Dr Caswell Barry and Dr Christian Doeller in **Professor Neil Burgess**'s group.

Identifying grid cells in humans is challenging. It is difficult to record from individual neurons in the human brain, while functional imaging techniques typically lack the spatial or temporal resolution to identify the localised neural activity that would reveal their existence. However, Professor Burgess's group reasoned that certain predicted features of grid cell activity, such as the fact that all of the grid patterns are aligned, and become sharpened during rapid locomotion, might provide a way to detect signs of their activity by fMRI in humans.

To test this idea, participants were scanned while they explored a virtual reality scene – a grassy plain bounded by cliffs which distant landmarks to help with orientation. Participants collected and replaced objects within this area.

Focusing on brain regions known to contain grid cells in rodents, the researchers saw tell-tale patterns of brain activity with sixfold symmetry as a function of running direction – precisely what would be expected from activation of grid cells in a triangular lattice. As predicted, the strength of the signal recorded varied with the speed at which participants moved within the virtual environment. The results confirmed that the entorhinal cortex in humans does indeed contain a triangular representation of external space.

A particularly interesting feature of grid cells, and associated systems that create an internal map of the world, is that they seem to be (at least in part) an innate feature of the brain. In rodents, a cognitive map is generated by integrating information from, in addition to grid cells, place cells (which provide a representation of specific locations within an environment) and head direction cells (which provide a kind of neural compass). Working with Professor Burgess, Dr Tom Wills and Dr Francesca Cacucci in Professor John O'Keefe's lab recently showed that head direction cells and place cells appear very early in rat development, before the animals leave their nest and explore the world around them. Thus they seem to be born with an innate sense of direction.

Doeller CF, Barry C, Burgess N. Evidence for grid cells in a human memory network. *Nature.* 2010;463(7281):657–61.

Wills TJ, Cacucci F, Burgess N, O'Keefe J. Development of the hippocampal cognitive map in preweanling rats. *Science.* 2010;328(5985): 1573–6.

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READING THE SIGNS

A study of reformed Colombian guerillas has revealed key brain areas and connections involved in learning to read.

The vast majority of children pick up spoken language skills automatically early in life. Learning to read and write, however, takes considerable effort and practice. Identifying brain functions important in developing literacy is challenging as children are typically developing in many different ways at the same time as they are learning to read, so it is difficult to disentangle the precise impact of language. Reintegration of illiterate Colombian guerillas into mainstream society provided **Professor Cathy Price** and colleagues with a unique opportunity to study brain changes associated with the acquisition of written language skills.

Working with colleagues in Spain and Colombia, Professor Price was able to compare brain structure of individuals who had learned to read Spanish as adults ('late-literates') with those of matched adults who were still illiterate. Late literates had enhanced grey matter volumes in five areas at the back of the brain previously implicated in reading abilities. They also showed connectivity differences, with additional white matter in a region of the corpus callosum, the cables linking the two hemispheres of the brain.

This information provided an opportunity to explore these regions and connections in adults who had learnt to read when young. Tractography revealed a pathway through the area of the corpus callosum identified in the late-literates, linking the left and right dorsal and angular gyri (regions previously implicated in language processing). Although tracts through the corpus callosum are laid down before birth, it is possible that the precise linkages can be reshaped later as adults learn to read.

Functional connections in the previously identified areas were explored in fMRI studies and computational modelling, with reading being compared to object naming. The results again pointed to the importance of connections between hemispheres, rather than between gyri on the same hemisphere. Furthermore, the left angular gyrus appears to play a 'top-down' modulatory role, possibly to aid discrimination of visually similar words, where context can provide clues to word identity.

Brain areas involved in reading have been well-characterised, but this study has provided a rare opportunity to study how they are formed. As well as revealing more about the structure and function of these brain networks, they may also shed light on conditions in which they go wrong. In dyslexia, for example, reduced grey and white matter volumes may be consequences of limited reading experiences rather than a cause of reading difficulties.

Carreiras M *et al.* An anatomical signature for literacy. *Nature.* 2009;461(7266):983–6.


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FROM SYNAPSE TO BEHAVIOUR

Statistical modelling may be a 'mathematical microscope' revealing synaptic events associated with specific behaviours.

One of the greatest challenges in neuroscience is to link observable human behaviours with specific changes at synapses. Only under exceptional circumstances can neuronal recordings be taken within the brain. However, using statistical modelling, **Dr Rosalyn Moran**, **Professor Karl Friston**, **Professor Ray Dolan** and colleagues have been able to extract information about molecular events at the synapse from MEG recordings.

MEG detects the magnetic fields generated by neuronal activity. One of its major advantages is its very high temporal resolution – in the millisecond time range. It is therefore well-suited to studies examining dynamic changes in neuronal activity.

MEG data are also amenable to analysis by 'dynamic causal modelling', whereby changes in brain activity are modelled as a sequence of activations through networks of brain areas (see main text). Hence, a particular dynamic pattern of MEG activations can in theory be modelled in terms of underlying causes, which can include information about the molecular properties of neurons and their interactions.

To test this, Dr Moran attempted to deconstruct the impact of dopamine on working memory. As expected, administration of a dopamine precursor, L-DOPA, generated a small but significant increase in working memory performance. Working memory is thought to involve areas of the pre-frontal cortex. Three classes of MEG recordings showed changes in this area during memory tasks, and one class was sensitive to the dopamine boost.

A dynamic causal model was developed to simulate these findings. It integrated various aspects of both excitatory (AMPA and NMDA receptors) and inhibitory (GABA receptor) signalling, as well as what is known about their sensitivity to dopamine. The model was then adjusted until it provided the best fit with the experimentally obtained MEG data.

This analysis suggested that the dopamine-associated improvements in working memory stemmed from effects on both AMPA and NMDA receptors. Notably, the strength of these effects predicted the degree of improvement in memory performance. Reassuringly, the results are also consistent with what is known from experimental studies of dopamine's effects on NMDA and AMPA signalling.

The study has provided proof of principle that the molecular basis of complex human behaviours can be inferred by modelling. It offers the exciting prospect of dissecting the molecular and cellular basis of behavioural phenomena non-invasively, and how they may be altered in conditions characterised by abnormal cognitive processing.

Moran RJ *et al.* An *in vivo* assay of synaptic function mediating human cognition. *Curr Biol.* 2011;21(15):1320–5.

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Professor Maguire's group has also made key contributions to one of the most intriguing areas of cognitive neuroscience – the ability to predict or decode mental states from patterns in brain activity. Their early work analysed hippocampal activity to predict the location of participants in a virtual reality environment[41]. Recently, it has even proven possible to predict which specific episodic memories participants were recalling solely by examining the patterns of activity in their hippocampus[42].

Automatic for the people

Professor Patrick Haggard is interested in two intriguing and related aspects of consciousness: how we form an internal mental representation of our bodily form and how we attribute agency to our own actions – how do we decide when we 'willed' something to happen rather than it happening automatically?

The sensory system in the skin provides information about the limits of our body, and it is well known that the brain includes a detailed 'somatosensory map'. But information from vision and proprioception is also used to generate a sense of our physical form, and the brain may contain a 'physical body map' of the internal world. Interestingly, this stored body model, like the somatosensory map, is hugely distorted – we perceive our fingers as much shorter and our hands much wider than they actually are[43].

Curiously, this body map is highly sensitive to temperature. Cooling hands increased the strength of the 'rubber hand' illusion – an experimental ploy where the brain is tricked into thinking an artificial limb is actually part of the body – while warmth reduced the strength of the illusion[44].

Professor Haggard has uncovered other curious influences on pain perception, such as vision (see page xx). This and other work, for example on phantom limb pain, hints at the importance of a coherent representation of our own body, and raises the possibility of novel psychological methods of pain control.

Language and learning

Development and rehabilitation of the brain systems responsible for language are the main interests of Professor Cathy Price. Unusually, work with South American colleagues provided a rare opportunity to look at the development of reading skills in an adult population – Colombian guerrillas being reintegrated into society (see page xx). A more general aim is to understand how speech and reading skills recover after damage to the brain, which may suggest new ways to restore impaired language abilities.

Language skills develop during childhood, and difficulty with language can create profound problems for young people. Interestingly, Professor Price has discovered that language areas of the brain are linked to fluctuations in IQ during childhood.

Although IQ is reasonably stable over the life course, the brain's dramatic rewiring during adolescence could potentially lead to changes over shorter time frames. Cross-sectional studies have shed little light on this issue, as so many uncontrollable variables could account for differences in IQ within a population.

Professor Price therefore undertook a longitudinal approach, measuring IQ and performing structural brain scans on 33 young people at average age 14 and then again around four years later. Two aspects of IQ were assessed, verbal and non-verbal. Interestingly, individuals' IQ scores varied markedly between assessments, some going up and some going down. Furthermore, IQ changes were associated with changes to specific areas of the brain – including speech areas of the brain for verbal IQ (and, oddly, areas associated with finger movements for non-verbal IQ). Hence, at this important stage in their education, young people's IQ scores show more plasticity than previously thought[45].

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44 Kammers MP, Rose K, Haggard P. Feeling numb: temperature, but not thermal pain, modulates feeling of body ownership. *Neuropsychologia.* 2011;49(5):1316–21.

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The Sainsbury Wellcome Centre will take advantage of new technological opportunities to draw links between neural circuits and behaviour.

MAKING CONNECTIONS: THE SAINSBURY WELLCOME CENTRE

Individual neurons – indeed, even subcompartments of neurons, dendrites – can perform computational tasks. Yet the nervous system's most sophisticated computational activities are likely to arise from the coordinated actions of networks of neurons. A critical readout of this computational activity is the observable behaviour of an animal, be it an experimental mouse or a person. However, the links between collective neural activity and behaviour are extremely poorly understood.

The problem to a large degree is technological. Many tried and tested methods exist to explore the electrophysiology of neurons. Much is now known at a molecular level about how neurons work and communicate with one another. Alongside this 'bottom up' approach, various forms of structural and functional imaging have provided 'top down' insight into high-level brain function. Many regions and networks of the brain have been implicated in a whole host of human behaviours. But there remains a significant gap – imaging techniques cannot yet provide the resolution to monitor the responses of individual neurons in neural networks.

Yet exciting ways forward are beginning to emerge. A raft of technological advances (see Box) is beginning to provide the tools for dissecting the neural pathways underpinning behaviour. Alongside this experimental progress, a further important role is being played by computational modelling. Huxley and Hodgkin's landmark studies of action potential generation included computational models, and they remain central to neuroscience, providing a theoretical framework for interpreting the results of experiments and a way of generating predictions that can be explored experimentally.

It is therefore a propitious time to be launching a new initiative in neural circuitry and behaviour. The Sainsbury Wellcome Centre, jointly funded by the Gatsby Charitable Foundation and the Wellcome Trust, is being established to apply existing and novel experimental tools and computational approaches to generate new insight into the neural circuitry underpinning behaviour. In time, as well as shedding light on fundamental neurobiological processes, it should also provide insight into neurobehavioural conditions such as schizophrenia, depression and autism.

CONNECTING BRAIN TO BEHAVIOUR

Research on neural circuitry is being transformed by a raft of new technologies.

Studies of neural activity in the living brain present a considerable technological challenge. Ideally, an investigator needs to stimulate and record from specific neurons – or parts of neurons – on a timescale consistent with the natural processes being studied, generally in the millisecond range.

Such studies have been greatly aided by recent technological innovations. The use of 'caged compounds' – neurotransmitters encased in chemical shells until released by a flash of light – has enabled neuron activation to be controlled with a high degree of spatial and temporal resolution.

A further advance has been to combine uncaging with 'two-photon excitation microscopy', which permits high-resolution three-dimensional imaging of living tissue. By tracking the responses of surrounding cells to this highly localised activation, functionally connected neural networks can be identified.

Even with such methods, in densely packed regions of the brain it can still be difficult to activate specific neurons efficiently. A great step forward has been the development of 'optogenetic' tools, which combine genetic targeting with precise light delivery to activate individual neurons with great precision.

The key principle is to engineer neurons so that they express light-sensitive ion channels (originally identified in phototoxic algae). These are generally delivered into cells by viral vectors. So, instead of electrical impulse, a brief flash of light is used to stimulate a cell by opening up newly introduced ion channels. Even with these and other new methods, electrophysiology is still likely to play a critical role – not least because of its great sensitivity and high time resolution.

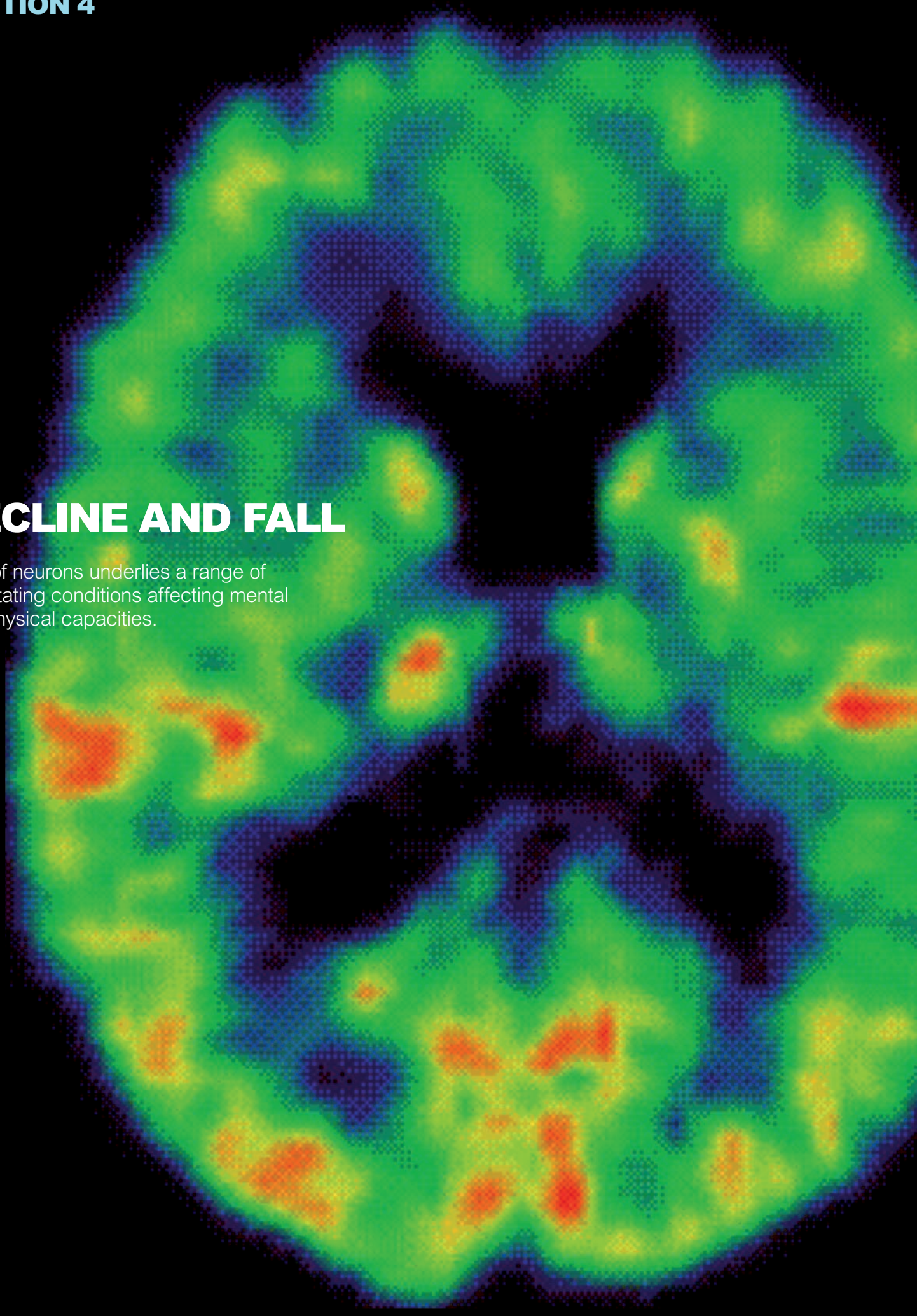
Equally important advances have been made in the detection of neural activity. As well as conventional electrical recording through patch clamping, it is now also possible to visualise dynamic intracellular processes through fluorescent reporters. These include voltage-sensitive dyes or calcium sensors, which are sensitive to intracellular calcium levels and reveal calcium fluxes within the cell. Exquisite specificity can again be achieved by using genetic techniques to engineer specific cells to express particular calcium indicators.

In combination, imaging systems can provide remarkable spatial detail over multiple scales – spanning a 1 µm dendritic spine, an individual dendrite, a neuron or a neural network.

Additional techniques are beginning to reveal neuromicrocircuitry, including 'Brainbow' or viral-based approaches for differential labelling of individual neurons and their connections. It is also possible to identify functional connections in such collectives (see page xx).

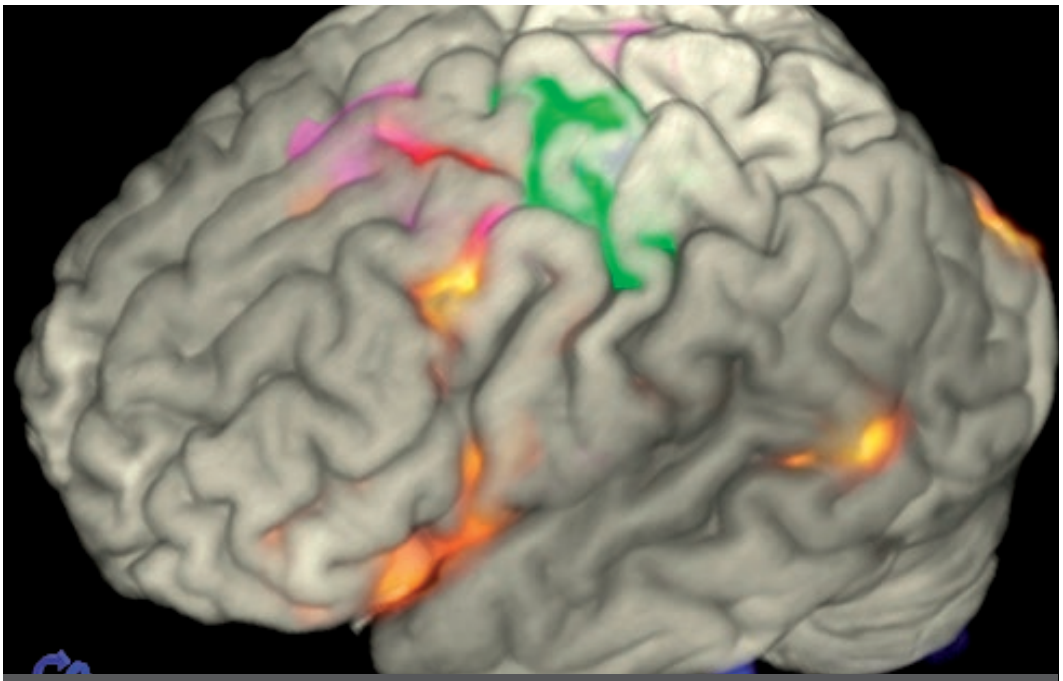
Equally importantly, this dissection of neural activity can increasingly be related to fine-scale analysis of complex behaviours. Sophisticated image recording and image analysis can generate data on freely moving animals. Furthermore, virtual reality set ups can be used to record from an immobilised experimental animal – typically a mouse – as it interacts with a highly controlled virtual environment. Through such methods, it may therefore be possible to close the gap between neuron and behaviour.

A new building is being constructed to house the Centre, close to UCL's main central London campus to encourage collaboration and interactions with UCL's world-leading community of neuroscientists. The building, designed by Ian Ritchie Architects Ltd, will house 12 groups. At its heart will be the Gatsby Computational Neuroscience Unit, led by Professor Peter Dayan, emphasising its centrality to the Centre's vision. A team led by Interim Director Professor John O'Keefe is currently identifying a suitable Director who will shape the long-term strategy for the Centre and decide its final composition. Building work is due to be completed in 2014.



DECLINE AND FALL

Loss of neurons underlies a range of devastating conditions affecting mental and physical capacities.



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Neurodegenerative and neuromuscular diseases wreak havoc on mental and physical function, and are very difficult to treat. In part, this is because the mechanisms of disease are poorly understood. Interestingly, although responsible for a relatively small number of cases, rare inherited forms of Alzheimer's disease and Parkinson's disease have provided considerable insight into the molecular mechanisms of disease.

In Parkinson's disease, for example, **Professor Nick Wood** has led genetic studies revealing significant insight into disease processes. By analysing three families, two from Italy and one from Spain, Professor Wood was able to pinpoint mutations in the *PINK1* gene as a cause of disease[46]. The sequence of the PINK1 gene suggested that PINK1 protein was located in mitochondria, reigniting interest in this organelle's role in Parkinson's disease. PINK1's normal role may be to protect mitochondria from cellular stress[47].

Rare forms of Alzheimer's disease and Parkinson's disease have provided considerable insight into the molecular mechanisms of disease.

A more common cause of inherited Parkinson's disease is *LRRK2*[48]. Although still rare, mutations in *LRRK2* are common enough to be considered a possible cause of disease in Parkinson's disease patients, particularly in certain populations where up to one in ten patients have *LRRK2* mutations[49]. *LRRK2* genetic tests are now commercially available, and are used to guide treatment and identify family members at risk.

Nevertheless, most patients do not have mutations in genes identified by traditional genetic approaches. Recently, insight into these cases has come from genome-wide association studies, which sweep the entire genome for factors influencing the risk of disease. Professor Wood has led a major international consortium in Parkinson's disease (see page xx), and has contributed to collaborations dissecting conditions such as multiple sclerosis and epilepsy.

Similarly, **Professor John Hardy**, who identified the first gene associated with Alzheimer's disease, the b-amyloid gene[50], while at Imperial College, has been involved in several international multicentre studies. These have pinpointed cholesterol

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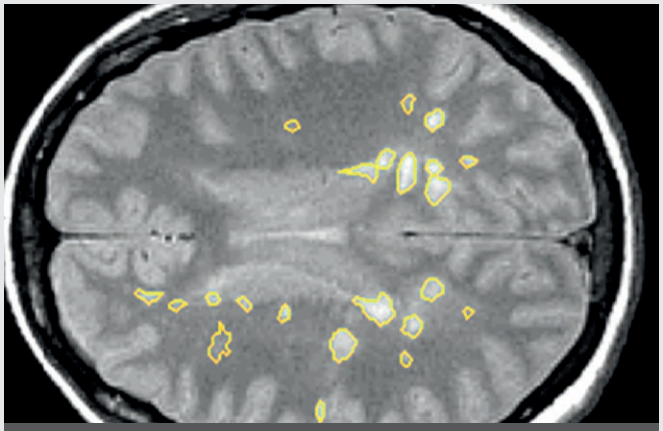
50 Chartier-Harlin MC *et al.* Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature.* 1991;353(6347):844–6.



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IMAGING THE FUTURE OF MULTIPLE SCLEROSIS

Can advances in imaging provide multiple sclerosis patients with a clearer view of their future?

When they receive a diagnosis, multiple sclerosis patients typically ask how their disease is likely to progress. Unfortunately, while some probabilities can be given, it is very hard to predict what will happen to any one individual. Thanks to advances in MRI, however, **Dr Olga Ciccarelli** is hoping to provide more specific answers.

However, confirmation of diagnosis and information about the speed of clinical progression require follow-up of cohorts of patients over several years. Early longitudinal studies revealed that MRI detection of white matter lesions in the earliest phases of disease was a useful indicator of multiple sclerosis in suspected cases, while recent multicentre studies have begun to provide a more nuanced picture of the types of damage seen and later symptoms.

Central to these advances have been enhanced tools for characterising structural and other abnormalities. Dr Ciccarelli and colleagues have applied new 'tractography' methods to assess deficits in white matter connectivity, to complement measures of white matter degeneration, as well as more sophisticated methods of characterising changes in grey matter volume.

Furthermore, MRI can also provide potentially important metabolic information. Recent evidence from Dr Ciccarelli and her colleagues have suggested that alteration of specific metabolites in some brain regions, and abnormal mitochondrial function in cells of the spinal cord, may be the major determinants of cognitive and physical impairment, respectively, beyond the structural damage to grey and white matter. Hence, Dr Ciccarelli and colleagues' work is also shedding light on the mechanisms underlying this still poorly understood disease.

Brex PA *et al.* A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med.* 2002;346(3):158–64.

Bodini B *et al.* T2 lesion location really matters: a 10 year follow-up study in primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2011;82(1):72–7.

Bodini B *et al.* Corpus callosum damage predicts disability progression and cognitive dysfunction in primary-progressive MS after five years. *Hum Brain Mapp.* 2012 Feb 13.

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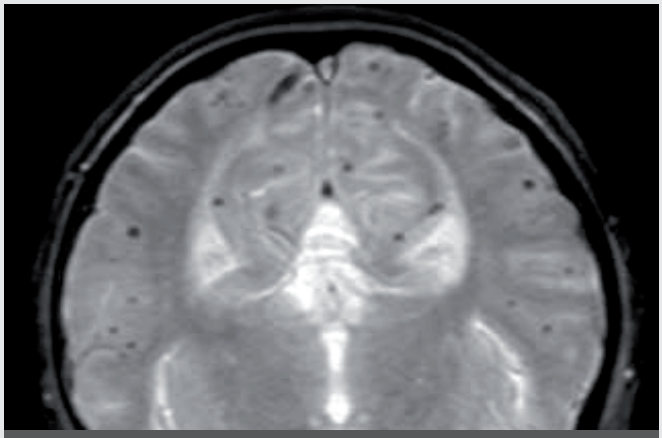
Ciccarelli O *et al.* Spinal cord repair in MS: does mitochondrial metabolism play a role? *Neurology.* 2010;74(9):721–7.



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BEWARE THE BLACK SPOT

Visible on MRI brain scans as black spots, 'microbleeds' may be more harmful than once thought.

Brain function depends intimately on blood flow through a network of small arteries ramifying through the brain. Damage to these tiny blood vessels can cause blood to leak into surrounding brain tissue (haemorrhagic stroke or intracerebral haemorrhage) while vessel blockage can disrupt oxygen supply (ischaemic stroke). Stroke patients – and indeed significant numbers of healthy older people – often also have one or more small areas of bleeding, cerebral 'microbleeds'. Advances in MRI have made microbleeds easier to detect, and **Dr David Werring** has found that they may be clinically more important than previously thought.

Although not seen on CT or conventional MRI scans, microbleeds are clearly visible as black spots in more advanced (T2*-weighted gradient echo) MRI. They are linked to the presence of a haemoglobin breakdown product, haemosiderin, and indicate areas of local blood seepage out of damaged small vessels.

Despite being relatively common and often present in key areas of the brain, they have generally been considered to be of little clinical significance. Dr Werring's studies have challenged this idea, suggesting not only that microbleeds are potentially harmful in themselves but also that they may be markers of the severity of underlying small-vessel abnormalities.

For example, using a battery of neuropsychological tests on stroke clinic patients, Dr Werring found an association between microbleeds and various kinds of cognitive impairment, even after controlling for other forms of cerebrovascular disease.

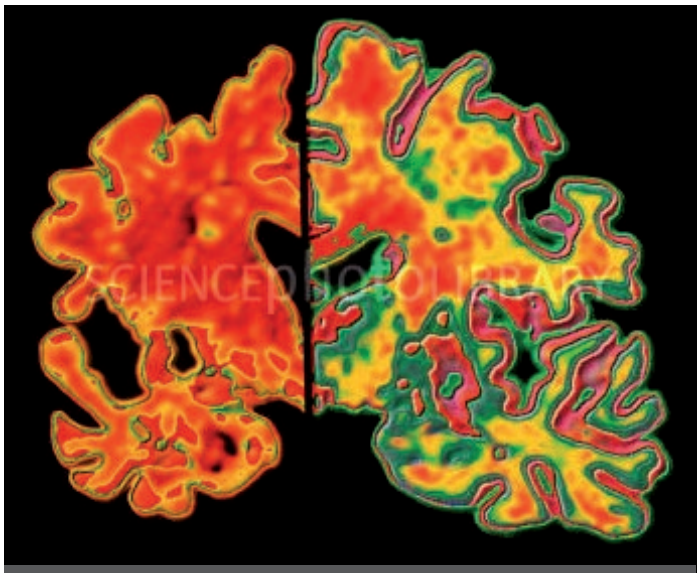
Longitudinal studies of ischaemic stroke patients suggest that the presence of microbleeds is a key indicator of the risk of further microbleeds. Clinically, microbleeds could be an important factor to consider in assessing future cerebral bleeding risk in such patients. Blood-thinning agents are often used to reduce the risk of further ischaemic events, but could also increase the risk of intracerebral haemorrhage, a risk that may be predicted by the presence of microbleeds.

As well as developing new methods to automate detection of microbleeds, Dr Werring is now leading a large multicentre study to explore their impact. The CROMIS programme, funded by the British Heart Foundation and the Stroke Association is following a cohort of stroke patients to see if blood-thinning treatments are associated with more severe bleeding. The programme will also look in more detail at the links between microbleeds and cognitive impairment, while genetic studies will aim to identify new genetic risk factors for microbleeds and haemorrhagic stroke.

Werring DJ *et al.* Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. *Brain.* 2004;127:2265–75.

Gregoire SM *et al.* MRI detection of new microbleeds in patients with ischemic stroke: five-year cohort follow-up study. *Stroke.* 2010;41(1):184–6

Seghier ML *et al.* Microbleed detection using automated segmentation (MIDAS): a new method applicable to standard clinical MR images. *PLoS One.* 2011;6(3):e17547.



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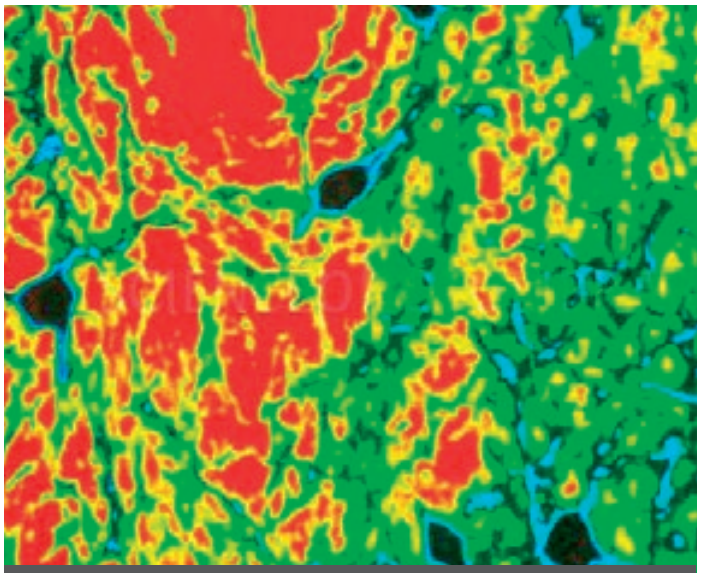

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metabolism and the immune system as potentially important factors in susceptibility to disease[51].

The main value of whole-genome studies is to identify biochemical pathways potentially involved in disease processes. These can then be followed up in functional studies, for example in animal knockouts. An increasing focus is on induced pluripotent stem cells, which can be differentiated in specific types of adult cell.

Tracking Huntington's

Huntington's disease is a scientific puzzle, a medical challenge, and a personal catastrophe. Caused by mutations affecting a protein known as huntingtin, its main impact is on the brain, where the death of neurons leads to the gradual loss of cognitive and motor skills. Symptoms typically appear in mid-adult life.

In a varied programme of research, Professor Sarah Tabrizi is making important contributions to both the scientific and medical challenges presented by Huntington's disease. Part of her work is on the mechanisms by which mutant huntingtin exerts its effects – a complex area, as many aspects of cell function are affected. Professor Tabrizi has a special interest in its effects on immune cell function – although death of neurons is of most clinical importance, mutant huntingtin also affects the immune system[52,53]. Such studies could identify new therapeutic leads or help to explain some of the variability in age of onset or speed of decline.

Potentially of more immediate significance is a major study examining changes in people with the Huntington's mutation before symptoms become apparent.

Potentially of more immediate significance is a major study examining changes in people with the Huntington's mutation before symptoms become apparent. Professor Tabrizi is leading an international multicentre study, TRACK-HD (see page xx), which has identified substantial changes in brain structure well before overt symptoms appear. During early stages, the brain's plasticity may enable other systems to compensate for neuronal death, leading to only minor loss of function[54]. Eventually, though, these compensatory mechanisms are overwhelmed.

The work is particularly important as it provides 'biomarkers' that could be used to track the impact of a new wave of therapeutics in clinical trials. Indeed, Huntington's disease could be a trailblazer for a radical new approach to treatment of neurodegenerative disease, with at-risk individuals being treated in advance of clinical disease. This bold new philosophy lies at the heart of UCL's new £20 million Leonard Wolfson Centre for Experimental Neurology (see page xx).

Dementia – not just Alzheimer's

Although dementia is generally associated with Alzheimer's disease, there are many other forms. A second important cause is frontotemporal lobar degeneration (FTLD), where neurodegeneration primarily affects the forebrain. FTLD covers a range of conditions, providing opportunities to identify associations between areas of damage and the appearance of particular symptoms.

Dr Jason Warren and colleagues, for example, have explored links between brain tissue loss and traits as diverse as personality changes[55] and the ability to distinguish flavours[56] and recognise people's voices[57]. While focal lesions, from injury or stroke, typically affect discrete areas of the brain, FTLD and similar conditions tend to affect wider areas and therefore reveal more about the impact of loss of connectivity across multiple brain regions.

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52 Wild E *et al.* Abnormal peripheral chemokine profile in Huntington's disease. *PLoS Curr.* 2011;3:RRN1231.

53 Björkqvist M *et al.* A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *J Exp Med.* 2008;205(8): 1869–77.

54 Klöppel S *et al.* Functional compensation of motor function in pre-symptomatic Huntington's disease. *Brain.* 2009;132(6):1624–32.

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56 Piwnica-Worms KE, Omar R, Hailstone JC, Warren JD. Flavour processing in semantic dementia. *Cortex.* 2010;46(6):761–8.

57 Hailstone JC *et al.* Voice processing in dementia: a neuropsychological and neuroanatomical analysis. *Brain.* 2011;134(9):2535–47.

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MUSIC IN THE BRAIN

The impact of neurodegeneration may shed light on how the brain processes music.

All human populations possess some form of musical culture, a sign of its great significance to human existence. Music making and musical appreciation are important aspects of many people's lives, and their loss in neurodegeneration can have a major impact. However, as **Dr Jason Warren** and colleagues have shown, such cases can also provide insight into the brain processes involved in this fascinating aspect of human behaviour.

Like language, music is a complex concept encapsulating several distinct aspects of brain function. As well as basic sound processing, music also incorporates emotion recognition, memory, symbolic representation (musical notes) and abstract concepts (such as songs). Understanding how the brain integrates such multidimensional elements could shed light not just on music but also on how other complex concepts are handled.

Neurodegenerative conditions degrade regions of the brain, impairing cognitive and other abilities. Although the areas of the brain affected are typically the same for any particular condition, the extent to which they are affected differs from person to person. Hence the loss of particular skills can often be linked to damage to specific brain regions.

Insight into expert music abilities has come from studies of two musicians, one with semantic dementia and one with Alzheimer's disease, who were compared to a control group of unaffected expert musicians. Interestingly, the patients showed marked differences in a set of tests examining their abilities across several areas of musical cognition. The patient with semantic dementia struggled to extract the emotional value of music or to identify sounds made by different musical instruments, while the Alzheimer's patient struggled to identify compositions and recognise musical notations.

In other studies, Dr Warren and colleagues have looked specifically at deficits in emotion recognition in patients with frontotemporal lobar degeneration, which often disrupts social and emotional functioning. As well as being less able to recognise emotions in faces and voices, patients also struggled to spot them in music. Deficits were specifically associated with loss of grey matter in an extensive cortical network which overlapped with areas previously found to be important in emotion processing and other skills such as conceptualisation and theory of mind.

Collectively the work begins to paint a complex picture of music processing that integrates many aspects of brain function: there is no discrete 'music area'. Somehow, though, the brain unites these disparate aspects into the experience of music.

Omar R *et al.* The cognitive organization of music knowledge: a clinical analysis. *Brain.* 2010;133(Pt 4):1200–13.

Omar R *et al.* The structural neuroanatomy of music emotion recognition: evidence from frontotemporal lobar degeneration. *Neuroimage.* 2011;56(3):1814–21.

Composed only of protein, infectious prion particles are responsible for lethal neurodegenerative conditions.

Changes in auditory processing are a particular focus of Dr Warren's work. As well as loss of musical skills (see page xx), Dr Warren has also examined how recognition of non-speech sounds deteriorates in a variety of dementia syndromes[58] – a potentially underestimated deficit, as an impaired inability to recognise everyday environmental sounds can affect quality of life[59].

More unusually, Dr Warren and Dr Jonathan Rohrer have proposed that the composer Ravel may have had a form of FTLD caused by mutation of a progranulin gene[60]. Ravel developed progressive apraxia and aphasia in later life, losing musical skills (but not his musical knowledge), and became withdrawn and listless during his final years – symptoms consistent with a diagnosis of FTLD. More generally, Dr Warren and Dr Rohrer are aiming to provide a more detailed view of the structural changes seen in FTLD, and to characterise changes associated with specific mutations[61].

The puzzle of prions

Prions are a fascinating but deadly biological curiosity. Composed only of protein, infectious prion particles are responsible for lethal neurodegenerative conditions such as Creutzfeld–Jakob disease (CJD) and bovine spongiform encephalopathy, the origin of variant CJD. A world-leading expert on prions, Professor John Collinge of the MRC Prion Unit at UCL has done much to unravel the complex biology of prions, alongside work on diagnostic tests and potential therapeutics.

Infectious prion proteins are thought to cause disease by catalysing the conversion of an endogenous (cellular) prion protein – of currently unknown function – into the infectious form. The abnormal form aggregates into large complexes.

One puzzling feature of prions is how a protein showing little genetic variation can nonetheless exist as different 'strains', with differing transmissibility and toxicity. The answers, suggests Professor Collinge, lie in the conformation of prion protein.

Important clues have come from the distinctive dynamics of prion infections. After experimental transfer of infectious prion protein, abnormal protein accumulates over a prolonged period but has little clinical impact. Then, once clinical signs do appear, neurodegeneration proceeds extremely rapidly.

The reason, suggests Professor Collinge, is that prion propagation and toxicity are entirely distinct. Toxicity is caused not by the infectious form of prion protein but by another structural variant – potentially, an intermediate on the

58 Goll JC *et al.* Auditory object cognition in dementia. *Neuropsychologia.* 2011;49(9):2755–65.

59 Goll JC *et al.* Non-verbal sound processing in the primary progressive aphasias. *Brain.* 2010;133(1):272–85.

60 Warren JD, Rohrer JD. Ravel's last illness: a unifying hypothesis. *Brain.* 2009;132(Pt 6):e114.

61 Rohrer JD *et al.* Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain.* 2011;134(9):2565–81.

conversion pathway from cellular to infectious prion protein[62]. Only when this form begins to accumulate do cells begin to suffer. Experimental infections in mice have provided strong support for this model[63].

In mice, depleting cellular prion protein prevents disease[64]. Less drastically, stabilisation of the endogenous conformation, preventing its conversion to a toxic intermediate, might also protect against disease. Using a battery of biophysical techniques, Professor Collinge and colleagues have identified a specific site where binding of a complex organic molecule stabilises cellular prion protein – a starting point for the rational design of prion-stabilising agents[65]. Professor Collinge has also identified how antibodies to cellular prion protein can block interaction with the infectious form, preventing its conversion to toxic form[66].

A further strand of work is focusing on blood-based assays to detect variant CJD[67]– an important tool, as the numbers of people with asymptomatic infections is still unknown.

Neuromuscular conditions

While neurodegenerative conditions have a devastating impact on mental function, neuromuscular diseases have a similarly catastrophic effect on physical abilities. As well as relatively common conditions such as muscular dystrophies and motor neuron disease, many rare conditions arise from abnormalities in the neuromuscular system.

Here again, rare conditions have shed light on disease mechanisms. Many conditions stem from abnormalities in ion channel function – hence the collective term 'channelopathies'. Defective mitochondria are a second major cause of serious disease.

Professor Mike Hanna leads a large interdisciplinary initiative integrating clinical care at the National Hospital and Great Ormond Street Hospital and translational research across multiple UCL departments. The aim is to gain a better understanding of disease processes and pursue new therapeutic leads, but also to make the transition to experimental medicine studies in people. This work falls under the umbrella of the MRC Centre for Neuromuscular Diseases, which also incorporates groups at the University of Newcastle, noted for its strengths in mitochondrial disease.

The Centre is coordinating a number of clinical trials and experimental medicine studies, including a promising approach to 'repurposing' an existing drug for a class of channelopathy patients (see page xx). Other exciting work, being led by **Professor Francesco Muntoni**, is exploring novel antisense RNA therapy for Duchenne muscular dystrophy (see companion volume on Translation and Experimental Medicine).

Other important strands of include intensive neuromuscular phenotyping of mutant mice, as well as an extensive muscle cell biobanking programme, which is collecting material from routine biopsies of both adults and children. The Centre is also playing a lead role in efforts to develop better assessment tools of mouse muscle function and biomarkers for tracking muscle deterioration – with MRI showing promise as a sensitive and reliable indicator of loss of muscle function.

Multiple sclerosis

Multiple sclerosis is caused by loss of the insulating myelin sheath surrounding nerves in the CNS, but the exact mechanisms of disease remain poorly understood. Dr Olga Ciccarelli, with Professor Alan Thompson and colleagues, is hoping that advances in imaging may reveal more about disease processes and also provide patients with a better idea of how their disease is likely to progress (see page xx).

MRI is now commonly used in diagnosis, revealing characteristic lesions in the brain and spinal cord. Advances in MRI are providing a more detailed view of these changes, and enabling links to be drawn between specific features of damage and symptoms, such as cognitive decline or loss of motor function.

M2100271-Multiple_sclerosis,_SEM-SPL.jpg

62 Collinge J, Clarke AR. A general model of prion strains and their pathogenicity. *Science*. 2007;318(5852):930–6.

63 Sandberg MK *et al.* Prion propagation and toxicity in vivo occur in two distinct mechanistic phases. *Nature*. 2011;470(7335):540–2.

64 Mallucci G *et al.* Depleting neuronal PrP in prion infection prevents disease and reverses spongiosis. *Science*. 2003;302(5646):871–4.

65 Nicoll AJ *et al.* Pharmacological chaperone for the structured domain of human prion protein. *Proc Natl Acad Sci USA*. 2010;107(41):17610–5.

66 Antonyuk SV *et al.* Crystal structure of human prion protein bound to a therapeutic antibody. *Proc Natl Acad Sci USA*. 2009;106(8):2554–8.

67 Edgeworth JA *et al.* Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay. *Lancet*. 2011;377(9764):487–93.

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A BRIEF HISTORY OF KURU

The epidemic of the prion disease kuru in Papua New Guinea is a powerful example of genetic selection in humans.

In the 1950s, Australian doctors became aware of a deadly neurodegenerative condition affecting large numbers of people, particularly women and children, in the Northern Highlands of Papua New Guinea. The disease, kuru, turned out to be a transmissible spongiform encephalopathy caused by an infectious protein (a prion). It was being spread by a local tradition in which the recently deceased were consumed by their relatives. Having studied the condition for 20 years, **Professor John Collinge** and colleagues are still making important discoveries about this extraordinary epidemic.

Although ritual feasting was halted, decades later people were still dying from kuru. Studies of these recent and historical cases have painted a surprising picture of human evolution.

Infectious prions trigger a change in endogenous (cellular) prion proteins, causing them to form large toxic assemblies. They are responsible for the late-onset neurodegenerative condition Creutzfeld–Jakob disease (CJD), as well as variant CJD, following transfer of cattle prion to humans.

Susceptibility to CJD is strongly influenced by genetics, particularly at codon 129 of the cellular prion protein gene. In all variant CJD patients identified to date, both copies of this gene have a methionine (Met) residue at codon 129. Heterozygosity at this site confers resistance to CJD, probably because non-identical proteins form assemblies less efficiently.

Among 3000 people from the Eastern Highlands, including 709 who had consumed human remains, 152 had died from kuru. Those exposed to human prion but who survived were typically heterozygotes, but an entirely new group of survivors was also seen. Some genetically vulnerable Met–Met homozygotes who had escaped kuru had a novel change at codon 127 – a variant not present in kuru-free areas of Papua New Guinea or anywhere else in the world.

Thus the codon 127 change seems to have undergone selection, thanks to the protection it provides against kuru. Since consumption of family members only began early in the 20th century, its spread has been remarkably quick.

Positive selection at codon 127 is superimposed upon balancing selection for heterozygosity at position 129. Further, the global distribution of the different prion protein variants led Professor Collinge and colleagues to propose that this balancing selection had occurred during past human evolution – suggesting that kuru-like epidemics may have happened at other times in our evolutionary history.

Mead S *et al.* Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. *Science.* 2003;300(5619):640–3.

Mead S *et al.* A novel protective prion protein variant that colocalizes with kuru exposure. *N Engl J Med.* 2009;361(21):2056–65.


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GENES AND DEGENERATION

Genome-wide scans have identified a host of genes influencing people's risk of Parkinson's disease.

The past decade has seen a surge in studies into the genetics of common diseases. The ability to track huge numbers of genetic markers across the entire genome, in large groups of patients, has enabled international consortia to identify genetic variants associated with increased risk of disease. **Professor Nick Wood** has led one such consortium, which has identified numerous variants linked to Parkinson's disease.

Although several genes have been implicated in Parkinson's disease, these generally represent rare cases in which a mutation is severe enough to trigger disease on its own. In most cases, genes are likely to play a more subtle role, influencing the risk of disease.

Because of their small effects, identifying such genes has been difficult. In recent years, a major breakthrough has occurred with the use of high-throughput screens comparing the presence of hundreds of thousands of genetic markers in large samples of patients and controls without the disease. Such large-scale studies usually depend on extensive collaboration, such as Professor Wood's International Parkinson's Disease Genome Consortium.

Since the impact of genetic variants is small, data from multiple studies are generally pooled in a meta-analysis to improve the statistical power to detect effects. Other statistical techniques can be used to discriminate 'real' association signals from 'noise'.

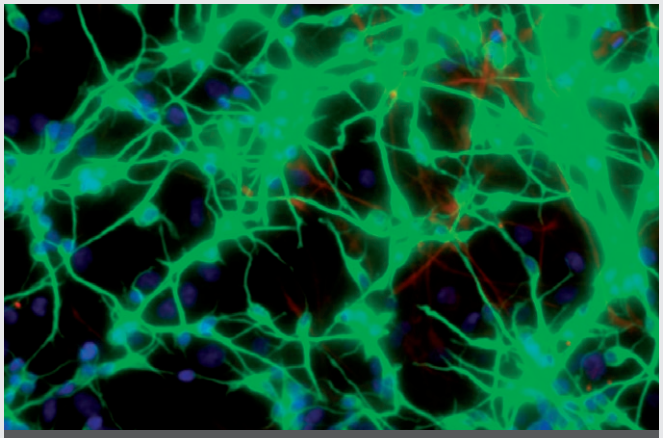
Using these approaches on more than 12,000 cases and 21,000 controls, and comparing findings with an independent study of 3000 cases, the Consortium identified 16 loci affecting disease risk. Some correspond to previously suggested risk loci, whereas others are entirely new.

The genetic markers used in genome-wide studies tag particular regions of the genome, so may not themselves be the actual genetic variants affecting disease risk. Using post-mortem brain samples from patients with neurological disease, Consortium researchers also analysed gene activity in regions around the loci implicated in the genome-wide study, which revealed several genes potentially contributing to increased disease susceptibility.

The challenge now is to examine the biological roles of the genes identified and how they influence disease risk, which may suggest new therapeutic approaches. In addition, the search continues for other genetic risk factors, as those identified to date explain only a proportion of the total genetic contribution to disease.

International Parkinson's Disease Genomics Consortium (IPDGC) *et al.* A two-stage meta-analysis identifies several new loci for Parkinson's disease. PLoS Genet. 2011;7(6):e1002142.

International Parkinson's Disease Genomics Consortium (IPDGC) *et al.* Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011;377(9766):641–9.



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ON TRACK FOR EARLY DIAGNOSIS

The TRACK-HD study has found significant changes in people with Huntington's disease mutations many years before clinical symptoms appear.

Huntington's disease is rare, affecting 5–10 of every 100,000 people, but is impossible to treat, ultimately lethal, and associated with highly distressing mental and physical deterioration. Unusually for a neurodegenerative condition, it is wholly genetic, and anyone who inherits a faulty Huntington's gene will succumb to the disease. Against this discouraging backdrop, **Professor Sarah Tabrizi** has been leading a major international study mapping early changes in pre-symptomatic individuals and patients with early signs of disease – work that could ultimately support interventions that slow or even prevent the onset of disease.

It is becoming clear that the clinical signs of Huntington's disease, which typically appear when patients are in their forties, follow a long period in which tissue damage is occurring the brain. Work in mice even suggests that, when mutant huntingtin is removed during this phase, nerve cells can actually recover. This raises hope that intervening at presymptomatic stages could delay or even prevent the development of clinical symptoms.

Although an appealing idea, testing it presents major challenges. Clinical trials in Huntington's disease are already difficult, as decline is gradual over many years. In presymptomatic or early disease, what are needed are 'biomarkers' that can be used to assess the impact of treatments.

The TRACK-HD study was set up to identify such biomarkers. By applying a battery of tests to carriers of the Huntington's disease mutation, including those with early disease and those in a presymptomatic phase, the study was able to document highly significant changes over just two years – even in individuals who would not be expected to show clinical symptoms for another decade. The most dramatic changes were seen in brain scans, with extensive loss of the striatum, white matter and, to a lesser extent, grey matter in the cortex.

The landmark TRACK-HD study has provided important evidence that sensitive and specific biomarkers exist for tissue damage in advance of symptom onset in Huntington's disease. As well as paving the way for clinical trials of new therapies in Huntington's disease, the work is also a pathfinder for 'early intervention' strategies in more common neurodegenerative conditions such as Alzheimer's disease – a principle now being applied in the new Leonard Wolfson Centre for Experimental Neurology (see page xx).

Tabrizi SJ *et al.* Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol.* 2009;8(9):791–801.

Tabrizi SJ *et al.* Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol.* 2011;10(1):31–42.

Tabrizi SJ *et al.* Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol.* 2012;11(1):42–53.

Following successful pilot studies, Dr Ciccarelli is now leading long-term projects to assess whether initial damage provides pointers to longer-term damage and symptoms in patients with the progressive form of the disease. She and her colleagues are also using imaging to try to understand why some people with multiple sclerosis and acute lesions in the spinal cord get better after an attack while others become increasingly disabled[68].

Surgery for seizures

Epilepsy can generally be controlled by drugs. But when the drugs do not work, surgery may be the best alternative if the source of the seizures can be identified. A unique long-term follow-up of more than 600 patients, carried out by Professor John Duncan and colleagues, has provided the clearest view yet of its therapeutic impact.

The National Hospital for Neurology and Neurosurgery has played a pioneering role in developing surgical interventions for epilepsy. Unlike other assessments, Professor Duncan's follow up spanned not just the initial period after surgery but also annual appraisals for up to 20 years[69].

The overall findings were very positive: around half of patients were seizure-free after ten years (apart from minor events with no loss of awareness) and 28 per cent of seizure-free patients had stopped taking anti-epileptic drugs. More than 80 per cent had at least one year with no seizures. The work also provided other useful information, such as the likelihood of further seizures and the varying outcomes of different surgical procedures, which should aid both surgical decision-making and later clinical management.

The information will also be of help to patients considering whether to undergo the procedure.

The risk with surgical intervention is that some other important neural systems will be damaged. These risks can be minimised by sophisticated brain imaging before surgery. As well as structural MRI, functional imaging and tractography can reveal key brain areas to be avoided in individual patients. With funding from the Wellcome Trust and the UK Department of Health, Professor Duncan's team has begun a study to superimpose images from these systems, and of the blood supply to the brain, into a common 3D image to identify the best routes to target areas of brain tissue.

This world-leading research has depended on an intimate association between clinical practice and research. A further important role has been played by the Epilepsy Society, a charity that provides substantial support for research and, in particular, has established outstanding imaging facilities at its national centre in Chalfont in Buckinghamshire, with UCL researchers housed in accompanying laboratory space.

68 Ciccarelli O, *et al.* Spinal cord repair in MS: does mitochondrial metabolism play a role? *Neurology.* 2010;74(9):721–7.

69 de Tisi J *et al.* The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet.* 2011;378(9800):1388–95.

The best approach in neurodegenerative diseases may be to identify those at risk and to begin treatment before the full ravages of the disease are irreversible, or even apparent.

NEURODEGENERATION: A PATH TOWARDS EARLIER INTERVENTION

Neurodegenerative conditions – such as Alzheimer's disease, Parkinson's disease and Dementia with Lewy bodies, Huntington's disease and Creutzfeld–Jakob disease – are devastating to individuals and their families, and impose a huge burden on health and social services. In the UK, the annual costs of caring for people with dementia, some £23 billion, exceed those of cancer and heart disease combined. With an ageing population, the numbers of people with neurodegenerative disorders are set to increase dramatically unless treatments are found that can delay or prevent onset.

Despite this enormous impact, treatments for neurodegenerative conditions are lacking. The treatments that do exist only provide only modest symptomatic benefit (e.g. for Alzheimer's disease) while the main therapy for Parkinson's disease, L-DOPA, eventually loses its beneficial effects. For many neurodegenerative diseases, no specific treatments have been shown to have any benefit.

For patients, slowing the decline associated with neurodegenerative conditions and preserving quality of life are the highest priorities. Scientifically, this may also make the most sense. By the time symptoms are obvious, considerable damage has already accrued in the brain. Treatments that target symptomatic disease have yet to show widespread, long-term benefits to patients. Furthermore, the later stages of neurodegenerative conditions may represent a self-perpetuating 'runaway phase', which interventions are powerless to prevent.

It may therefore make more sense to target this runaway train before it gains momentum, delaying the onset of serious damage and symptoms. As neurodegenerative diseases are generally late-life conditions, this approach could yield substantial benefits: delaying the onset of Alzheimer's disease by five years would halve its prevalence.

This is the principle underpinning the £20 million Leonard Wolfson Experimental Neurology Centre at UCL. Spanning all the major neurodegenerative conditions, it draws on the world-leading research of eight internationally recognised principal investigators (see Box) and the clinical expertise and patient resources of the National Hospital for Neurology and Neurosurgery (and UCLH more generally). Its ambitious long-term aim is to boost the translation of new therapies, with a particular focus on early-stage clinical studies.

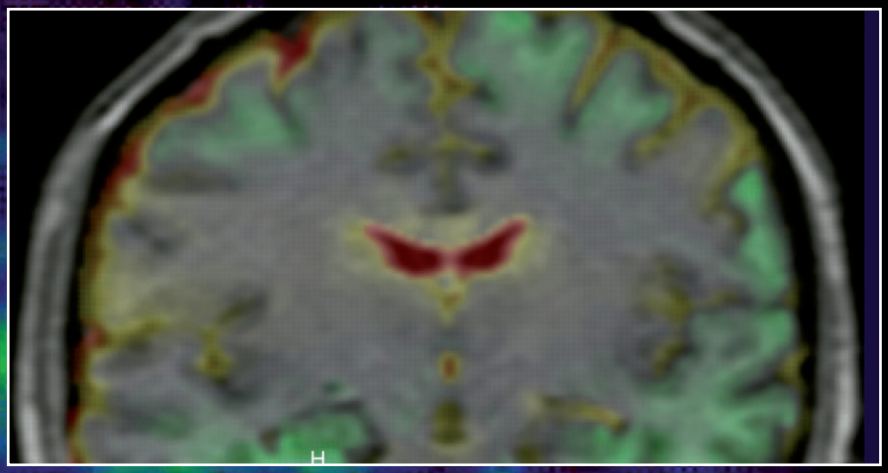
Early signs

The challenges are undoubtedly considerable. One of the biggest is whether it is possible to identify individuals at early stages of disease, or even presymptomatically. Exciting recent research suggests this may be an achievable goal.

Alzheimer's disease has historically been diagnosed at post-mortem examination, which reveal the characteristic protein accumulations and damaged brain tissue typical of the disease. Diagnosis based on symptoms is difficult, particularly when it comes to distinguishing between Alzheimer's disease (or other dementias) and normal ageing – especially at critical early stages.

There has long been hope that brain imaging might provide a way to diagnose neurodegenerative conditions, to track their progression over time, and to link symptoms to specific neurological changes. Professor Nick Fox has led extensive research suggesting that this may indeed be possible. In Alzheimer's disease, structural imaging by MRI can reveal early neurodegeneration, while PET can now also be used to identify specifically the beta-amyloid deposits characteristic of the disease.

In fact, imaging is just one strand of work on potential 'biomarkers' of neurodegenerative disease. Objective, accurate and quantifiable measures of disease progression are needed to assess patients' status and to monitor their progress. Importantly, they are valuable tools in intervention studies,



CENTRE PRINCIPAL INVESTIGATORS

Professor John Collinge
Professor Nick Fox
Professor John Hardy
Professor Martin Rossor
Professor Anthony Schipara
Professor Sarah Tabrizi
Professor Alan Thompson
Professor Nick Wood

identifying early signs of beneficial change. And, given the emphasis on early intervention, they have the potential to reveal harmful neurological events before symptoms become apparent. Indeed, it may even be possible to identify 'proximity biomarkers' – signs that clinical deterioration is imminent and treatment a matter of urgency.

As well as brain imaging, several other approaches will be taken to identify informative biomarkers. A particularly promising area is analysis of key metabolites and breakdown products in cerebrospinal fluid. Neuropsychological tests, to assess abilities such as concentration and memory, will also be used, though their sensitivity needs to be improved before they can be used as reliable guides to different stages of illness.

Crucially, biomarkers are needed that span the critical phase before symptoms are apparent and early disease. To identify such biomarkers, cohorts are required not just of patients but also those likely to develop conditions. UCL researchers have extensive collections of families with known inherited forms of neurodegenerative conditions, who are much more likely to develop disease than the general population.

Important information will also come from a sample of the 1946 Birth Cohort. Considerable health and lifestyle information has been accumulated over many years – since birth – and this will allow changes on imaging or cognitive testing to be related to lifelong data sets.

The Centre will also integrate genetic and genomic studies. Genetic characterisation has the potential to add further levels of discriminatory information to identify at-risk patients or for understanding differences in responses to therapies.

Treatments

Early characterisation will only truly pay off if interventions can be found to limit the loss of brain tissue. The Centre will therefore also carry out early human trials of new interventions – a key bottleneck in the translational pathway.

The Centre will aim to test promising new leads, rapidly identify drugs suitable for testing in bigger trials, and explore novel preventive treatments in presymptomatic at-risk individuals. In the longer-term, the Centre will act as a focal point for collaborations with UCL's internationally leading basic scientists, promoting two-way flows of knowledge to drive forward the development of new remedies.

Although drug development in neurodegenerative conditions has been disappointing, there are reasons to be optimistic. Immunotherapy-based targeting of beta-amyloid and other features of Alzheimer's disease hold promise, while the work of Professor Mark Pepys (see companion volume on Translation and Experimental Medicine) hints at future possibilities. Encouraging progress is being made in rare conditions, such as prion disease and Huntington's disease. Potentially, the Centre can play a nationally and internationally significant role in accelerating the validation of new treatments, increasing the likelihood of success in phase III trials.

A further important role will be in training. The Centre will offer novel fellowships in neurodegeneration, for neuroscientists, for clinical academics and for engineers who will all focus on different aspects of the problem. The four-year fellowships will include an initial year in which fellows are exposed to a range of diseases and scientific specialities, before they specialise in their final three years.

With its unmatched range of scientific expertise and close clinical connections, UCL is uniquely placed to undertake this groundbreaking initiative. It has the potential to make a profound impact in an area where the potential benefits for people, and for society more generally, are almost immeasurable.

Bateman RJ *et al.* Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimer's Res Ther.* 2011;3(1):1

Schott JM, Bartlett JW, Fox NC, Barnes J. Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid Abeta1-42. *Ann Neurol* 2010; 68:825–34.

Freir DB *et al.* Interaction between prion protein and toxic amyloid β assemblies can be therapeutically targeted at multiple sites. *Nat Commun.* 2011;2:336.

Ridha BH *et al.* Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. *Lancet Neurol.* 2006;5:828–34.

SECTION 5

BRAINS AND BEHAVIOUR

As well as the physical environment, humans have to navigate the complex social space of human interactions. The brain both shapes and is shaped by these social interactions.

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Complex human behaviours depend on the brain's sophisticated neural engineering. The brain must also be flexible enough to develop, learn and adapt. Furthermore, humans are strikingly social animals: interactions with other people are therefore a significant influence on the brain and its development.

The developing brain

Abnormalities in brain development can lead to cognitive impairment. A common form of learning disability, Down syndrome, has been associated with trisomy 21 for more than 50 years, yet the links between chromosomal abnormality and symptoms have been difficult to establish.

Much insight has been provided by a mouse model of the condition, developed by **Professor Elizabeth Fisher** and Professor Victor Tybulewicz of the MRC National Institute of Medical Research. Professor Fisher and Professor Tybulewicz are contributing to a new London Down Syndrome Consortium, led by **Dr Andre Strydom** and supported by a £2.5 million Strategic Award from the Wellcome Trust. The interdisciplinary team, which also includes UCL's **Professor John Hardy**, Professor Dean Nizetic (Queen Mary, University of London) and Professor Annette Karmiloff-Smith (Birkbeck College), will explore the origins of the cognitive deficits seen in individuals with Down syndrome, as well as their increased risk of dementia.

While childhood development has been extensively studied for decades, the critical period around adolescence and the transition to adulthood has been relatively neglected.

The brain undergoes profound changes after birth, reflected in the emergence of increasingly sophisticated behaviours. While childhood development has been extensively studied for decades, the critical period around adolescence and the transition to adulthood has been relatively neglected. **Professor Sarah-Jayne Blakemore** and colleagues have done much to identify the neurobiological basis of behavioural changes, particularly in social cognition (see page xx).

In autistic spectrum disorders, social skills development is highly abnormal. The exact nature of autism remains unclear and, as **Professor David Skuse** has pointed out, shifts in diagnostic criteria could influence the support provided to vulnerable young people (see page xx). Furthermore, he suggests, autism is best seen as the extreme of a continuum. Less severe deficits in social and language skills may predispose to disruptive behaviour in young children, with inevitable impact on education and well-being.

Dr Eamonn McCrory and **Professor Essi Viding** have explored how behavioural traits in young people are linked to emotional brain structures such as the

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amygdala. One strand of research has examined amygdala activity in children with conduct disorder and 'callous-unemotional' traits – a seeming disregard for the feelings of others (see page xx). A second focus is on children who have suffered or been exposed to violence in the family home.

Family violence is generally hidden from view, but up to 16 per cent of children may experience direct physical abuse and up to 25 per cent witness violent acts between their care-givers. As well as the initial distress, the experience significantly raises the risk of later mental health problems such as anxiety and post-traumatic stress disorder.

Physically abused children appear to be particularly sensitive to signs of anger, which in turn is associated with heightened levels of anxiety. In functional imaging studies of 20 children exposed to family violence, but with normal levels of anxiety, activity in the amydala and anterior insula was abnormally high on exposure to angry faces (but not to faces showing other emotions such as sadness). Furthermore, the degree of activation correlated with the extent of exposure to family violence[70].

In healthy adults, the amydala and anterior insula are known to be part of a network that detects threat and anticipates pain. Activity in these regions is particularly high in individuals with anxiety disorder and in troops exposed to combat (but without any psychiatric conditions). Hence exposure to family violence appears to leave children in a state of heightened 'threat readiness'. This may be advantageous in the short term, enabling them to avoid potentially violent situations, but over the longer term it leaves them at significantly increased risk of anxiety and other psychiatric conditions.

Social interactions

Social behaviours depend critically on empathy and 'theory of mind', appreciating that other people have needs, desires and motivations.

With Dr Tania Singer, now at the University of Zurich, Professor Chris Frith has explored the neurobiological basis of empathy and fairness. Seeing someone else in pain, for example, which can trigger feelings of empathy, is characterised by activity in the brain's pain pathways, though not those associated with the sensory experience of pain[71]. Hence observers genuinely 'feel' the pain of others.

Notably, though, these responses can be modulated by our feelings towards others. When brain responses were assessed after an economic game, the strength of responses was lower when pain was inflicted on those who had been felt to be playing unfairly[72]. Indeed, an associated increase in activity in reward areas correlated with expressed wishes for revenge – a signature of Schadenfreude in the brain.

Such findings suggest that humans have an innate sense of fairness, a characteristic repeatedly seen in economic games where people distribute sums in ways that, contrary to economic models, do not simply maximise their own gains. In work with Masahiko Haruno in Kyoto, Professor Frith has found that the amygdala is central to pro-social attitudes[73]. Among a group of pro-social participants, the greater the perceived unfairness of distribution, the greater the activity in the amygdala.

Furthermore, similar responses were seen when participants carried out a challenging cognitive test, suggesting that they were automatic rather than calculated. This challenges the idea that automatic responses are typically selfish and need to be overridden by the 'thinking brain', the prefrontal cortex.

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TWO HEADS ARE (USUALLY) BETTER THAN ONE

Joint decision-making is a good idea – but only when certain important conditions are met.

It may seem self-evident that sharing of information and collective decision-making is a good idea. It will certainly be important as humans face difficult and profound questions requiring collaborative action. A study carried out by **Dr Bahador Bahrami**, **Professor Chris Frith** and colleagues does indeed suggest that two heads are, in general, better than one – but sometimes performance is actually made worse by joint decision-making.

The research was based on a simple paradigm in which pairs of participants were presented with a difficult perceptual test. The participants could share varying amounts of information, in order to test a range of possible models of joint decision-making. The models differed in how much information was shared between participants, such as their confidence in their choice, and how much feedback they received about their decisions.

Overall performance was best when participants communicated their degree of confidence about their answers. However, when the sensitivity of one participant was artificially reduced by introduction of 'noise' into the visual image, performance actually dropped below that achieved by the superior partner. So, under these circumstances, two heads were definitely not better than one.

The collective model involves both communication and feedback learning. In further experiments, the researchers found that communication, as might be expected, was essential for high performance but, surprisingly, explicit feedback was not. Even though they were not aware of it, pairs communicating their uncertainty performed better.

The results suggest that a cooperating pair can outcompete an individual, if they share information and, importantly, one of them is not particularly poor at the task being undertaken.

This is notable, as past studies of groups have found that they are rarely as good at decision-making as the highest-performing individual members of the team. Many ideas have been put forward to explain why groups underperform, from 'social loafing' to 'groupthink'. This study suggests that, by contrast, when the validity of shared information cannot be checked, ordinary decision-making strategies may automatically become suboptimal.

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THE BRAIN AND BAD BEHAVIOUR

Neuroscientific techniques are being used to identify different subgroups of children with conduct problems.

Conduct problems can seriously disturb children's education (and that of their peers), and raise the risk of longer-term behavioural problems with significant personal and public health impact. The neurobiological basis of conduct disorder is beginning to be unravelled, and **Professor Essi Viding** and **Dr Eamon McCrory** believe that a subgroup showing distinct 'callous/unemotional' traits may exist – with important implications for treatment.

Children scoring highly on measures of callous/unemotional traits lack empathy. They may behave cruelly and typically show little remorse, and their behaviour is not swayed by usual threats and punishments. There is already some evidence that they represent a distinct subgroup – twin studies, for example, suggest that such traits are markedly more heritable than conduct problems in general.

Signatures of behavioural abnormalities can also be seen in the brain. In particular, children with conduct problems and callous/unemotional traits typically show reduced activation of the amygdala, part of the brain's emotional system, when shown images of fearful (but not sad) faces. This effect, also seen in adults with psychopathy, implies a reduced ability to respond to fear in people's faces.

Recently, Professor Viding and Dr McCrory examined the response of boys with conduct problems in tests based on more complex social scenarios that required processing of other people's thoughts or emotions. Brain responses to other people's thoughts were the same in boys with conduct problems as in their typical peers. However, they showed lower activation in the amygdala when responding to other people's emotions.

This suggests that boys with conduct problems know what other people think, but are less responsive to how other people feel. Within the group of boys with conduct problems, the degree of amygdala activation fell with increasing callous/unemotional scores.

The results therefore suggest that poor conduct is linked to atypical amygdala activity. In some children, the amygdala appears to be less responsive to other people's emotions. It is possible that children with callous/unemotional traits represent a distinct subgroup within the broader population of children with conduct problems. The findings also suggest that it may be more difficult to promote empathy in this group because they are intrinsically less able to generate emotional responses.

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Sebastian CL *et al.* Neural responses to affective and cognitive Theory of Mind in children with conduct problems and varying levels of callous-unemotional traits. *Arch Gen Psychiatr*. (in press)

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DIAGNOSIS UNCERTAIN

Is autism a discrete condition or at the extreme end of a continuum? The hotly debated answer could have important implications for both treatment and policy.

Autism research is a highly charged field. As well as the much-publicised controversies about its possible causes, a more subtle debate has centred on the precise categorisation of autism and related conditions. As the work of **David Skuse** and colleagues indicates, the outcomes are of more than academic interest.

The definitions of autism and autistic spectrum disorders such as Asperger's have evolved over time but rest on assessment across a 'triad' of traits: abnormal social interactions, impaired language use in social situations, and a mixed bag of abnormalities including sensory sensitivities and stereotyped and repetitive behaviours.

Few would argue that this current diagnostic situation is satisfactory, but in the absence of well-established biological markers, categorisation inevitably means attaching labels to particular constellations of symptoms. In psychiatry, standardised labelling is achieved primarily through so-called DSM guidelines. Currently being revised, the latest DSM guidelines sweep away existing categories, leaving a far more narrowly defined 'autistic spectrum'.

The debate touches upon both theory – what exactly is 'autism' – and practice: what happens if new diagnostic criteria are applied? Professor Skuse's work touches upon both issues.

His argument is that autism represents one end of a spectrum, rather than being a discrete, separable entity. Furthermore, insisting that a diagnosis of autism must include repetitive behaviours, as the latest DSM guidelines do, would exclude many children with significant social communication and language difficulties.

In support of this view, his work with the Bristol-based Avon Longitudinal Study of Parents and Children (ALSPAC) cohort and in London has revealed that poor conduct in primary school is often linked to undiagnosed social communication and language deficits. Moreover, the biological evidence also points to a link between autism and more general abilities. Research on the ALSPAC cohort has shown a clear association between an autism risk allele and social and language skill deficits in a general population.

While the academic debate rages, the social consequences could be considerable. Unrecognised social and language skill deficits are likely to be holding back the education of numerous young children. Restricting diagnoses still further could mean even fewer children receive the specialist help they need to overcome their problems.

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St Pourcain B *et al.* Association between a high-risk autism locus on 5p14 and social communication spectrum phenotypes in the general population. Am J Psychiatr. 2010;167:1364–72,

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BRAIN CHANGER

Extensive rewiring of the brain occurs during adolescence, with profound implications for social interactions.

As well as adult behaviour, psychologists have long been fascinated by childhood, when many interesting aspects of behaviour first appear. Between the two, however, is the sometimes troubling period of adolescence, a time of profound change that has come under far less scrutiny. **Professor Sarah-Jayne Blakemore**'s group is redressing the balance, aiming to relate changes in the behavioural and emotional development of adolescents to the dramatic remodelling going on in their brains.

Adolescence is marked by significant changes in both grey matter and white matter, and by considerable new synapse formation and synaptic pruning. Externally, young people change profoundly as they make the transition to adulthood – redefining relationships with parents, forming stronger bonds with peers, and generally asserting their own independence. At the heart of these changes are shifts in social relationships.

Alongside structural remodelling, Professor Blakemore's functional imaging studies have revealed significant changes during adolescence. For example, although both adults and adolescents used broadly similar neural circuits when thinking about people's intentions, the regions of these circuits activated shifted noticeably between adolescence and adulthood.

Other studies examined the ability to switch between externally prompted and internally generated thoughts, as well as resistance to distraction. While the latter increased gradually with age, the ability to switch between internal and external viewpoints jumped markedly at adolescence. Furthermore, the brain areas pressed into action did not correspond exactly to those showing structural changes, suggesting that the differences reflected more than just structural maturation of brain tissue.

Interesting differences were also seen when processing of 'basic' emotions (disgust, fear) was compared with that of 'social emotions' (guilt, embarrassment) in adolescents and adults. Both the areas activated and functional connections differed in the two groups. And while theory of mind is generally assumed to have emerged by around age 4, tests examining the ability to adopt the viewpoint of others showed clear improvements with age during adolescence.

Collectively, the results hint at complex changes in brain function during adolescence, significantly affecting social interactions. As well as feeding into important areas such as education, such work may also shed light on psychological and psychiatric disorders, most of which first appear during adolescence.

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Emotional expressions are very ancient, and hard-wired into the brain

Sound patterns

Vision is one way in which we gain insight into the emotional state of others, but speech can also convey meaning. And other sounds we make, from shrieks of laughter to sighs of despair, also reveal our state of mind.

In the 1950s, Professor Paul Ekman famously confirmed that facial expressions of emotions were shared across cultures. Working with Professor Ekman, Dr Sophie Scott has identified a similar phenomenon with auditory emotional traits[74].

Dr Scott looked at how two very different groups – westerners and an isolated Namibian tribe – responded to emotional utterances such as laughter, sighs and so on. The meaning of many expressions was common to both cultures, and each could correctly interpret the others' expressions. For some, though, meanings did not travel – the Namibians found western sighs ambiguous for example.

Interestingly, the culturally common expressions were mostly associated with basic negative emotions, such as disgust or fear. More positive expressions (with the exception of laughter) tended to be more culturally specific. Possibly, positive expressions may develop as a way of binding groups together and excluding outsiders. The results imply that emotional expressions are very ancient, and hard-wired into the brain.

Dr Scott has also explored the brain processing underlying emotional encoding in speech. When transcranial magnetic stimulation was used to temporarily disable brain areas involved in emotional responses to visual stimuli, participants could still recognise a speaker's identity, but struggled to identify the emotion being conveyed[75]. Hence the same brain areas appear to be involved in extracting emotional information across a range of sensory systems.

Non-verbal communication

Communication is not just based on language – multiple other systems come into play when we communicate in person. In sign language, physical gestures are integral to communication. Neuroscientific studies of sign language are relevant to signing, but also shed more general light on how the brain handles language.

Using functional imaging and other techniques, **Dr Mairead MacSweeney** and colleagues have shown that sign language and spoken languages are processed similarly in the brain, though there are some notable differences[76]. Ultimately the research should help children born profoundly deaf, who generally find it difficult to learn to read.

Dr MacSweeney's research is part of a large programme of research falling under the umbrella of the Deafness, Cognition and Language (DCAL) Centre, the largest of its kind in Europe. Led by **Professor Bencie Woll**, its main aims are to understand how communication is shaped by deafness and use of sign language, and how deafness and early language experience impact on cognition. Strikingly, as **Professor Gary Morgan** and colleagues have discovered, lack of sign language exposure can significantly affect the development of theory of mind skills in young deaf children[77].

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NEUROSCIENCE AND MENTAL HEALTH RESEARCH AT UCL

Component institutes

Most of the neuroscience and mental health research at UCL is carried out by groups in the **Faculty of Brain Sciences**, which comprises:

- UCL Division of Psychology and Language Sciences
- UCL Institute of Ophthalmology
- UCL Ear Institute
- UCL Institute of Neurology
- UCL Mental Health Sciences Unit
- UCL Institute of Cognitive Neuroscience

Dean: Alan Thompson

http://www.ucl.ac.uk/brain-sciences

The **Neuroscience Domain** encompasses researchers across the whole of the UCL School of Life and Medical Sciences and their work with colleagues outside the school.

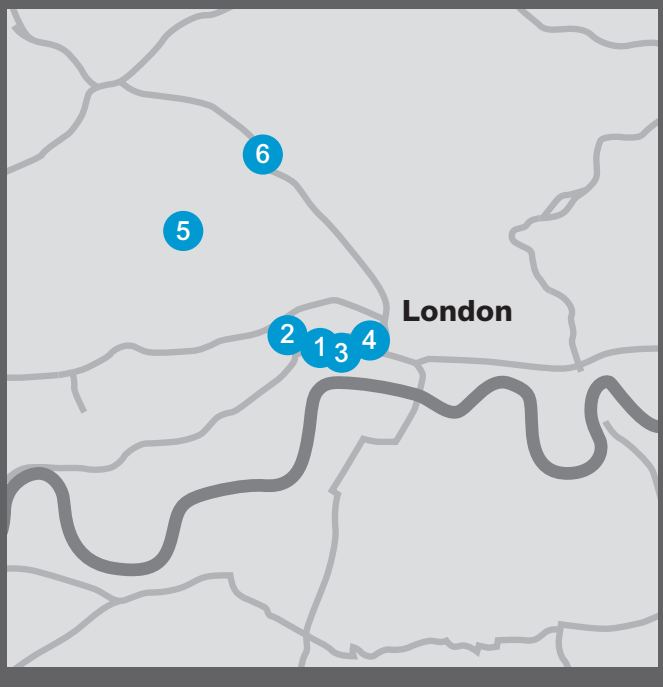
Domain Chair: Professor Trevor Smart

http://www.ucl.ac.uk/neuroscience

UCL in London

Researchers in the UCL School of Life and Medical Sciences occupy a range of buildings on UCL's central Bloomsbury Campus, at the nearby Royal Free Hospital and Whittington Hospital/Archway Campus sites, and other central London locations.

1 UCL Main Campus
2 UCL Hospital
3 Great Ormond Street Hospital and UCL Institute of Child Health
4 Moorfields Eye Hospital and UCL Institute of Ophthalmology
5 Royal Free Hospital and UCL School of Medicine
6 Whittington Hospital and Archway Campus



Partners

UCL School of Life and Medical Sciences works closely with a range of local, national and international partners. Of particular significance are its close links to local NHS bodies, collectively forming UCL Partners, one of just five UK Academic Health Science Centres. These links underpin UCL's NIHR Biomedical Research Centres at UCLH, the UCL Institute of Child Health (with Great Ormond Street Hospital) and the UCL Institute of Ophthalmology (with Moorfields Eye Hospital).

The School has also developed ties with nearby academic centres, including the London School of Hygiene and Tropical Medicine and Birkbeck College. As well as many joint research initiatives, the institutions also liaise at a strategic level.

With the MRC, Wellcome Trust and Cancer Research UK, UCL is also a founding partner of the Francis Crick Institute, led by Professor Sir Paul Nurse, which is due to open in 2015.

UCL also establishes wider partnerships in the UK, for example with Imperial College to set up the London Centre for Nanotechnology, and with Imperial, King's College London, the MRC and GlaxoSmithKline on the 'Imanova' clinical imaging initiative. The agreement was forged under the umbrella of the Global Medical Excellence Cluster (GMEC), a public–private partnership bringing together world-leading academic, health and industrial partners in South-East England.

As well as numerous international research collaborations, UCL has developed a strategic alliance with Yale University, the Yale–UCL Collaborative, to promote cross-fertilisation and joint ventures across education, research and application.

Support: Resource centres and platforms

The scale of UCL's research enables it to provide a range of technical infrastructure platforms to support research. These include outstanding facilities and technical expertise in **molecular and cellular imaging**, as well as **pre-clinical and clinical imaging**, and several sites specialising in **high-throughput sequencing and genome analysis**.

Other core platform technologies cover **small-chemical libraries**, **proteomics**, **biological services** and **transgenics**, and **informatics**. UCL researchers are also involved in numerous **biobanking** initiatives and **cohort studies**, providing access to extensive collections of materials and data.

UCL also provides **capital infrastructure** funding to enable labs to develop their equipment base.

For clinical research, a **Research Support Centre** provides access to essential support for work on people and patients, including liaison with the UCLH/UCL NIHR Biomedical Research Centre, UCL Clinical Trials Unit and UCLH/UCL Clinical Research Facility.

The **Translational Research Office** works to promote the translation of research into therapies, techniques and products with therapeutic value.

www.ucl.ac.uk/platforms/

www.ucl.ac.uk/slms/research_support_centre

UCL Research Strategy

The UCL Research Strategy calls for a transformation of the understanding of the role of our comprehensive research-intensive university in the 21st century.

In addition to highlighting the need to nurture and celebrate individual curiosity-driven research, the strategy sets out for UCL an innovative cross-disciplinary research agenda – designed to deliver immediate, medium- and long-term benefits to humanity.

UCL will marshal the breadth of its expert perspectives, in order to address issues in their full complexity and contribute to the resolution of the world's major problems. Its key aims are to:

- continue to foster **leadership grounded in excellence** in discipline-based research
- expand the distinctive **cross-disciplinarity** of our research, collaboration and partnerships
- increase the **impact** of our global university's research, locally, regionally, nationally and internationally.

Research income

'Live' grants as at 1 September 2011

NIHR and other UK Government	£177.1m
MRC	£194.6m
Other UK Research Councils	£83.3m
UK charities	£500.4m
Commercial (UK and international)	£53.6m
EU	£78.4m
Other international, inc. NIH	£62.6m
Other	£14.7m
Total	**£1164.7m**

Figures refer to research within the UCL School of Life and Medical Sciences.
NIHR: National Institute for Health Research; MRC: Medical Research Council;
NIH: National Institutes of Health.

Sponsors of research

We are grateful to all the individuals and organisations who support research in the UCL School of Life and Medical Sciences.

Abbott France, Abbott Laboratories, Ablynx NV, Academy of Medical Sciences, Action Medical Research, Action on Hearing Loss, Adam Dealy Foundation, Against Breast Cancer, Age UK (Formerly Research Into Ageing), Agennix AG, Aims 2 Cure, Alcohol Education and Research Council, Alder Hey Children's NHS Foundation Trust, Alexion Pharmaceuticals, Allergan Inc., Alpha-1 Foundation, Alzheimer's Society, Alzheimer's Research UK, Amyotrophic Lateral Sclerosis Association, Anatomical Society of Great Britain & Ireland, Anna Freud Centre, Anthony Nolan Bone Marrow Trust, Apatech Ltd, Apitope Technology (Bristol) Ltd, Aqix Ltd, Argonne National Laboratory, Ark Therapeutics Ltd, Arthritis Research UK, Arts and Humanities Research Council, Assisted Conception Unit, Association for International Cancer Research, Association Francaise Contre les Myopathies, Association Monegasque Contre Les Myopathies, Association of Coloproctology of Great Britain and Ireland, Asthma UK, Astra Zeneca (UK) Ltd, Ataxia UK, Autonomic Disorders Association – Sara Matheson Trust, AVI BioPharma Inc., AXA Research Fund, Bachmann-Strauss Dystonia and Parkinson Foundation, Baily Thomas Charitable Trust, Baily Thomas Charitable Trust, Barts and The London Charity, Batten Disease Family Association, Baxter Healthcare Corp., Bayer – AG, Bayer SAS, Big Lottery Fund, Bill & Melinda Gates Foundation, Biochemical Society, Biocompatibles Ltd, Biogen, Biogen Idec Inc., Biomarin Pharmaceutical Inc., Biorex R&D, Biotechnology and Biological Sciences Research Council, Birkbeck College, Biss Davies Charitable Trust, Boehringer Ingleheim, Bone Cancer Research Trust, Brain Research Trust, Breast Cancer Campaign, Bristol Myers Squibb, British Academy, British Council for Prevention of Blindness, British Heart Foundation, British HIV Association, British Lung Foundation, British Medical Association, British Neurological Research Trust, British Orthodontic Society, British Pharmacological Society, British Psychological Society, British Retinitis Pigmentosa Society, British Skin Foundation, British Society for Haematology, British Tinnitus Association, British Urological Foundation, BUPA Foundation Medical Research Charity, Burdett Trust for Nursing, Burroughs Wellcome Fund, Cambridge University Hospital NHS Foundation Trust, Camden and Islington Health Authority, Canadian Institutes of Health Research, Cancer Fund, Cancer Research Institute USA, Cancer Research UK, Carbon Trust Ltd, Carl Zeiss Surgical GMBH, Celera Corp., Cell Medica Ltd, Centocor Inc., Central and East London CLRN, Central Research Fund, Cephalon Inc., Charles Wolfson Charitable Trust, Chemel AB, Child Growth Foundation, Child Health Research Appeal Trust, Children Living with Inherited Metabolic Diseases (CLIMB), Children With Cancer UK, Children's Brain Diseases, Children's Cancer and Leukaemia Group, Children's Liver Disease Foundation, Children's Research Fund, Children's Trust, Chordoma Foundation, Chronic Fatigue Syndrome Research Foundation, Chronic Granulomatous Disease Trust, Chugai Pharma Europe Ltd, Cincinnati Children's Hospital Medical Center, Circulation Foundation, CLEFT – Bridging The Gap, Clement Wheeler Bennett Trust, CMT UK, Cobra Bio-Manufacturing PLC, Cochlear Research and Development Ltd, Coda Therapeutics Inc., Cogent (Holdings) Ltd, Colgate-Palmolive Europe, College of Optometrists, Colt Foundation, Creating Resources for Empowerment and Action Inc., Cure Parkinson's Trust, Cure PSP – Society for Progressive Supranuclear Palsy, Cyberonics Inc., Cystic Fibrosis Research Trust, Cystinosis Foundation Ireland, Cystinosis Research Network Inc., David and Elaine Potter Charitable Foundation, Davis Schottlander & Davis Ltd, Deafness Research (Formerly Defeating Deafness), Defense Advanced Research Projects Agency, Department for Children, Schools and Families, Department for Education and Skills, Department for International Development, Department of Health, Department of Health and Human Services, Department of Trade and Industry, Dermatitis and Allied Diseases Research Trust, Deutsche Forschungsgemeinschaft, Diabetes Research and Wellness Foundation, Diabetes UK, Diagenode SA, Doctors Laboratory, Dowager Countess Eleanor Peel Trust, Duchenne Parent Project, Dystonia Medical Research Foundation, Dystrophic Epidermolysis Bullosa Research Association, East Midlands Specialised Commissioning Group, Economic and Social Research Council, Edinburgh University, Edmond J Safra Philanthropic Foundation, Effort – Eastman Foundation, Efic, Eisai (London) Research Laboratories Ltd, El.En. S.p.A, Elan Pharmaceuticals Ltd, Eli Lilly and Co. Ltd, Emergency Nutrition Network, Engineering and Physical Sciences Research Council, Epic Database Research Company Ltd, Epilepsy Action, Epilepsy Research UK, Eular – European League Against Rheumatism, Eurocoating S.P.A, European and Developing Countries Clinical Trials, European Association for the Study of Liver, European Commission, European Huntington's Disease Network, European Organisation For Research and Treatment of Cancer, European Orthodontic Society, European Parliament, European Respiratory Society, European Society for Immunodeficiencies, Eve Appeal, Experimental Psychology Society, F Hoffmann La Roche Ltd, Fidelity Foundation, Fight For Sight, Fondation de France, Food Standards Agency, Foundation for Fighting Blindness, Foundation for Liver Research, Foundation for the Study of Infant Deaths, Foundation Leducq, Frances and Augustus Newman Foundation, Frost Charitable Trust, Fundacao Bial, Gatsby Charitable Foundation, Gen-Probe Life Sciences Ltd, Genentech Inc., General Charitable Trust of ICH, General Medical Council, Genethon, Genex Biosystems Ltd, Genzyme Corp., Gilead Sciences Inc., GlaxoSmithKline, Glaxosmithkline (China) R&D Co. Ltd, Global Alliance for TB Drug Development, Government Communications Planning Directorate, Great Britain Sasakawa Foundation, Great Ormond Street Hospital Charity, Great Ormond Street Hospital Special Trustees, Grifols UK Ltd, Grovelands Priory Hospital, Grunenthal GMBH, Guarantors of Brain, Guide Dogs for the Blind Association, Gynaecological Cancer Research Fund, H J Heinz Co. Ltd, Harbour Foundation, Health and Safety Executive, Health Foundation, Health Protection Agency, Healthcare Commission, Healthcare Quality Improvement Partnership, Heart Research UK, Helpage International – Africa Regional Development, Henry Smith Charity, Hestia Foundation, High Q Foundation, Histiocytosis Research Trust, Hospital For Sick Children, Human Early Learning Partnership, Human Frontier Science Program, Human Genome Sciences Inc., Huntington's Disease Association, Ichthyosis Support Group, Illumina Cambridge Ltd, Imperial College Consultants Ltd, Imperial College of Science, Technology and Medicine, Inhibox Ltd, Institut de Recherche Servier, Institut Straumann AG, Instrumentarium Science Foundation, Intensive Care Society, International Association for the Study of Pain, International Balzan Foundation, International Child Development Programme, International Glaucoma Association, International Primary Care Respiratory Group, International Serious Adverse Events Consortium, International Spinal Research Trust, Ipsen Fund, Ipsen Ltd, Iqur Ltd, ISTA Pharmaceuticals, ITI Foundation, Jabbs Foundation, James S McDonnell Foundation, James Tudor Foundation, Janssen Pharmaceutica NV, Janssen-Cilag Ltd, Japan Society for the Promotion of Science, Jean Corsan Foundation, Jerini Ophthalmic Inc., John Templeton Foundation, John Wyeth & Brother Ltd, Johns Hopkins University, Johnson & Johnson Consumer Services EAME Ltd, Juvenile Diabetes Foundation, Katherine Dormandy Trust, Kay Kendall Leukaemia Fund, Kidney Research UK, Kids Company, Kids Kidney Research, King's Fund, King's College London, Legal and General Assurance Society Ltd, Leonard Cheshire Disability, Leukaemia and Lymphoma Research, Leverhulme Trust, Lincy Foundation, Linkoping University, Linnean Society of London, Lister Institute of Preventive Medicine, Liver Group, London Borough of Camden, London Deanery, London School of Hygiene and Tropical Medicine, Lowe Syndrome Trust, Lowy Medical Research Institute, Ludwig Institute for Cancer Research, Lund University, Lupus UK, Lymphoma Research Trust, Macmillan Cancer Relief (UK Office), Macular Disease Society, Marc Fisher Trust, Marie Curie Cancer Care, Mars Symbioscience, Mary Kinross Charitable Trust, Mason Medical Research Foundation, Matt's Trust Fund for Cancer, Maurice Hatter Foundation, Max Planck Institute for Molecular Genetics, Max Planck Institute of Biology and Ageing, Medac GmBH, Medical Research Council, Medical Research Council of Canada, Medical Research Foundation, Melford Charitable Trust, Mend Central Ltd, Meningitis Research Foundation, Meningitis Trust, Merck Ltd, Merck Serono, Mermaid, Michael and Morven Heller Charitable Foundation, Michael J Fox Foundation for Parkinson's Research, Middlesex Hospital Special Trustees, MIND, Mologic Ltd, Monument Trust, Moorehead Trust, Moorfields Eye Hospital (LORS), Moorfields Eye Hospital Development Fund, Moorfields Eye Hospital Special Trustees, Moorfields Hospital NHS Foundation Trust, Motor Neurone Disease Association, Moulton Charitable Trust, Mr and Mrs Fitzpatrick, MRCP(UK), MSS Research Foundation, Multiple Sclerosis International Federation, Multiple Sclerosis Society of Great Britain and Ireland, Mundipharma Research Ltd, Muscular Dystrophy Association, Muscular Dystrophy Campaign, Myasthenia Gravis Association, Myeloma UK, National Association for Colitis and Crohn's Disease, National Brain Appeal, National Cancer Institute, National Centre for Social Research, National Centre for the

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