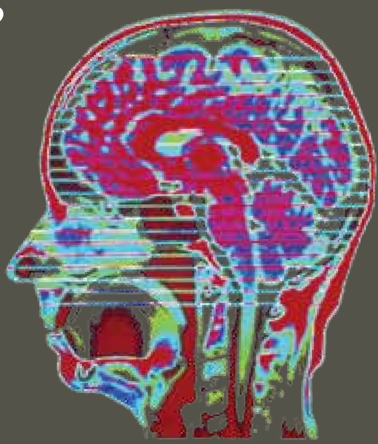
Portfolio Review

Human Functional Brain Imaging 1990–2009



September 2011

wellcome trust

Acknowledgements

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The views expressed in this report are those of the Wellcome Trust project team, drawing on the evidence compiled during the review. We are indebted to the independent Expert Group and our industry experts, who were pivotal in providing the assessments of the Trust's role in supporting human functional brain imaging and have informed 'our' speculations for the future. Finally, we would like to thank Professor Randy Buckner, Professor Ray Dolan and Dr Anne-Marie Engel, who provided valuable input to the development of the timelines and report.

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Contents

Overview and key findings

Key abbreviations used in the report			
CT	computed tomography	MEG	magnetoencephalography
BCNI	Behavioural and Clinical Neuroscience Institute	MR	magnetic resonance
BOLD	blood oxygenation level dependent	MRC CBU	MRC Cognition and Brain Sciences Unit
BOLD-fMRI	blood oxygenation level dependent fMRI	MRI	magnetic resonance imaging
EEG	electroencephalography	NMR	nuclear magnetic resonance
EPSRC	Engineering and Physical Sciences Research Council	NIRS	near-infrared spectroscopy
FIL	Functional Imaging Laboratory	PET	positron emission tomography
fMRI	functional magnetic resonance imaging	SPECT	single photon emission computed technology
FMRIB	Oxford Centre for Functional MRI of the Brain	SPM	statistical parametric mapping
GABA	gamma-aminobutyric acid	TMS	transcranial magnetic stimulation
GE	General Electric	WTCN	Wellcome Trust Centre for Neuroimaging

"And that is why it is big science because we have to get this population together, working in the same environment."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

1. The Wellcome Trust has provided substantial funding for neuroscience and mental health research. Much of its funding over its history has been directed to neuroscience in the quest to understand the brain and find improved approaches for treating brain and mental health disorders.

2. Within its neuroscience funding portfolio, and particularly since the early 1990s, the Trust has provided significant funds for the research and development of imaging techniques to help understand brain function and cognition. Brain imaging techniques fall into two broad categories: structural imaging and functional imaging (Figure 1). Structural imaging enables the non-invasive analysis of the anatomy of the human brain and is used in the diagnosis of disease and brain injury. Functional imaging enables the non-invasive analysis of brain function, using direct and indirect measures of neural activity to show the living human brain at work. For the most part, functional imaging is used as a research tool in cognitive neuroscience to determine when and where neuronal activity in the brain is associated with a particular cognitive task. Both of these brain imaging techniques have their own advantages and each provides different information about brain structure and function. As a consequence, more and more scientists are conducting studies that merge two or more of these brain imaging techniques. In this report, we focus on human functional brain imaging.

3. Between 1990 and 2008, the Trust committed £114 million to human functional brain imaging research, accounting for around 2 per cent of its total funding commitment.

4. In late 2009 and 2010, the Trust conducted a major retrospective study of the key breakthroughs in the field of human functional brain imaging over the past 20 years, attempting to identify its role within this. As in any review of the outcomes of research, an intrinsic challenge for a funder – particularly one supporting basic and fundamental research – is to understand its role among the plethora of influences and factors that are involved in shaping and delivering research. Indeed, to attempt to attribute breakthroughs and landmarks in the field solely to an event, researcher and/or funder is to take an improbable view of the way in which science and knowledge progress. To counter this, with the support of independent experts in the field, we have attempted to identify where the Trust is thought to have played a significant and influential part in the field, but we by no means claim to have been the only influence.

5. We also wanted to use this review in a formative way, to inform future funding strategy; therefore, this review brings expert reflections on past developments and crucial breakthroughs together with views on remaining challenges and future opportunities for research in human functional brain imaging – for the Trust, for other funders and for all those involved in this promising but technically challenging field.

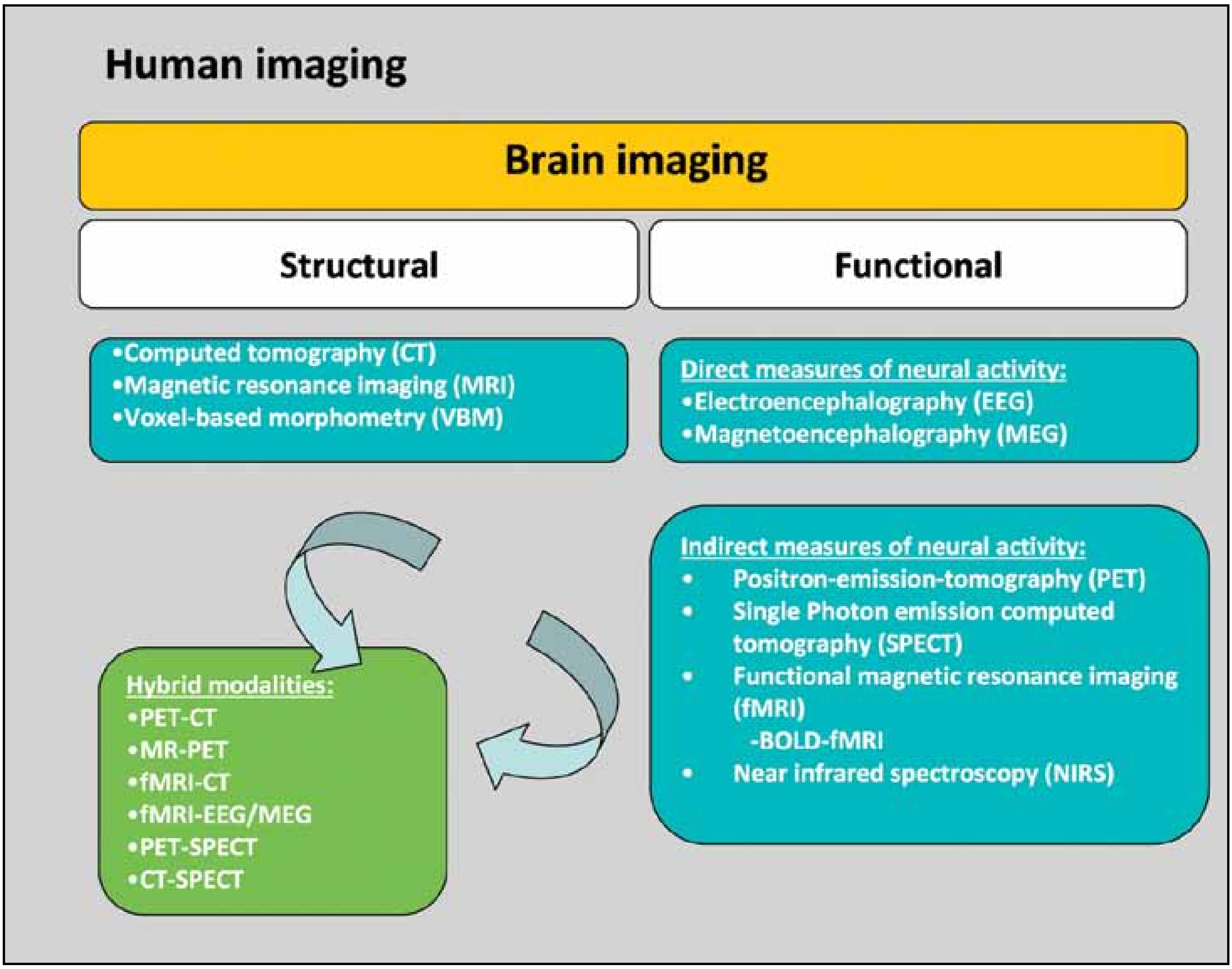
6. Given the key part that technology and industry have played in supporting the development of human functional brain imaging, we have incorporated the perspectives of industry experts into our analysis.

7. In comparison with 20 years ago, we know considerably more about how the living brain functions. In this review, overall, we found that much of the development of brain imaging as a field has emerged after collaborations across research disciplines: successes seem to have come particularly where research has taken place in dynamic 'hubs' where individuals from a range of disciplinary backgrounds and sectors have come together.

8. The most significant scientific breakthroughs to date have emerged after the application of technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), providing new perspectives in the cognitive neurosciences. These are beginning to be translated into diagnostic tools for neurodegenerative disorders (such as Alzheimer's disease), for treatment stratification and/or outcome assessment in epilepsy and stroke syndromes, and for an improved understanding of neuropsychiatric diseases such as schizophrenia. Progress in these areas has necessarily required the involvement of academia, industry, and clinical and health care practitioners.

9. In terms of the Trust's investments in human functional brain imaging research over the past 20 years, its contributions are thought to have been particularly notable in the following areas:

Figure 1 Overview of human brain imaging methods



- Providing a sustained stream of funding specifically for equipment, tools and technologies that have enabled key breakthroughs in brain imaging to emerge.
- Providing long-term and sustained funding for multidisciplinary research hubs, such as the Wellcome Trust Centre for Neuroimaging (WTCN)[1] and the Behavioural and Clinical Neuroscience Institute (BCNI),[2] which have been vital to advancing this particular field.
- Supporting researchers in building independent research careers through training programmes and Fellowship funding. Several Trust-supported researchers are currently world leaders in the field and have contributed to some of its most important breakthroughs, including statistical parametric mapping, voxel-based morphometry, the application of computational models of brain activity to brain imaging time series, understanding the mechanisms responsible for pathological impulsive behaviours and the pioneering development of new technologies such as magnetoencephalography (MEG) (see the Landmarks in Human Functional Brain Imaging Timeline).[3]

10. The Timeline demonstrates how far we have come; however, our experts were keen to emphasise that there is some way to go. There was a general consensus that the field has reached a crossroads. Although there have been major advances in the field, current human functional brain imaging techniques are still primarily used as research tools. For these tools to have a significant impact upon clinical practice and the wider health of populations, greater integration between professions is required; researchers and scientists across disciplines and sectors need to consider research questions together and work to develop solutions.

11. More work is needed to develop new clinical diagnostic tools, such as tracers and molecular probes, and to further refine existing technologies such as PET/fMRI and their associated algorithms to enable routine, real-time brain imaging in diagnostic and treatment regimes.[4] Improvements are also needed in the technical delivery of imaging, particularly to support the analysis, standardised quantification and interpretation of imaging data.

12. In summary: with the help of our experts, we have identified a range of specific and current challenges and opportunities for the functional brain imaging research and funding community. The Trust is already beginning to address some of these issues.

- **The benefits of a solution-based 'grand challenge' approach to human functional brain imaging research**
  One of the conclusions of this review is that if human functional brain imaging is to have a significant impact upon human health and wellbeing, the field needs to connect more closely with clinical settings. There is a need for researchers and scientists across disciplines and sectors to consider research questions together. The breadth of disciplinary backgrounds and skill sets required in brain imaging research lends itself to a strategic, 'solution-based' research approach, rather than the organic growth of the field that has occurred through responsive mode funding.

  An approach akin to the 'grand challenge' model – in which specific goals are identified and research organised to best deliver them – may provide a timely way to progress human functional brain imaging beyond the crossroads our experts described. Our experts suggested this might be facilitated through an international frontiers meeting on human functional brain imaging – bringing together people from across disciplines and sectors to work collaboratively to identify the current step limiting factors and work out what the goals and targets for brain imaging research could or should be.

1 The WTCN's funding was renewed in 2010 for approximately £7.5m and will commence in October 2011.

2 The BCNI's funding was renewed in October 2010 for approximately £3.5m. The Wellcome Trust's contribution was approximately £1.5m.

3 This timeline provides a historical overview of key developments and landmarks that assisted in the development of the field of human functional brain imaging. In the most recent two decades, the emphasis is on the contributions of the Wellcome Trust. A more extensive timeline is given in Annex E.

4 A tracer (radiotracer) is a compound that includes a radioactive atom or isotope that is used as an imaging agent in a branch of molecular imaging called nuclear medicine. Radioactive imaging agents are introduced into the body, where they accumulate in a target organ or attach to specific cells. They are then detected by an imaging device, which creates pictures of how the agent is distributed in the body (**www.molecularimagingcenter.org**).

"I think big questions are driven by people with big vision and understanding of the field. I think the problem one faces in imaging is that asking questions has been so closely linked to the tools. But the tools are really just catalysts for people being able to ask the right question. You constrain your question because you know what you can and can't measure."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

The Trust is currently in the process of organising a 2011 frontiers meeting focusing on the current status of brain imaging technology and the possibilities for the future; it is hoped this might reveal some of the 'challenges' for those in the field to work together to resolve.

- **Multidisciplinary and sector research hubs remain an important part of the future**
  There is no doubt that the future of functional brain imaging research requires continued input from a wide range of disciplines and sectors; the question is how to make this collaborative effort most effective at delivering real impact. The importance of physical research hubs and co-location of the key researchers, scientists and technicians remains crucial. In addition, there is a need to facilitate collaboration across and between research hubs to enable research findings and data to be shared and pooled where appropriate, to maximise the opportunities for collaboration and to minimise the potential for duplication.

"For this type of activity, which is very multidisciplinary and increasingly so…you almost need to have let's call it an institute, a grouping, that is put together with a common source of funding, which in effect can cut itself loose from the discipline boundaries, or subject specific boundaries, which isn't the way that universities and so on are organised."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

Training researchers remains key to the future. For researchers in the field of brain imaging, the value of experience of working with different contributory disciplines and across sectors should not be underestimated. Broad cross-disciplinary training is essential to ensure that a sufficient cadre of high-quality researchers are coming through to sustain researcher capacity.

The Trust is working to support a cadre of researchers in this field through its PhD studentship (which allows students to rotate across different laboratories and have exposure to a variety of disciplines and skills during a foundation training year), its Fellowship programmes and its recently introduced Investigator Awards. In addition, the availability of funding for infrastructure and equipment are essential for research hubs to thrive.

- **A need for novel approaches to funding human functional brain imaging research**
  Bringing together disciplines and research sectors has traditionally not been easy. Contributory factors include the disciplinary structures inherent in universities and research institutes in the UK and beyond, the fragmentation of funding sources, and the challenges of forging industry–academic collaborations. Supporting a more solution-based approach to human functional brain imaging research, involving a range of disciplines and sectors, calls for novel and tailored funding mechanisms that can transcend traditional funding barriers.

  New international approaches to funding this field could include: public–private partnerships; tripartite initiatives involving public and charitable funders, the pharmaceutical industry and the NHS; and common cross-funder financial pools. Independent funders, such as the Trust, could play a key part in brokering and facilitating interactions among the research leaders and funders to help ensure that the types of funding available are appropriate to the field.

- **Creating clinical applications and bringing functional brain imaging to the clinic**
  In addition to involving clinicians in discussions about the biggest research challenges, funders across sectors should do more to ensure the involvement of world-class clinicians in the evaluation of new functional brain imaging technologies. For real impact on patients, it is important that the clinical requirements for brain imaging techniques are shared with the basic neuroscience research community, so the real challenges in the diagnosis and potential treatment of brain disorders are shared with researchers and technicians in the best place to resolve them.

- **New developments in molecular imaging are needed to drive innovation in drug development**
  In addition to greater links with clinicians, our industry experts emphasised the opportunities for

brain imaging researchers to work more closely with industry to help improve current paradigms for drug development. There are important opportunities for funders such as the Trust to develop strategic partnerships with pharmaceutical companies, especially in the support of high-risk, high-reward research to revolutionise molecular imaging (e.g. to support the development of molecular probes), the availability of which is crucial to the continuing development and widespread use of molecular imaging methods and their translation to the clinic.

- **Multi-centre approaches and studies to improve diagnostic capabilities in the field**
  There is a need for more large-scale research on populations to increase sample sizes and the robustness of some imaging studies exploring specific brain structures and conditions. Comparing human functional brain imaging studies in a clinical setting can be challenging, partly because of methodological variability and the variability between human brains, and only very limited epidemiology-based work has been conducted to date in this field.

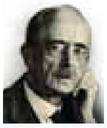
  By encouraging greater collaboration across research hubs (i.e. more multi-centre analysis), there might be opportunities to share datasets and research findings, thereby increasing sample sizes and thus future predictive and diagnostic potential.

- **A need to continue developing human functional brain imaging techniques through basic research**
  Our experts largely agreed that the future for the field will involve combining existing techniques and new technological innovations that could substantially improve existing imaging equipment, such as PET cameras and fMRI scanners, and extend capabilities in novel ways, such as by developing lightweight benchtop cyclotrons.[5] Specific technological challenges and research needs were highlighted; in the short term, these include improvements in quantification, sensitivity, temporal precision and spatial resolution for current scanning technologies. The development of broader ranges of radiotracers for the PET community is urgently needed and this, in turn, requires new approaches to the chemistry and biology.

- **Managing the social and ethical implications of brain imaging research**
  Key emerging challenges in the field of human brain imaging include reporting clinically relevant research findings to study participants and managing the increasingly large and complex datasets generated by research in this field. In neuroscience, as in other fields, much work is needed to build and sustain the infrastructure, tools and culture that are needed to underpin this. It remains crucial that we, as funders, work together with the research community and other key funders to address the issues of incidental findings and data protection.

Although this portfolio review demonstrated that much has been achieved in the field of human functional brain imaging in the past two decades, there is also a perception that there is much to be done, including the translation of these achievements for clinical benefit. The use of collaborations across disciplines, between funders and across sectors is thought to be the way forward.

5 A cyclotron is a machine used to accelerate particles. It is used to create the radionuclides, or tracers, required for PET.



1878
Blood flow and brain function linked

1924
Hans Berger records the first human electroencephalogram (EEG)

1931
Ernest Lawrence at Berkeley, California invents the cyclotron

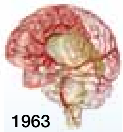
1932
Cockcroft, Walton and Rutherford split the atom

1946
Magnetic resonance phenomenon discovered

1950
First positron imaging device developed

1953
Brownell and Sweet (Massachusetts General Hospital, Boston) publish the use of positron coincidence counting for imaging the distribution of the positron emitter ^{74}As to delineate brain tumours

1955
Hammersmith cyclotron established to produce radioisotopes and to undertake neutron therapy of cancer and radiobiology research



1963
Brain blood flow linked with behaviour

1968–72
Magnetoencephalography (MEG) introduced

1870 | 1920 | 1930 | 1940 | 1950 | 1960 | 1970

1868
Mental chronometry introduced

1928
Paul Dirac theoretically predicts the positron

1931
Mallinckrodt Institute of Radiology, Washington University, founded

1938
First cyclotron solely for medicine and biology (Berkeley, California) commissioned

1948
UK MRC decides to establish the world's first hospital-based cyclotron at Hammersmith Hospital

1955
Brain blood flow studied with radioisotopes

1956
Infrared imaging introduced

1961
First single-plane PET instrument, the 'head-shrinker', developed at Brookhaven

1968 onwards
Single photon emission computed tomography (SPECT) developed for brain imaging

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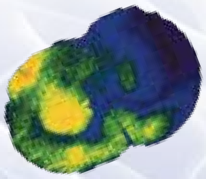
Landmarks in human functional brain imaging



1990
Blood oxygen level dependent (BOLD) contrast in MRI identified

Diffusion imaging introduced

1992
fMRI imaging using BOLD introduced

1994
First intraoperative use of MRI

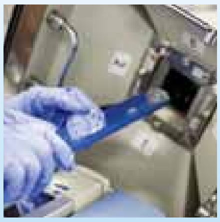
Image-guided surgery introduced

DuPont Merck Pharmaceutical's brain SPECT tracer, Neurolight®, approved

Functional Imaging Laboratory (FIL) at UCL founded

1996
Oxford Centre for Functional MRI of the Brain (FMRIB) founded

Combined CT–SPECT imaging introduced



1998
PET approved by Medicare

Scottish Funding Council Brain Imaging Research Centre (Edinburgh) founded

Cognition and Brain Science Unit refurbished (Cambridge)

2000
Longitudinal scanning intr

Voxel-based morphometry developed

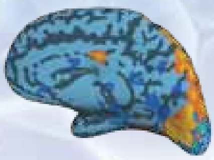
Hybrid PET–C developed

Brain–compu interface tech developed

SPECT imag DatSCAN™ (Healthcare) a in Europe

1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 200

1991
Functional MRI (fMRI) in humans introduced



KEY
Scientific advance
Funding development
Policy development

1992–95
Sensitivity of commercial MRI scanners improved

Early 1990s
SPECT used routinely in clinic

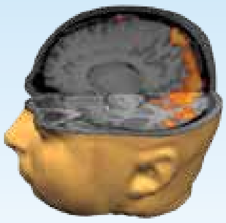
1994–95
Functional connectivity measures of evoked and intrinsic activity demonstrated

1995
FDA introduces PET guidelines

Wolfson Brain Imaging Centre (WBIC), Cambridge, founded

Johns Hopkins Center for Imaging Science established

1996
Event-related fMRI developed



1997
MRI-compatible PET scanner developed

1998
The software package Brain Voyager developed

1999
MRC Cyclotron Unit separates clinical and non-clinical research

Wellcome Trust lab for MEG established (Aston University, Birmingham)

Images: 1868 Frans Cornelius Donders/*Wellcome Library.* **1878** Sir Charles Sherrington/*Wellcome Library.* **1924** Hans Berger. **1928** Paul Dirac/*Ramsey et Musprat, courtesy AIP Emilio Segre Visual Archives.* **1963** The arteries of the brain/*Medical RF.com, Science Photo Library.* **1971–72** Sir Godfrey Hounsfield/*Corbin O'Grady Studio, Science Photo Library.* **1973** LightSpeed CT scanner/*Ilianski, Wellcome Images.* **1976** SPEC *Wellcome Images.* **1988** Statistical parametric mapping. **1990** Reperfusion, blood flow through brain/*Dr I M Macrae, Wellcome Images.* **1991** fMRI data superimposed on the brain showing visual cortex/*Mark Lythgoe and C* showing the visual cortex in yellow/*Mark Lythgoe and Chloe Hutton, Wellcome Images.* **2003** Diagram of multivariate pattern classification. **2003** Model of the brain. **2006** Wellcome Trust Centre for Neuroimaging.

Portraits: 1868 Frans Cornelius Donders, **1878** Sir Charles Sherrington, **1924** Hans Berger, **1928** Paul Dirac, **1931** Ernest Lawrence, **1932** John Cockcroft, Ernest Walton and Ernest Rutherford, **1938** Dor

1970
St Louis group measures regional cerebral blood flow and oxygen utilisation using carotid artery administrations of $^{15}O_2$ and $H_2{}^{15}O$

1973
PET invented

First images of the human brain metabolism recorded using $^{15}O_2$ at the MGH, Boston

MRI principles first described

1975–78
Jones et al. at Hammersmith use qualitative gamma camera imaging of inhaled $^{15}O_2$, $H_2{}^{15}O$ and $C^{15}O_2$ in a range of brain disorders

1977
Echo-planar imaging (EPI) developed

1979
Clinical MRI introduced

1980s
MRI applied routinely to clinical diagnostics

1981
^{18}FDG brain tumours – forerunner of today's clinical PET for oncology

1983
PET for brain receptor imaging first demonstrated

PET imaging of ^{18}F-L-DOPA in striatum of humans demonstrated

1984
McConnell Brain Imaging Centre (McGill, Montreal) founded

Pioneering PET-based tumour pharmacokinetic study reported

1988
Early image processing techniques developed

PET applied to cognitive studies

1980 — 1990

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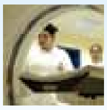
1971–72
X-ray computed tomography (CT) introduced

1973
Whole-body CT scanner marketed



1973–74
St Louis group develops quantitative PET

1976
^{18}FDG is imaged in human brain using SPECT

1978
Functional imaging with PET introduced

Commercial PET scanner available

1979
Quantitative regional cerebral oxygen utilisation and blood flow demonstrated at Hammersmith using PET and inhaled $^{15}O_2$ and $C^{15}O_2$

1982
MRI used to measure oxygen utilisation *in vivo*

1983
Commercial MRI scanner installed in Europe

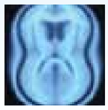
Laboratory of Neuroimaging founded (St Louis)

1986
A new cyclotron installed at Hammersmith for PET

1987
High axial resolution PET introduced

First brain SPECT tracer, Ceretec™ (Amersham), is developed

1988
Statistical parametric mapping (SPM) developed to analyse PET data



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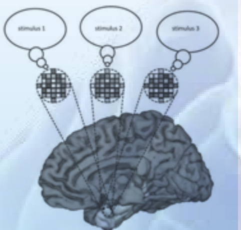
2000–03
Development of fluorophores for near infrared (NIR) imaging

2003
Multivariate pattern classification developed



2004
First human study of novel amyloid-imaging PET tracer, Pittsburgh Compound-B (PIB)

GSK establishes first clinical imaging centre (CIC) at Hammersmith Hospital for PET/MRI in drug development

Centre for Neuroimaging Sciences (CNS) founded (KCL, IoP and Maudsley)

UK's first 7-Tesla MR whole-body system established (Nottingham)

2006
FIL becomes Wellcome Trust Centre for Neuroimaging

2008
Ernst-Strüngmann Institute (ESI), Frankfurt, founded

New MRI scanner at WBIC (Cambridge)

Donders Institute for Brain, Cognition and Behaviour (DCCN), Nijmegen, established

…0 — 2001 — 2002 — 2003 — 2004 — 2005 — 2006 — 2007 — 2008 — 2009 — 2010

2000
FDG and other PET ligands announced safe by FDA

2001
MRC and Amersham fund cyclotron (Hammersmith)

Neurophysiological basis of the fMRI signal investigated

2003
Dynamic causal modelling developed

High Field Magnetic Resonance Centre (Tübingen) founded

2004
Alzheimer's Disease Neuroimaging Initiative launched

Foundation of the Brain Imaging Center (BIC), Frankfurt

PET decommissioned at the FIL

2005
fMRI scanner commissioned (CBU)

2007
Disorders identified using MEG

Simultaneous MR–PET demonstrated

Oxford MEG centre founded

SINAPSE initiative launched

2010
NIH Human Connectome Project launched

1931 Ernest Lawrence/*Nobel Foundation.* **1931** Mallinckrodt Institute of Radiology/*Courtesy of Washington University in St Louis.* **1932** John Cockcroft, Ernest Walton and Ernest Rutherford/*Getty Images.* …T exam of human brain/*Living Art Enterprises, Science Photo Library.* **1977** Sir Peter Mansfield/*Anne-Katrin Purkiss, Wellcome Images.* **1979** Digitally enhanced MRI of the human head/*Mark Lythgoe and Chloe Hutton,* …*Chloe Hutton, Wellcome Images*. **1992** fMRI imaging of the brain/*Wellcome Library.* **1992–95** MRI showing Moyamoya disease/*Wellcome Images.* **1996** Nano SPECT/CT imaging equipment/*Wellcome Library.* **1996** fMRI

…nald Cooksey and Ernest Lawrence (imglib.lbl.gov), **1971–72** Sir Godfrey Hounsfield, **1977** Prof. Sir Peter Mansfield FRS

1. Introduction and background

13. As part of moves to strengthen the Wellcome Trust's evaluation activity, in 2008 the Assessment and Evaluation team developed an approach to evaluate the impact of its funding at a macro, subject portfolio level. This report describes the second portfolio review, which was conducted in the second half of 2009 and focuses on the development of human functional brain imaging over the past 20 years and the role of the Trust within this landscape. The first portfolio review focused on human genetics from 1990 to 2009.[6]

14. Brain disease – including neurological, neurosurgical and psychiatric disorders – is responsible for an estimated 35 per cent of Europe's total disease burden and is a major component of the world's overall morbidity.[7] However, our knowledge of how the brain works and the processes and causes of brain diseases remains limited.

15. Phrenologists once believed they could understand the brain by examining the shape of the skull.[8] One of the major achievements of brain research in the latter part of the 20th century was the development of imaging techniques enabling us to capture images of the structure and function of the living brain. The development of functional brain imaging methods to understand the brain, map movement and function, and measure blood flow in humans has revolutionised neuroscience. It has given us a new understanding of the 'normal' emotional and behavioural circuitry of the brain, the consequences of which are now affecting the fields of clinical research and drug discovery. Using imaging techniques, researchers from across disciplines and sectors have developed new perspectives on brain-impairing conditions such as Alzheimer's disease, Parkinson's disease and stroke.

16. This makes the story of brain imaging particularly interesting. The progression of the field necessarily requires the input of researchers, engineers and technologists – a classic tale of the need for multidisciplinary research and scientists. The funding models for supporting research and technology are often not the same, however, and funding sources are different – and often competing. In this portfolio review, it has been interesting to reflect on what has worked well (and what has worked less well) in the past, and to draw lessons from this and consider the best approach to assure major advances in the future.

17. Since its inception in 1936, providing funding for neuroscience research has been one of the Trust's priorities. The first grant awarded in neuroscience – and, indeed, the first grant ever awarded by the Trust – was made in 1938 to Dr Otto Loewi.[9] Dr Loewi shared the 1936 Nobel Prize in Physiology or Medicine with Sir Henry Dale, one of the first Trustees.[10] Understanding the brain remains a key part of the Trust's strategy today.[11]

6 **www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtx063661.pdf**

7 Olesen J, et al. Consensus document on European brain research. J Neurol Neurosurg Psychiatry 2006;77 Suppl 1:i1–49.

8 Neuroscience: Science of the brain. British Neuroscience Association (2003)

9 The Wellcome Trust First Annual Report: 1937–1956

10 Tansey EM. The first Wellcome medical Trustees: Dale and Elliott and their early collaboration. J Physiol 1986;382:29P

11 **http://www.wellcome.ac.uk/About-us/Strategy/index.htm**

18. This review is both reflective and prospective and has three specific aims:

- to identify the **key landmarks and influences on the human functional brain imaging research landscape** over the past two decades (1990–2009)
- to consider the **key features of the Trust's impact** on this research landscape
- to consider the **future direction** of human functional brain imaging and identify where there may be opportunities for Trust strategy and funding.

To achieve these aims, we undertook four complementary streams of work (see Annex B for detail):

- **Landscape analysis**
  Including funding, policy and bibliometric analysis.
- **Narrative case studies**
  Used to provide key examples of major impacts of Trust funding for people working in, and breakthroughs in the science of, brain imaging.
- **An Expert Group**
  Convened to provide an independent view of key landmarks in the development of human functional brain imaging, to provide an independent view of the role and key impacts of the Trust, and to speculate on potential future directions.
- **Semi-structured interviews**
  Conducted with brain imaging experts working in industry to gather perspectives on the role of industry-based research and development and challenges for the future.

19. We intend to use this review to learn from our support of research to date and to inform potential future directions. In addition, however, we hope that this review is of value to other stakeholders – including funders – involved in supporting brain imaging research, both by highlighting where new and continued research is required and in guiding the selection of mechanisms and, potentially, policies to support research.

2. Human functional brain imaging today: the global research landscape

"[In this field] It is so important that you have a mixture of people that understand the physics as well as people who understand the biology and people who have the mathematical and software processing skills etc. to try and bring it all together."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

2.1 The global scene

20. Researchers in the USA have helped it become a world leader in brain imaging-related research; groups embedded in US institutions have dominated the field, particularly those at Harvard University, the University of California (UCLA), Massachusetts General Hospital, the National Institutes of Health (NIH), Stanford University, the University of Pittsburg and Washington University, St Louis.

21. Some of the most notable contributions to the field stem from these prominent groups, including: Marcus Raichle's group in Washington University, St Louis, where non-invasive imaging techniques have been developed to map the functional architecture of the living human brain; Arthur Toga's team at the Laboratory of Neuro-Imaging, UCLA, where pioneering mathematical and statistical techniques for quantifying the structure and function of the brain have been developed; and John Mazziotta's group at the UCLA Brain Mapping Centre, who are currently leading an international team of researchers to create the first comprehensive atlas of the structure and the function of the normal adult human brain.

22. Within the USA, the NIH is the primary source of funding for neuroscience research, with a total budget of over $4 billion per annum in 2006.[12,13] In 2000, the NIH established a funding institute devoted to developing and translating new imaging devices and other cutting-edge technologies: the National Institute of Biomedical Imaging and Bioengineering (NIBIB), which is the newest of the NIH institutes.[14]

23. Several key international and collaborative projects involving several research hubs are largely funded by the NIH, including the Neuroscience Blueprint and the Human Connectome Project – a $30m project that aims to use brain imaging technologies to map the circuitry of the healthy adult human brain. The NIBIB also works in partnership with the Howard Hughes Medical Institute to support Interdisciplinary Graduate Education[15] grants made in 2005, one of which was the University of Pennsylvania's integrated graduate training programme in clinical imaging and informational sciences.[16] In addition, the National Institute of General Medical Sciences supports many basic researchers who use imaging as a primary tool to elucidate the fundamental mechanisms of life.

24. Other US funding agencies that provide significant funding for brain imaging research include the Dana Foundation,[17] the Howard Hughes Medical Institute,[18] and several US-based charities, such as the James S McDonnell Foundation and MacArthur Foundation.

25. When considering other countries that have invested heavily in functional brain imaging research, Japan and Canada feature prominently. The NIH has developed several close links with neuroscientists in Japan through the US–Japan Brain Research Cooperative Program,[19] an agreement between the National Institute of Neurological Disorders and Stroke and the National Institute for Physiological Sciences, Okazaki National Research Institutes, Japan.

26. RIKEN Brain Science Institute (Japan)[20] includes the Laboratory for Advanced Brain Signal Processing,[21] which aims to develop novel ways of extracting and recognising functional connectivity and brain activity, which can be used to analyse electroencephalography (EEG), fMRI and near-infrared spectroscopy (NIRS),[22] as well as emerging technologies. The Functional Probe Research laboratory[23] – also part of RIKEN – has developed methods to monitor brain activity, behavioural features and pathogenesis in the brain using PET technologies.[24] RIKEN also sponsors the Neuroimaging Platform (NIMG-PF),[25] a network

12 officeofbudget.od.nih.gov/pdfs/FY10/Tabular%20Data.pdf
13 www.humanconnectomeproject.org/
14 www.nibib.nih.gov/
15 neuroscienceblueprint.nih.gov/
16 www.hhmi.org/grants/office/graduate/gradstudent/interfaces_opportunities.html#uop
17 www.dana.org/
18 www.hhmi.org/
19 grants.nih.gov/grants/guide/notice-files/NOT-NS-10-014.html
20 www.brain.riken.jp/en/about/index.html
21 www.riken.jp/engn/r-world/research/lab/nokagaku/bstyle/open/index.html
22 NIRS is a non-invasive technique used for imaging brain function.
23 www.riken.jp/engn/r-world/research/lab/cmis/func/index.html
24 RIKEN Center for Molecular Imaging Science
25 nimg.neuroinf.jp/modules/nimgdocs/index.php?docname=about_NIMGPF

that provides experimental data, methods of data analysis and tutorials to support people conducting neuroimaging research.

27. The National Research Council Canada[26] funds the Biomedical Technology cluster, including the Institute for Biodiagnostics (IBD), which uses advanced imaging to study neurological disorders. The IBD is spread over three sites: the Commercialisation Centre in Winnipeg and biodiagnostics and imaging laboratories at both Halifax and Calgary. The IBD's multidisciplinary approach and collaborations have led to nine spin-off companies and commercial support organisations.[27] The IBD in collaboration with the Winnipeg Health Science Centre has developed a technique, magnetic resonance spectroscopy imaging (MRSI), that improves visualisation of brain tumours; it can be used in radiosurgery and is entering pilot patient trials.[28] Furthermore, the IBD has a neuroscience research programme that develops imaging techniques to improve the diagnosis and treatment of neurological disorders. The programme involves work in the neuroimaging laboratory at the health science centre, as well as work at the Biomedical MRI Research Laboratory and the new Laboratory for clinical MEG in the Izaak Walton Killam Health Centre, which was announced in 2010.[29,30]

2.2 The UK

28. Within the UK, over time, a range of funders have provided significant funding for functional brain imaging research. These funders include the research councils (notably the Medical Research Council, the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, or EPSRC,[31] and the National Institute of Health Research), the Wellcome Trust, and several other medical charities, including the Stroke Association, Action Medical Research,[32] the UK Multiple Sclerosis Society,[33] the Parkinson's Disease Society of Great Britain,[34] the Brain Research Trust,[35] and the Alzheimer's Research Trust.[36]

29. Among brain imaging research funders in the past century, the UK Medical Research Council (MRC) has had perhaps the most pivotal role – establishing several key imaging units, including the MRC Cyclotron Unit at Hammersmith Hospital, London, and the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB). The MRC's decision to install the world's first hospital-based cyclotron unit at Hammersmith Hospital in 1948, established in 1955 (Timeline), helped pave the way for the development of PET.

30. In addition to helping to build research hubs, the MRC has supported several pioneers of brain imaging techniques in the UK, including several Nobel Laureates. Working in the Department of Physics, British physicist Sir Peter Mansfield managed to apply the principles of nuclear magnetic resonance (NMR) to clinical imaging – magnetic resonance imaging (MRI). Sir Peter and his team showed how the radio signals from MRI could be mathematically analysed, making their transformation into useful images possible. A medical diagnostic application was progressed further by the development of a rapid imaging technique called echo-planar imaging. The team presented their first human image (of Mansfield's abdomen) in 1978, and the first full MRI was described in 1979, turning it into a viable tool for medical imaging (Timeline). Sir Peter – along with Paul Lauterbur (who at the time was based at the University of Illinois) – was awarded the Nobel Prize for Physiology and Medicine in 2003 for this work.

31. The MRC also played a major part in supporting the development of computed tomography (CT) imaging (also known as 'CAT scanning'), which uses X-rays to create images of parts of the body. CT imaging builds up 3D images from large numbers of low-dose X-rays transmitted across the body. Sir Godfrey Hounsfield, an engineer at EMI Central Research Laboratories in Middlesex, and Professor Allan Cormack, a South African-born physicist, developed the technology of CT scanning. CT head and body scanners were tested separately in the early 1970s.

26 www.nrc-cnrc.gc.ca/index.html
27 www.nrc-cnrc.gc.ca/eng/ibp/ibd/about/index.html
28 www.nrc-cnrc.gc.ca/obj/ibd/doc/NRC-IBD_report.pdf page 13
29 www.nrc-cnrc.gc.ca/eng/ibp/ibd/about/research-groups/neuroscience.html
30 www.nrc-cnrc.gc.ca/eng/news/nrc/2010/03/15/meg-lab.html
31 www.epsrc.ac.uk
32 www.action.org.uk/
33 www.mssociety.org.uk/
34 www.parkinsons.org.uk/research/about-our-research.aspx
35 www.brt.org.uk/
36 www.alzheimers-research.org.uk/

32. Hounsfield and Cormack's work followed research at the MRC Laboratory of Molecular Biology, led by Sir Aaron Klug,[37] who in the early 1970s collated 'slices' – layered electron microscopy images – to form a detailed picture with depth. Sir Aaron combined conventional electron microscopy with the use of X-rays to enhance the resolution of images of proteins. Sir Godfrey and Professor Cormack shared the Nobel Prize in Physiology or Medicine in 1979. In 1982, Sir Aaron won the Nobel Prize in Chemistry. The development of the CT scanner has had a massive impact on diagnostic radiology, and its principles have been applied to other areas, including ultrasound imaging. The Hounsfield scale is still used as a quantitative measure of radio density used in evaluating CT scans.

33. While on sabbatical from Hammersmith Hospital, British physicist Professor Terry Jones worked with Professor Michel Ter-Pogossian and his team (Professor Edward Hoffman and Professor Michael Phelps) in the Mallinckrodt Institute of Radiology at the Washington School of Medicine while they were developing the first human PET scanner (1973). Professor Jones spent the second part of his sabbatical working with Professor Gordon Brownwell and Professor Charlie Burnham at the Massachusetts General Hospital, Boston. Both centres had established medical-hospital-based cyclotrons at the time. In Boston, at the Massachusetts General Hospital, Professor Jones – using positron-emitting radioisotope $^{15}O_2$ and the positron camera they had developed – undertook the world's first imaging of human brain metabolism. While at the MRC Cyclotron Unit, Professor Jones explored pre-PET clinical research studies, which provided the case for initiating PET in the UK and led to the introduction of PET at the MRC's Cyclotron Unit at Hammersmith Hospital in London in 1979. His emphasis on non-invasive techniques and the biological relevance of imaging signals has underpinned many methodological advances in the field of functional imaging.

34. The hub at Hammersmith has remained at the fore of international imaging research. The Hammersmith site is now home to the GlaxoSmithKline (GSK) Clinical Imaging Centre and Imaging Science Department (Imperial College London) and the MRC Clinical Sciences Centre, which includes the Biological Imaging Centre. In 2011, a public–private partnership was formed to assume responsibility for GSK's Clinical Imaging Centre. The partnership – between the MRC, Imperial College London, King's College London, University College London and GSK – creates a new model for academia, pharmaceutical and biotechnology organisations and aims to play a key part in the translation of biomedical research in the UK.

35. The Wellcome Trust's GlaxoSmithKline Translational Medicine Training Programme is also based on the Hammersmith Campus and provides PhD training for clinician scientists in experimental medicine, particularly clinical imaging. Three other current PhD programmes, based at the University of Cambridge, the University of Newcastle, and a Consortium of Scottish Clinical Medical Schools (the Universities of Aberdeen, Dundee, Edinburgh and Glasgow) involve clinical imaging.

36. Several other research hubs for functional and clinical imaging research have developed, particularly in the UK in the past two decades. Alongside the Hammersmith hub, the WTCN at UCL (formerly the Functional Imaging Laboratory, or FIL) has been key. Professor Richard Frackowiak project managed the establishment of the WTCN, which he directed from 1994 to 2002, with an initial £20m of Wellcome Trust funds in 1993. Researchers at the WTCN have been responsible for many of the key breakthroughs in our knowledge of the functional capabilities of the brain (see WTCN case study). Today, in 2011, under the direction of Professor Ray Dolan (Director, 2006–present), the WTCN is considered a world leader in brain imaging research and is a unique and valued resource for training and nurturing young scientists.

37. The FMRIB developed the FMRIB Software Library for image analysis. The FMRIB Software Library is freely available to researchers across the world and jointly leads the NIH-funded Connectome Project, which intends to provide a comprehensive connectional 'map' to define the substrate for brain functions.

37 www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Medicalimaging/index.htm

38. The BCNI in Cambridge, which is led by Professor Trevor Robbins (Director) and Ed Bullmore (Clinical Director), was established in 2005 and was initially funded through a joint MRC and Wellcome Trust grant worth approximately £4.8m (the Wellcome Trust's contribution was £2.4m). This funding was renewed in October 2010 with a grant of £3.5m (Wellcome Trust's contribution: £1.5m). Professor Robbins has had successive Wellcome Trust programme grants since 1990, which have involved significant components of functional brain imaging (Table 4, Annex C); his most recent grant commenced in March 2010 (see Trevor Robbins case study).

39. The MRC Applied Psychology Unit (renamed the Cognition and Brain Sciences Unit, or CBU) at the University of Cambridge, established in 1944, is another major brain imaging research hub. In 2005, the MRC invested approximately £1.7m to house an fMRI (3-Tesla) scanner and in 2007 invested a further £1.5m to install a MEG facility on the premises to enable its internationally competitive research to continue. In 2010, the Assistant Director of the MRC CBU, Dr Adrian Owen, was named as one of the UK's 100 most influential people in science in the Times Eureka Science Magazine list. Dr Owen and his team have since moved to the University of Western Ontario, Canada, where he has taken up the Canada Excellence Research Chair in cognitive neuroscience and imaging and continues to maintain strong collaborative links with Cambridge neuroscience.

40. Between 2000 and 2007, Professor Terry Jones played a key part in the conception and establishment of the PET-based Wolfson Molecular Imaging Centre at the University of Manchester. This facility is currently considered one of the most advanced of its type and from the mid-2000s has been linked directly to the Manchester Wellcome Trust Clinical Research Facility, which provides an environment in which patient-focused research can be easily conducted.

41. Reflecting the multidisciplinarity of the field of brain imaging, many of the research hubs in the UK have recently been funded through partnerships between different agencies with different but complementary aims. The MRC has worked with several partners over the past two decades, including the National Cancer Research Institute and the Medicines and Healthcare products Regulatory Agency, to advance translation and facilitate academic–industry interactions to strengthen UK PET imaging. Further academic–industry centres for PET imaging are currently being considered.

42. In 2010, the MRC initiated three specialist postdoctoral pilot programmes to boost neuroscience research using PET techniques. Three awards were made, averaging £1.6m. Two went to Imperial College London: one to Professor Paul Matthews and his colleagues at GSK's Clinical Imaging Centre, to establish the world's first training programme in advanced neuro-PET radio chemistry for tracer development, and one to Dr Federico Turkheimer in the Centre for Neuroscience for research into PET biomarker tracking. Dr Franklin Aigbirhio's group at the Cambridge Wolfson Brain Imaging Centre received the third award for research into the development of novel PET ligands for brain disease research. Awardees have since established a neuro-PET network to help coordinate the UK's resources and better integrate UK centres conducting molecular imaging.

2.3 Europe

43. Across Europe, several organisations and institutions have had key roles in functional brain imaging research, including the Karolinska Institute, Sweden, and the University of Tübingen, Germany.

44. Before 1990, the CEA Service Hospitalier Frederic Joliot (Orsay, France) were the pioneers of neurochemical imaging of the brain with PET. Several imaging biomarkers were introduced by this lab.

2.4 Industry

45. Although many of the successes of brain imaging research to date have been rooted in university-based research, the contributions of industry and industry-based researchers have been pivotal in many of these developments. In this field, academia and industry have a somewhat symbiotic relationship:

> *"They (academics) teach industry, industry develops the user interface, they criticise – we go back to them."*
> **Wellcome Trust Industry Expert, December 2010**

46. The development of CT scanners is a case in point. Sir Godfrey Hounsfield was an electrical engineer working at the Central Research Laboratory at Electrical Musical Industries (EMI), UK. His research led to the development of one of the most important medical diagnostic tools now in use. The development of the first EMI CT prototype (in 1971)

was supported by the MRC; the first CT scan on a human patient took place in Atkinson Morley's Hospital, London. In 1979, Sir Godfrey – alongside physicist Professor Allan McLeod Cormack – won the Nobel Prize for Physiology and Medicine. The exploitation of Hounsfield's innovation by the medical industry triggered the development of further scanning and imaging techniques and paved the way for the development of other imaging modalities, such as MRI and PET. The combination of PET and CT has had a profound impact (on cancer diagnosis, for example).

47. The concepts produced by Terry Jones and his colleagues at the MRC Cyclotron Unit at Hammersmith Hospital, London, in the 1970s and early 1980s were also taken forward in partnership with industry; a group of small academic spin-off companies, such as EG&G ORTEC – a spin-off company from Oak Ridge National Laboratories, USA – developed the hardware and provided the engineering expertise, designing the first commercial PET scanner (the ECAT II) in collaboration with Michael Phelps and Edward Hoffman in 1978. In the 1980s, EG&G ORTEC developed into a new company called Computer Technology and Imaging, Inc., within the partnership of Ron Nutt, Terry Douglas, Mike Crabtree and Kelly Millum, and this was the start of a key industrial commitment to PET. Today, PET systems are produced worldwide by leading manufacturers such as Siemens, General Electric (GE), and Phillips; the role of industry in the development of PET scanners in clinical settings remains vital.

48. In the USA, Bell Labs (formerly known as AT&T Bell Laboratories) has been a key partner in imaging research. Perhaps most notably, Bell Labs has worked with Robert Shulman, Emeritus Professor at Yale University, USA, on the development of NMR and MRI to study biochemical processes. Professor Shulman led a small group in Bell Labs devoted to exploiting NMR for understanding living systems and brought spectroscopy forward in key areas, particularly carbon 13. Several research leaders have emerged from this academic–industry collaboration, including Dr David Van Essen (Edison Professor of Neurobiology and Department Head of Anatomy and Neurobiology at Washington University) and Dr Kamil Urgubil (founding Director of the Centre for Magnetic Research at the University of Minnesota and pioneer in the arena of high-field magnetic resonance development). Today, Drs Urgubil and Van Essen jointly lead the NIH-funded Human Connectome Project.

49. Another key figure is Professor Seiji Ogawa, who is currently the Director of fMRI Research at the Neuroscience Research Institute, Gachon University of Medicine and Science, Korea, and is a retired Bell Labs scientist. Professor Ogawa's research at the Biological Computation Research department at Bell Laboratories in the 1980s established the basis of blood oxygenation level dependent fMRI. As a non-invasive technology with many benefits over PET – including more flexibility, reduced data collection and a non-hazardous nature – its development opened up new opportunities in neuroscience, which ultimately led to the development of fMRI. He has received numerous awards and prizes, among them the prestigious Japan Prize, for his contribution to fMRI.

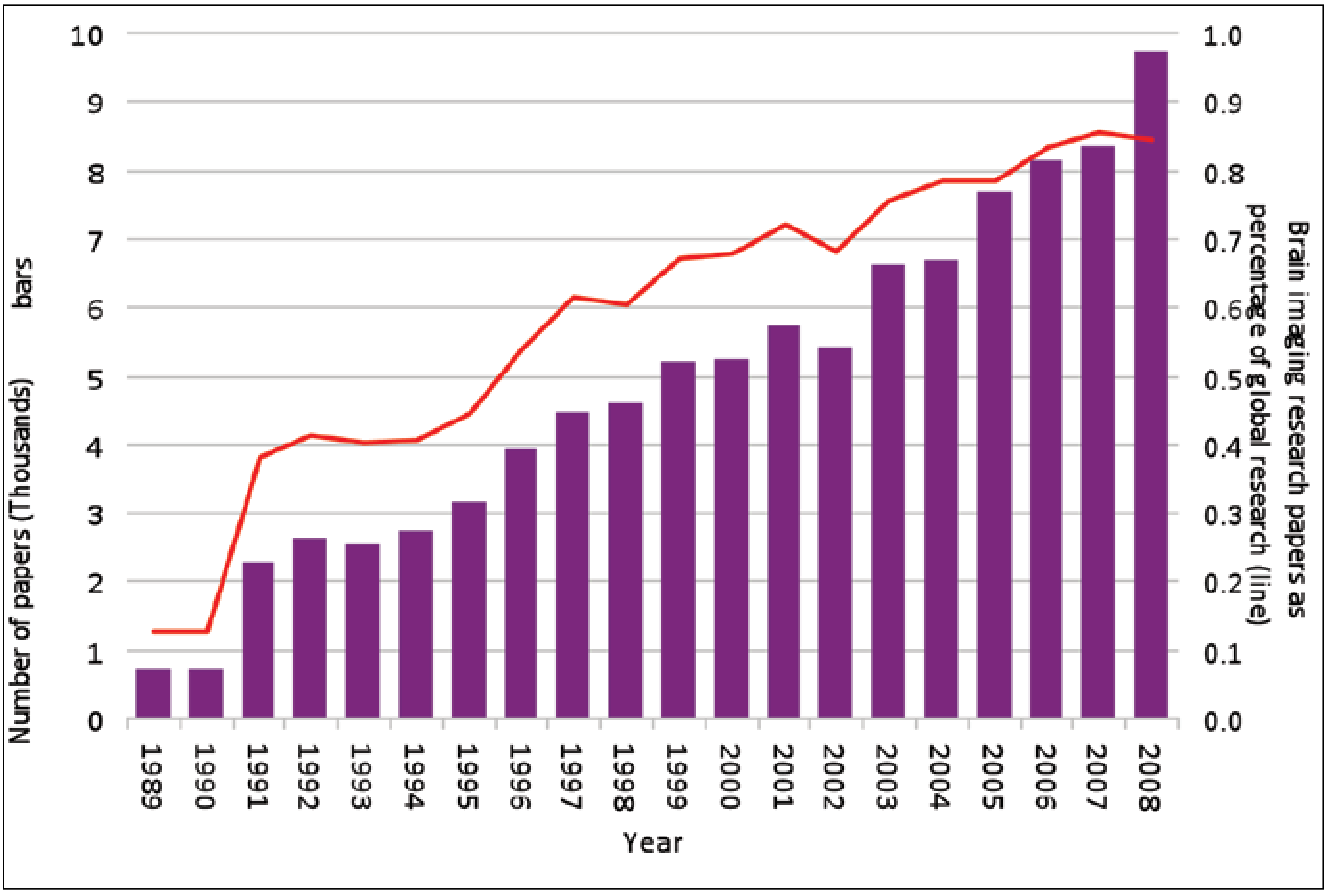
50. The recent GSK Clinical Imaging Centre is a pioneering collaboration between industry, academia and the public sector. In 2011, collaboration opportunities at the state-of-the-art medical imaging centre were expanded when a unique public–private collaborative agreement was signed between the MRC, Imperial College London, King's College London, UCL and GSK, substantially increasing the research base in medical imaging in the UK.

2.5 Human brain imaging publication output: 1989–2008

51. The development of fMRI in the early 1990s by Ogawa et al coincided with a major increase in the number of brain imaging papers published in neuroscience journals. The overall volume of publications related to human functional brain imaging research has increased steadily over the past two decades. There has been a four-fold increase in the number of functional brain imaging-related papers, from 2300 in 1991 to nearly 10 000 in 2008. In 1991, human brain imaging research represented approximately 0.4 per cent of all global research publications; by 2008, this proportion had doubled to 0.8 per cent of global research output (Figure 1).

52. Over the past two decades, human functional brain imaging research has been produced by a core set of countries, and the relative positions of these countries have not changed significantly (Figure 2). Over the 20-year period, the proportion of papers linked to the UK has grown from 6.4 per cent of the world's total in 1989 to 10.6 per cent in 2008 (578 and 4321, respectively) (Figure 2, Figure 3 and Table 1, Annex D). Much of this increase in the UK is associated with the establishment of the WTCN at UCL. Overall, throughout the period, the UK has retained its 'third place' behind the USA and Germany when ranked by output over the 20-year period (Figure 3).

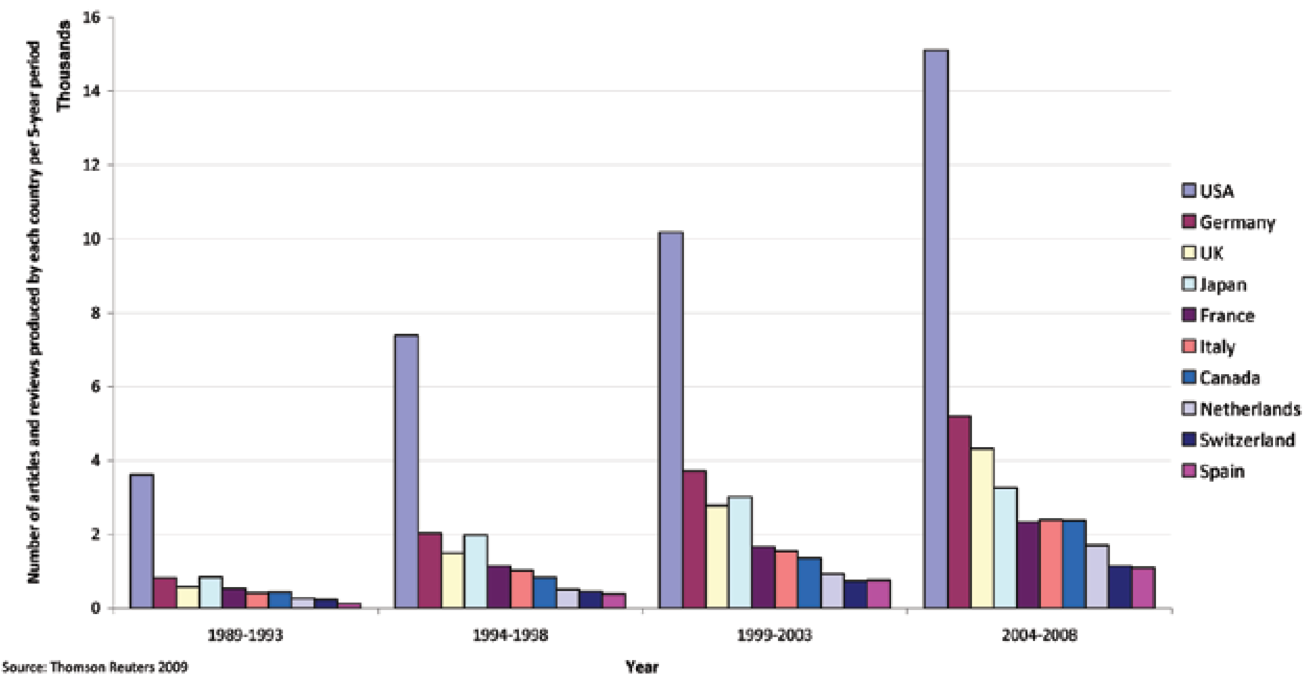
Figure 1 Number of brain imaging papers and as percentage of all research papers, 1989–2008



53. Surprisingly, over the 20-year period, the UK and Japan published almost the same number of papers about brain imaging research (9161 and 9112, respectively), reflecting a strengthening UK portfolio in recent years (Table 1, Annex D). In the earlier part of this period (1989–1998), Japan published a similar number of papers to Germany, but this dropped radically in 1999 (from 9.4 per cent in 1989 to 7.4 per cent in 1999, in terms of world total publication outputs in the field) and has not increased significantly over the past decade (Figure 2, Figure 3 and Table 2, Annex D). The USA has maintained its leading position in share of global output with approximately 40 per cent and remains the single biggest producer of brain imaging research publications (Figure 2, Figure 3 and Table 1, Annex D).

54. China-based researchers have also contributed to the increasing amount of brain imaging-related research over time. During the past decade alone, there has been growth of over 260 per cent – albeit from a low base – in the number of brain imaging research papers that include China-based researchers (Table 2, Annex D). In terms of world publication outputs, China was ranked 16th in 2008 (Table 1, Annex D), when it was linked to 2.8 per cent of total brain imaging papers (compared to 0.5 per cent in 1989).

Figure 2 Brain imaging papers published in five-year periods by country (top ten), 1989–2008



Source: Thomson Reuters 2009
Analysis: Evidence, Thomson Reuters (Scientific UK)
Base: Total global brain imaging output (articles and reviews): 1989-1993, n=9,009; 1994-1998, n=19,006; 1999-2003, n=28,327; 2004-2008, n=40,709

55. Other countries showing substantial growth in brain imaging research output include South Korea, Turkey and Brazil, which showed growths of 150 per cent, 125 per cent and 105 per cent, respectively, between 1999–2003 and 2004–08 (Table 2, Annex D).

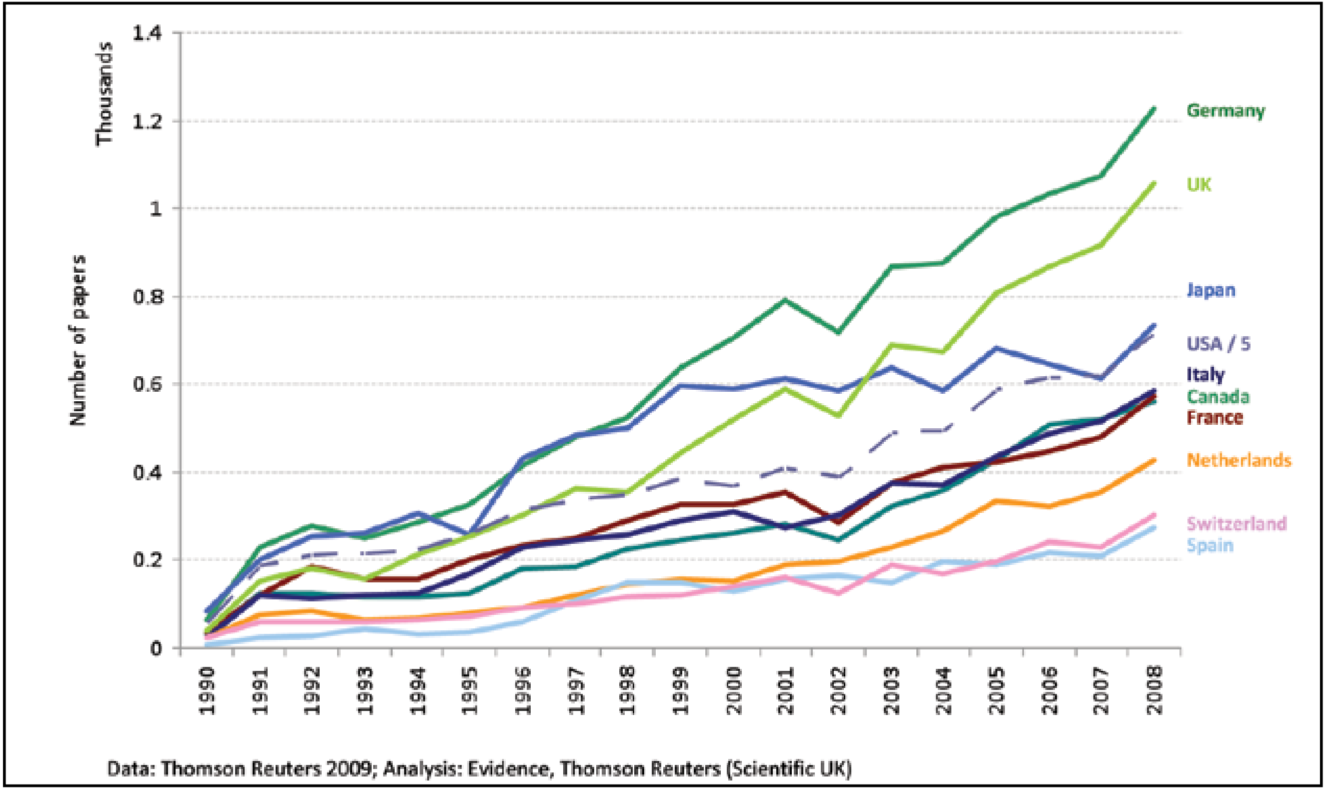
56. In terms of the subject focus of brain imaging research being published over time (see Annex B for bibliometric methodology and Annex D for charts), brain imaging-related research has been published predominantly in clinical neurology and neuroscience journals, with some growth in the field of experimental psychology. There has, however, been a substantial increase in the volume of brain imaging papers being published in non-neuroscience journals – notably in computer science, artificial intelligence, and computer science, theory and methods journals (Table 3, Annex D). This increase is explained, at least in part, by the advent of brain–computer interface technology. In addition, brain imaging laboratories worldwide are now using increasingly sophisticated imaging tools (such as fMRI), which require advanced software to perform statistical analyses of MRI datasets and produce fMRI activity maps and time series, used in research and clinical applications.

57. Going beyond the volume of output, citation analysis has been conducted to help identify the origins of high-quality, highly cited research. Citation data for 20 years (1989–2008) were used to determine the origins and affiliation of the most highly cited brain imaging research papers worldwide.

58. Over the period, three of the top 20 institutions linked to the most highly cited papers are UK institutions. University College London remained in first place throughout the 20-year period, and the University of Oxford and King's College London are at positions 7 and 11, respectively (Table 4, Annex D). Researchers at all of these sites received significant Wellcome Trust funding over the period to conduct brain imaging-related research.

59. Of the top 20 authors linked to the most highly cited papers in brain imaging worldwide, nine are UK-based, at University College London and King's College London. Karl Friston, Ray Dolan, Richard Frackowiak and Chris Frith – all of whom received significant funding from the Wellcome Trust over the period, predominantly while at the FIL – appear in the top five (Table 5, Annex D).

Figure 3 Time trends in brain imaging output – top ten countries (by volume), 1990–2008



3 Looking back: the Wellcome Trust and human functional brain imaging

"Wellcome has driven this, not just the people but also the level of funding needed to make a significant step change.
Wellcome Trust Expert Group on human functional brain imaging, October 2009

60. The Timeline (Annex E) sets out the major landmarks in the field of human functional brain imaging, from the perspective of the Wellcome Trust and the Expert Group, with particular emphasis on the past two decades. The introduction of fMRI in the 1990s has led to a major shift in the use and accessibility of brain imaging techniques because of its low invasiveness, lack of radiation exposure and relatively wide availability. The accessibility of this 'user-friendly' imaging technique enabled researchers from other disciplines, particularly psychologists, to examine human brain function – not only resulting in a major increase in neuroimaging publication outputs but also contributing, in part, to the development of an important interdisciplinary field: cognitive neuroscience. The Trust has been a major global player in providing funding support for human functional brain imaging over this time.

61. Between 1990 and 2008, the Trust committed approximately £114m (Table 1, Figure 1, Annex C) to 218 human functional brain imaging-focused grants, accounting for 2 per cent of the Trust's funding commitment. Almost all (98.6 per cent by value) of this funding was awarded to UK institutions; only 1.4 per cent of funding (£1.6m) was committed to non-UK-based human functional brain imaging research (Figure 4, Annex C).

62. Almost one-third (32 per cent by value, or £36m; 104 grants) of this funding has been career-based, supporting individual researchers doing projects based on human functional brain imaging via personal support schemes (Table 2, Figure 3, Annex C). This can be broken down further into:

- studentships (£2m)
- Early Career Fellowships (£6m)
- Intermediate Fellowships (£4m)
- Senior and Principal Research Fellowships (£24m).

63. More than two-thirds of funds (69 per cent by value, or £79m; 114 grants) have been awarded to research and project support (equipment, Strategic Awards, buildings, Joint Infrastructure Funding, and project and programme grants; see Table 2, Figure 3, Annex C).

64. Of the total Wellcome Trust funding awarded to this field, nearly half (£50m; 39 grants) has gone to the WTCN at UCL (Figure 1 and 2, Annex C).

65. This review highlighted three areas in which the Wellcome Trust has made a significant impact on the field of human functional brain imaging over the past two decades: through its support for equipment, technology and research tools; through its support for multidisciplinary research 'hubs'; and through its training and support for a generation of research leaders in the field – all of which have proved to be essential factors thus far in many of the developments in human functional brain imaging.

3.1 Building technology capacity: supporting the hardware, technology and research tools

"The thing about the Wellcome's funding was that it was sustained funding of a sufficient magnitude to create critical mass and drive the science forward. And that was very special."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"A lot of the money for JIF came from Wellcome, if I remember, with the Research Councils putting in some top up. And that really changed things in a very positive way."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

66. Over the past 20 years, the Wellcome Trust has provided key hardware and has funded several laboratories that have developed specific imaging technologies, providing resources and new imaging tools for multidisciplinary teams across the UK and beyond.

67. Our experts described a relative paucity in funding for research infrastructure in the mid- to late-1980s, and this had a major impact on a field that necessarily involves multidisciplinary teams and expensive, 'big' equipment. To tackle chronic underinvestment in research infrastructure in UK universities, the Joint Infrastructure Fund (JIF) was set up in 1998.

68. The Wellcome Trust's partnership with the UK Government (and Research Councils) via the JIF was cited as a key turning point in the landscape of funding that kick-started a period of sustained

investment in Britain's scientific infrastructure. In terms of brain imaging research, most notably, with additional funding for equipment and infrastructure, JIF was thought to have transformed the working environment and enhanced the research capability of the UK academic neuroimaging community by responding to the real needs of the brain imaging community; providing substantial funding to enable many UK-based pioneers to remain internationally competitive.

69. Recipients of JIF awards in imaging facilities include Professor Richard Frackowiak at UCL, for the purchase of two improved MRI scanners (£2.6m), Professor Steve Williams at KCL, to set up a Neuroimaging Centre for Developmental Disorders (£2.7m), and Professor Peter Morris at Nottingham University to establish an fMRI facility (£2.8m) – the UK's first 7-Tesla MR whole body system was established at Nottingham University through a JIF award. In 2004, Professor Martin Eimer, Birkbeck College was awarded a Science Research Infrastructure (SRIF) award (£2.4m) for his work on 'The Neural Basis of Learning, Development, and Attentional Selectivity in Visual Cognition' and in 2001 Professor Andy Young, University of York, was awarded a SRIF (£1.4) award to create a Centre for Language, Mind and Emotion.

70. Other imaging facilities established through JIF awards include the Wellcome Trust Laboratory for MEG Studies based in the Aston Brain Centre (a centre of excellence in Aston University, Birmingham), established in 1999 with a grant worth approximately £1.5m. The NMR laboratory at the Centre of Magnetic Resonance in the University of York, was funded through a £3.5m SRIF award. More recently, in 2010, the University of York's Neuroimaging Centre (YNiC), in conjunction with the Department of Chemistry, has been awarded a grant from the Wellcome Trust and the Wolfson Foundation to establish a £7m research centre into hyperpolarisation.

71. The Wellcome Trust has not just focused on transforming the working environment of the UK academic neuroimaging research community; it has also played a part in providing an environment in which health professionals can focus on research on, or using, brain imaging techniques. In 2000, the Wellcome Trust established five Wellcome Trust Clinical Research Facilities (WTCRFs) through a funding collaboration with the English and Scottish Executive Departments of Health. Three of the WTCRFs provide MRI imaging facilities (Manchester, Edinburgh and Cambridge).

72. Phase two of the original WTCRF initiative – the Clinical Research Initiative (CRI) – was launched in 2007 and has since provided for 3-Tesla MRI capability at the existing Cambridge and Edinburgh WTCRFs, and for the new CRFs established at the Institute of Cancer Research (ICR), at the Royal Marsden Hospital in Sutton, and at the University of Oxford, at the John Radcliffe Hospital.

3.2 Building research capacity: the emergence of multidisciplinary research hubs

"I think big questions are driven by people with big visions and understanding the field. Technology is driven typically by aggregates of people driven by vision and I think the problem one faces in imaging is that asking questions has been so closely linked to the tools. But the tools are really just catalysts for people being able to ask the right question. You constrain your question because you know what you can and can't measure."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"It is about getting the people who can really ask the most intelligent questions using these fantastic tools."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

73. A key theme that has emerged in this review is that in recent decades, functional brain imaging has benefited from collaborations between researchers from across scientific disciplines and different sectors. Many of the key developments in brain imaging research have required 'basic' biologists to work closely with engineers, mathematicians, physicists and technicians to help deliver the solutions to research questions. Where such collaboration is an essential part of the solution, creating 'hubs' and even co-locating the key researchers is perhaps critical to the continued development of the field.

74. Once neuroimaging tools became accessible to the wider scientific community from the late 1970s, scientists from a range of disciplines became interested in using the methods to further their fields. The potential to measure and map blood flow in the brain enabled new research agendas and questions to be explored. New fields such as cognitive neuroscience emerged, and new collaborations became important to help realise research goals.

Multidisciplinary research teams became the norm, and the co-location of these teams in research hubs became the logical next step. The emergence of the imaging hub at Hammersmith Hospital and the establishment of the WTCN at University College London are exemplars of the progression of this in the UK.

3.2.1 Wellcome Trust Centre for Neuroimaging

"If you go back a decade or more we had real problems with infrastructure in the UK, there was no way you could get hold of major equipment, you certainly couldn't write an MRC grant and expect to get an MRI system. I think Wellcome put a lot of money in at that point."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I think the impact that FIL had on the worldwide acceptance of MRI as a tool for analysis of higher cognitive and receptive functions in the human brain is outstanding and he [Sir Stanley Peart] should have a prize for that, and everybody accepts that I think. Without Wellcome the FIL wouldn't exist."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

75. The WTCN at UCL (see WTCN case study) is thought to have arisen serendipitously. In the early 1990s, Semir Zeki, a Professor of Neurobiology at UCL, had a discussion with Sir Stanley Peart (then a Wellcome Trust Trustee) and David Gordon (then a Wellcome Trust programme director) about the possibility of creating a self-sufficient brain activation laboratory at Queen Square. David Gordon subsequently suggested that Richard Frackowiak, who was leading an active research group based at the MRC Cyclotron Unit at Hammersmith Hospital, submit a novel bid for a multidisciplinary research centre equipped with the technology to enable cutting-edge brain research.

76. The application (which, at the time, was one of the largest ever considered by the Wellcome Trust at £20m) was successful. In 1993, funding for the Department of Cognitive Neurology and the FIL at UCL began. An additional £5m over ten years was allocated to establish an fMRI and PET facility at the Institute of Neurology, Queen Square, making it the only centre in the world with both scanning techniques at the time. Richard Frackowiak, much of his research group and a host of new scientists from across disciplines (including Chris Frith, Ray Dolan, Karl Friston and John Ashburner) were relocated to the central London site. Many of the key breakthroughs in our knowledge of the functional capabilities of the brain from the mid-1990s to the present day emerged from or have links to the FIL or the WTCN at UCL (WTCN case study).

77. In 2006, after a successful bid for a Wellcome Trust Strategic Award, the facility was awarded 'centre status', becoming the WTCN. The WTCN is thought to have facilitated essential multidisciplinary approaches to brain imaging, enabling the development of technologies, tools and methods that have been disseminated to the brain imaging community, both nationally and internationally. Today, in 2011, under the direction of Professor Ray Dolan (Director 2006–present), the WTCN is one of the world's leading centres for brain imaging research and constitutes a unique and valued resource for training young scientists. With approximately 40 PhDs attached to the Centre since 2006, its collaborative environment makes it a model laboratory in the field.

78. Over time, and with the Wellcome Trust as its predominant funder, the WTCN evolved from conducting predominantly PET-based studies into a multidisciplinary centre accommodating the latest neuroimaging technologies and focusing particularly on the widespread development and adoption of MRI in brain imaging research.

79. The WTCN is home to the Statistical Parametric Mapping (SPM) resource, a tool for the collation and analysis of functional imaging data from multiple imaging sources. Ongoing theoretical advances and technical improvements of the original version, SPM classic, have been developed, including SPM'94, SPM'96, SPM'99, SPM2, SPM5 and SPM8. SPM was initially developed by Karl Friston for the routine statistical analysis of functional neuroimaging data from PET. SPM was made available to the emerging imaging community in 1990 and promoted a collaborative culture within the neuroimaging field by providing a common, free, open-source analysis programme across imaging laboratories worldwide.

80. The location of the WTCN has been important; its proximity to the many central London research units and medical institutes is considered to have been a major factor in the WTCN's success to date. Its location in Queen Square facilitates collaborations with nearby researchers and clinicians, including the Gatsby Unit, which is considered to be among the

best computational neuroscience institutes in the world. The relationship between the Gatsby Unit and the WTCN has enabled research into the relationship between macro circuits and neural computation. The WTCN has strong collaborations with other groups at UCL, including the Institute of Cognitive Neuroscience, and clinical colleagues at the National Hospital for Neurology and Neurosurgery.

81. Overall, between 1993 and 2008 (inclusive), the Wellcome Trust committed £50m to the WTCN – nearly half (44 per cent) of all Wellcome Trust funding for functional brain imaging research (Figure 1 and 2, Annex C).

82. The imaging work at the WTCN and at UCL more generally is consistently highly cited, with brain imaging work linked to the WTCN more cited than that linked to any other institute, outranking Harvard University in terms of overall citations in the period from 1989 to 2008 (Table 4, Annex D). Since becoming the WTCN in 2006, more than 600 peer-reviewed publications have been produced by researchers based at the centre, which is clearly contributing to the UK's relative dominance in brain imaging research. Today, of the 20 most cited authors in brain imaging, the top four – Karl Friston, Ray Dolan, Richard Frackowiak and Christopher Frith – are currently or recently associated with the WTCN (Table 5, Annex D). In a recent publication analysis on basic neurosciences 1996–2007 in *Lab Times*, these authors were also listed as four of the top 25 most cited scientists worldwide in 'behaviour' and 'neuroscience'. Several Wellcome Trust-funded researchers focusing on brain imaging-related research have received prestigious awards for their contributions to the field (Table 6, Annex D). Without the prior long-term investment of the MRC in the development and application of PET, the WTCN would not exist.

3.2.2 The Centre for Neuroimaging Sciences

83. The Centre for Neuroimaging Sciences, a joint venture between the King's College London Institute of Psychiatry and the South London and Maudsley NHS Foundation Trust, was established through a Wellcome Trust Joint Infrastructure Fund (>£6m), which was matched in funding by the South London and Maudsley NHS Foundation Trust. This thriving interdisciplinary centre brings together scientists – including clinicians, technicians, chemists, physicists, engineers and students – and industrial collaborators from across the world, who are using brain imaging techniques to help understand and treat a range of neurological and psychiatric disorders. In particular, Professor Steve Williams (Steve Williams case study) and his colleagues at the KCL Institute of Psychiatry have had significant interactions with large pharmaceutical companies, such as GE Healthcare, to streamline the translation of neuroimaging tools used for the diagnosis and treatment of psychiatric disorders in the clinic.

84. Developments in human functional brain imaging have contributed to the growth of the field of psychiatry and to ongoing psychiatric research efforts over the past two decades. Research efforts using functional brain imaging techniques to diagnose psychiatric disorders have moved from simple hands-on experiments to more insightful techniques, such as those used to assess the effect of a drug for a psychiatric illness. Sustaining such research efforts requires funding and expertise from a variety of sources and depends on extensive interactions between academic psychiatry and the pharmaceutical industry. Although their overall agendas are different, academic and pharmaceutical collaborations are proving crucial for maintaining a high degree of innovation in medicine. One of the pioneers of this type of collaboration is Steve Williams and his colleagues at the KCL Institute of Psychiatry.

3.2.3 Behavioural and Clinical Neuroscience Institute

85. The BCNI was established in Cambridge in 2005 with a five-year MRC–Wellcome Trust award (£4.8m). This funding was renewed in 2010 for £3.5m, and the Wellcome Trust's contribution was approximately £1.5m. Functional neuroimaging modalities, including PET and fMRI, are key components of the research undertaken at this institute.

3.2.4 Cardiff University Brain Imaging Centre and Oxford Centre for Functional MRI of the Brain

86. Through its fellowships, the Wellcome Trust supports world-leading, collaborative multidisciplinary research projects at the Cardiff University Brain Imaging Centre and the FMRIB – both multidisciplinary neuroimaging research

facilities using state-of-the-art brain imaging techniques, including structural and functional magnetic resonance imaging (MRI and fMRI), EEG and transcranial magnetic stimulation (TMS).

3.3 Supporting excellent people: training and the support and creation of research leaders

"They [Wellcome Trust] weren't driving. They gave a group of young people the ability to drive it."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"If you want to have something that resembles an imaging researcher of the future you actually need to give them some kind of common grounding while they are doing their PhD so that they come out of that with some understanding of anatomy or basic image processing methods in addition to whatever they did in their PhD. Common features of study design, how to work interactively with people from very different backgrounds, all of those sorts of things. And you need to kick start that with things like PhD programmes which the Wellcome Trust has done and other groups have done."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

87. The Wellcome Trust is generally well known for its provision of training and fellowship funding; as described, one-third of its funding for brain imaging work over the past two decades has been via personal support funding mechanisms (Table 2, Table 4 and Table 5, Annex C).

88. Our experts highlighted the importance of building capacity in this field directly through training programmes and particularly where the research area is potentially so multidisciplinary. The Wellcome Trust four-year PhD training programmes were thought to be a good mechanism to support the acquisition of broad skills given the first-year laboratory rotation, where students gain experience of different laboratories and/or research areas to help them learn new skills and make the choice of their final PhD project more informed.

89. At the other end of the spectrum, our experts felt that Wellcome's support for senior fellows was well balanced and well structured, providing the freedom to enable researchers to pursue a vision over a sustained period. The Investigator Award initiative – for which the first Investigators were funded in mid-2011 – presents a further opportunity for the Wellcome Trust to support visionary researchers and offer them considerable scientific freedom.

"I thought the Wellcome Trust was very good at that. I think trusting the scientists is a very good policy."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

90. The approach of funding leading brain imaging researchers through multidisciplinary research 'hubs' was also thought to have been beneficial, enabling research leaders to grow their teams to help provide answers to key questions.

"The question whether Wellcome had got the right team of people, and clearly it did in terms of the leadership that Richard provided and the skills of Karl and the others brought along as well."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

91. Through its support of multidisciplinary research hubs and excellent research leaders, there is a sense that in the early 1990s, the Wellcome Trust facilitated a step change in human functional brain imaging by funding high-risk research at the right time, with the right people – the best and brightest. This was crucially important in facilitating the subsequent growth of the field of human functional brain imaging in the UK (see the WTCN, David Gadian, Steve Williams, Tim Griffiths and Trevor Robbins case studies).

3.4 Advancing knowledge and making discoveries

92. Over the past two decades, through those it has funded, the Wellcome Trust has contributed to some of the most important developments in the field – perhaps most notably through the establishment and maintenance of the WTCN at UCL (WTCN case study).

93. Specific landmarks in human functional brain imaging to which the Wellcome Trust is linked are listed in Table 1 (see Timeline, Annex E for more detail):

Table 1 Key discoveries in human functional brain imaging with major input from the Wellcome Trust

Key date	Who	Discovery
WTCN at UCL		
1995	**Karl Friston** Karl Friston was supported by the Wellcome Trust through a Senior Research Fellowship in Clinical Science, which started in October 1994. Karl Friston was first employed on a Wellcome Project Grant awarded to Professor Peter Liddle, 1988–1993.	The development of spatial registration and normalisation of images.[2]
1996	**Tim Griffiths** and colleagues Tim Griffiths was supported by the Wellcome Trust through a Senior Research Fellowship in 2000,[1] which was renewed in 2005 and 2010.	The identification of the specific frequency and time characteristics of sounds associated with people's experiences of unpleasantness. This work included the development of methods that have been used for dissecting the cognitive mechanisms involved in sound perception, which could potentially be used to improve understanding of the cortical mechanisms involved in other brain disorders, including schizophrenia and dyslexia.
1996	**John S Morris**, **Christopher Frith** and **Ray Dolan** Christopher Frith was supported by the Wellcome Trust through a Principal Research Fellowship, which started in April 1996. Ray Dolan was supported by a Senior Research Fellowship in Clinical Science, which started in October 1994.	The first direct demonstration that the human amygdala is crucial to the perceptional analysis of fear.[3]
1997	**Eleanor Maguire**, **Richard Frackowiak** and **Christopher Frith** Richard Frackowiak was supported by the Wellcome Trust through a Principal Research Fellowship, which started in January 1994. Christopher Frith was also supported by the Wellcome Trust, as above.	Pioneering work led by Eleanor Maguire demonstrated the potential development of hippocampi through her work with London's taxi drivers: the drivers all had enlarged hippocampi because of having to navigate the city's streets.[4]
2000	**Karl Friston** and **John Ashburner** Karl Friston was supported by the Wellcome Trust through a Principal Research Fellowship in Clinical Science, which started in October 1999.	Voxel-based morphometry.[5]
2003	**Karl Friston** and colleagues Karl Friston was supported by the Wellcome Trust through a Principal Research Fellowship, as above.	Dynamic causal modelling.[6]
2003	**Ray Dolan** and **Jay Gottfried** This work was supported by a Wellcome Trust Programme grant.	The neurobiological basis of predictive reward value encoding in the human brain.[7]
2004	**Ray Dolan**, **Peter Dayan** and **John O' Doherty** This work was supported by the Wellcome Trust through a Wellcome Trust Programme Grant awarded to Ray Dolan, WTCN.	The dissociable roles of ventral and dorsal striatum in classical and instrumental conditioning.[8]
2005	**Ben Seymour** and colleagues This work was supported by the Wellcome Trust.	Opponent appetite-aversive neural processes underlie the predictive learning of pain relief.[9]
2006	**Mathias Pessigilione** and colleagues This work was supported through a Wellcome Trust Programme Grant and the Fyssen Foundation.[10]	Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans.[11]
2006	**Konstantinos Moutoussis** and **Semir Zeki** This work was supported by the Wellcome Trust through a Wellcome Trust Programme Grant (July 2002–June 2007).	Stimulus-specific activation of higher cortical areas does not necessarily result in awareness of the underlying stimulus.[12]
2008	**Stefan Klöppel** and colleagues The Wellcome Trust supported Richard Frackowiak and John Ashburner in this study. Jonathan D Rohrer, from the Institute of Neurology, UCL, was supported by a Wellcome Trust Research Training Fellowship.	The automatic classification of Alzheimer's with MRI.[13]

Key date	Who	Discovery
2009	**Demis Hassabis** and colleagues This work, led by Eleanor Maguire, was supported by the Wellcome Trust (a Sir Henry Wellcome Postdoctoral Fellowship to Demis Hassabis in July 2010) and the Brain Research Trust.	Highly abstracted representations of space are expressed in the human hippocampus.[14]
Institute of Psychiatry, King's College London		
2008	**Cynthia Fu** and colleagues This work was supported by the Wellcome Trust.	The significant classification of patients in an acute depressive episode using whole brain pattern analysis of fMRI data.[15]
MRC Cognition and Brain Sciences Unit and the University of Cambridge		
2010	**Luca Passamonti**, **Andy Calder** and colleagues This work was jointly funded by the Wellcome Trust and the MRC.	Young adults with conduct disorder display an abnormal pattern of brain activity compared with their peers without the disorder.[16]
Institute of Cognitive Neuroscience, UCL		
1994 onwards	**David Gadian** and colleagues David Gadian was supported through a Wellcome Trust Programme Grant and Action Research.	Professor David Gadian and colleagues were among the first in the UK to show that fMRI is robust and accurate and reported the first studies using it to look at seizure activity.[17]
		MRI and MRS techniques for the identification of structural, biochemical and functional abnormalities in children with epilepsy.
1997	**Faraneh Vargha-Khadem** and colleagues This work was supported in part through a Wellcome Trust project grant and Action Research.	The previously unrecognised disorder developmental amnesia.[18]
2005		Elucidation of brain structure–function relationships in a family with an inherited (*FOXP2*) speech and language disorder.[19]
University of Cambridge, Addenbrooke's Hospital, and Behavioural and Clinical Neuroscience Institute		
2008	**Trevor Robbins**, **Barbara Sahakian** and colleagues This work was supported in part by a Wellcome Trust Programme Grant and by a joint Wellcome Trust/MRC Award to the BCNI.	Distinctive brain activity in people with psychological disorders, including the identification of abnormally reduced activation of several cortical regions (including the lateral orbitofrontal cortex) during reversal learning in OCD patients and their clinically unaffected close relatives, supporting the existence of an underlying previously undiscovered endophenotype for this disorder.[20]
Oxford Centre for Functional Magnetic Resonance Imaging of the Brain		
2002	**Heidi Johansen-Berg** and colleagues This work was supported in part through a Wellcome Trust PhD studentship, by the Royal Society and by the MRC.	TMS patients depend on new areas of the brain for movement after strokes.[21]
2003	**Timothy E J Behrens**, **Heidi Johansen-Berg** and colleagues This work was supported in part through a Wellcome Trust Research Training Fellowship in Mathematical Biology and by the MRC, the EPSRC, the Rhodes Trust, the EPSRC-MRC IRC, the Multiple Sclerosis Society of Great Britain and Northern Ireland, and Action Research.	The development of diffusion MRI has provided researchers with a new way to study connections within the brain.[22]
Centre for Brain and Cognitive Development, Birkbeck, University of London		

Key date	Who	Discovery
2010	**Tobias Grossmann** and **Mark H Johnson** This work was supported by a Sir Henry Wellcome Postdoctoral Fellowship awarded by the Wellcome Trust and the UK MRC.	Selective prefrontal cortex responses to joint attention in early infancy.[23]
Wellcome Trust Clinical Research Facilities (Addenbrooke's Hospital Cambridge)		
2006	**Adrian M Owen**, **Martin R Coleman** and colleagues This work was supported by an MRC programme grant, the Smiths Charity, the Belgian Fonds National de la Recherche Scientifique and the Mind Science Foundation. The Wellcome Trust CRF at Cambridge was used for this study.	The detection of awareness in a persistent vegetative state using fMRI, which might influence the diagnostic criteria for persistent vegetative states.[24]
2006	**Samuel R Chamberlain** and colleagues This work was supported by a Wellcome Trust Programme grant, a MRC Pathfinder grant, an MRC priority studentship and a Wellcome Trust/MRC joint Award to the BCNI.	Mapping the chemical pathways, which regulate two aspects of cognitive brain function, might have implications for the treatment of attention deficit hyperactivity disorder and understanding the effects of antidepressant drugs.[25]

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24 Owen A et al. Detecting awareness in the vegetative. Science 2006;313:1402.
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4 Looking forward: speculations on the future of human functional brain imaging

94. This review of the past two decades has demonstrated that the field of human functional brain imaging has had a major impact upon our understanding of the function of the human brain. There is a sense that we are now at a crossroads, however, and a shift in gear is required if we are to build on what we know and move to resolve what we want to know about how our brains work.

95. Our experts were tasked with thinking about the current challenges facing the field and where a successful future might lie. In this section, we describe the themes emerging, some of which are under consideration at the Trust in direct response to our challenge 'understanding the brain', as set out in our 2010–20 Strategic Plan. As with any review or consultation, the list that follows does not claim to be exhaustive, and we acknowledge that a different set of researchers and/or experts might have had a different set of conclusions or priorities. Nevertheless, we believe that by highlighting and sharing what we see as today's research needs and opportunities and by working together, all those involved in the field of human functional brain imaging will help drive the field forward.

4.1 More solution-focused research? A 'grand challenge' approach to transform the field

"We do need more grand challenges to really arrest attention and bring it back to major problems."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"It's about setting objectives, which will be game changers in the field."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"It is vital, if you could brainstorm and tell us what is the vision of neuroscience, I would like to hear neurochemists talk, I would like to hear psychiatrists talk, get us some benchmarks."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Focused application science that pushes the envelope in ways that are important, asking big questions."
Industry expert, December 2010

96. It was thought to be time for some solution-based, 'grand challenge' thinking in functional brain imaging. Our experts highlighted the need for concerted action and commitment from research funders across sectors to work with scientific leaders and identify the challenges to drive the field forward. The achievements of concerted action among the physics community (evident in the Large Hadron Collider project) and the biology community (evident through the International Human Genome Project) were cited as examples of what could happen with a more solution-based research agenda.

"Look at what has happened in genetics over the last five years, a very short time, go back three or five years ago and there were still multiple groups trying to fight their own way. Suddenly people began to realise that that wasn't going to wash. No one had enough data, no one was thinking big enough. It was a wonderful thing to have watched, within one to two years there was a tremendous nucleation and it has fundamentally changed genetics. The sociology of genetics is now utterly different than it was 12 months ago. And I think that could happen in neuroscience but it also needs real strategic commitment from the standpoint of the funders."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

97. One of the structural issues thought to be inhibiting the growth of brain imaging is that its constituent disciplines are often funded by different funders in different places, with different requirements. A more strategic, solution-based approach to functional imaging research is likely to require cross-funder and cross-sector collaboration across all key stakeholders in functional brain imaging: between governments, universities, research councils, funding agencies and industry. This view was also evident in the Royal Society's recent Brain Waves project.

98. The Expert Group suggested that the UK could become a model for concerted action in the field, if the Wellcome Trust were to engage and join forces with other key UK funders of – and stakeholders in – human functional brain imaging, including the MRC and EPSRC, and with industry and the health service. The Wellcome Trust's independence was thought to position it well for fostering strategic partnerships and facilitating cross-sector and community working.

"The Wellcome Trust doesn't have to have a stake hold in the same way as a government agency does, it can be idiosyncratic and break the mould. These meetings need to be terribly small, so that they can be very informal, very interactive, like having a limited number of wise

men, be they governors with some neuroscientists and a couple of physicists or some other group."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

99. An international frontiers meeting on human functional brain imaging was suggested as the first stage in identifying goals and potential road maps. The Trust is currently in the process of organising a brain imaging frontiers meeting focusing on the status of brain imaging tools and the possibilities for the future.

4.2 The value of multidisciplinary hubs, collaboration and networks

"The reality is, to tackle something like this – generally large scale science – needs teams. That team may be made up of individuals, and you need the engineering and physical sciences as well as what the Wellcome Trust can really bring in; the basic sciences, the clinical sciences. It has got to be groups of funders as well as groups of researchers. It has to be EPSRC and Wellcome working together to try and drive an agenda."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Everything in the last ten years is moving to removing disciplinary boundaries, putting people together, multi-disciplinary PhD programmes, a lot of mathematics and so on."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

100. Different disciplines are thought to be essential to the future of functional brain imaging. Our experts described a field in which, over the past couple of decades, human functional brain imaging has evolved from single disciplinary efforts into major collaborations and multidisciplinary research programmes.

101. The Expert Group also emphasised the crucial importance of research leaders; a head of diverse, multidisciplinary research teams must be able to 'speak' across disciplines and identify opportunities to take research forward effectively. Multidisciplinary hubs require experienced, credible research leaders with vision and strong leadership, who can adapt and coordinate the efforts of large, diverse research groups.

102. The Expert Group also emphasised the importance of 'blue skies' research within this landscape: a research leader should be able to identify talented researchers and provide space for new thinking and to explore new avenues. Given the sense that functional brain imaging is at a crossroads and in need of some solution-focused thinking, this protected time for blue skies thinking seems especially pertinent. Perhaps by advancing PET imaging of the human brain's neurochemistry which underlies every functional process. Challenges include identifying which chemical systems need researching, developing specific imaging probes for these systems, disseminating the methodology more widespread through the use of the new generation of micro-cyclotron and developing the next generation of PET brain scanner – all of which require more involvement from chemists, biologists, physicists and engineers.

"Create centres of excellence and where blue sky can happen."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Find the right people, trust them and let them get on with it."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

103. Our experts thought that greater networks and pathways between hubs – and not just in the UK – are an essential part of the future; again, the human genome research community was cited as an example of how this might work. Encouraging greater networking between research hubs would facilitate the free flow of information, knowledge and best practice and identify potential areas of future collaboration across different imaging communities.

"The PET communities are over here and the MRI communities are over here, the two have rarely spoken. And as soon as you get the two sitting next to each other amazing things can happen."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Over PET, we have discovered that the chemistry is in UCL, the patients are in King's and the machines are in Imperial. Trying to get these guys to talk to each other is impossible."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

104. A key part of building multidisciplinary research hubs and sustaining them into the future is ensuring sufficient researcher capacity and the potential research leaders of the future. Training of researchers remains a key to the future and our experts expressed some concern that we – particularly in the UK – are not doing enough.

"One of the problems I see is that we are still not training people in sufficient numbers to be able to take our science forward. We still haven't got the competitive edge at the level."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I think Massachusetts General Hospital, if you look at the number of scientists they have got there involved in it, it is massive, 150 to 200, we haven't got anything near that. They are much more efficient."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

105. In the field of brain imaging, the value for researchers of awareness and experience working with the different contributory disciplines and across sectors should not be underestimated. Broad cross-disciplinary training is essential to ensure that a sufficient cadre of high-quality researchers are sustaining researcher capacity. The Wellcome Trust is working to support a cadre of researchers in this field through its PhD studentship (which allows students to rotate across different laboratories and have exposure to a variety of disciplines and skills during a foundation training year), its Fellowship programmes, and – more recently – through the introduction of its Investigator Awards.

106. In summary, therefore, our Expert Group identified several specific actions that funders could take to help develop a critical mass of functional brain imaging researchers:

- work with funders across disciplines and sectors to support multidisciplinary teams and facilitate the creation of a cohesive network across hubs
- recruit individuals who have the scientific vision, leadership, skills and experience to drive large multidisciplinary teams and work across sectors
- transform the culture of funding and training to ensure the creation of research leaders of the future.

4.3 New models of collaboration and funding of functional brain imaging research

"There is an absolute critical link in the tripartite relationship between researchers funded by the Wellcome Trust and government organisations, disease charities, the pharmaceutical industry and the diagnostics imaging industry and the care delivery NHS or other care delivery mechanisms."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Molecular imaging could and should be transformed by interactions with the pharmaceutical industry and, in turn, could help to transform the industry."
Wellcome Trust Industry Expert, December 2010

"It is the academic industry; the importance of the academic industry in the development of imaging really can't be underestimated. And it really goes down to GE, if you look at the history of GE particularly, there was a rich cross fertilisation of people moving back and forth, repeatedly in fact, between industry and the outside. There were a number of examples of companies working terribly closely with universities."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Look for strong links with industry. And if those strong links are there they stand a much better chance of being a long term player."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

107. Our experts agreed that research funders could do more to consider new ways of ensuring that their financial support encouraged cross-disciplinary research and a more solution-focused, or 'grand challenge', approach.

108. In addition, the current financial climate makes it timely for us to consider how best to support such a field in the most effective way. Partnerships, and the opportunities for leverage of both funds and expertise across organisations, are important.

"The strength that the Trust can bring to these sorts of things, it can provide that glue. The next five years are going to be bloody hard for the public funders, MRC, EPSRC, whatever. The Treasury is going to be looking for what it calls leverage, it is the hot topic, anybody wants a term to throw into a Treasury discussion, leverage. And people who have a bit of money, Wellcome, some of the other charities, have the opportunity over the next three to five years to influence where public funding is going by providing that bit of leverage, that in doing so directing the way in which that research is being funded."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"This requires visionary leadership, it needs a concerted investment and it needs protected space. And my sense is that the Wellcome Trust is almost the only strategic organisation in the country, because it can move where no one else can."
Industry expert, December 2010

109. Given the range of stakeholders required in addressing today's functional brain imaging challenges, more novel public–private partnerships and funding across sectors seems entirely sensible. Such funding partnerships between academia, industry and health care providers have the potential to transform the field, leading to improved patient outcomes. The Expert Group cited several examples of innovative modes of funding that might be appropriate within this field. Although it has only been in existence since 2007, the Health Innovation Challenge Fund (funded by a partnership between the Trust and the Department of Health), set up to stimulate the delivery of technologies, products and interventions with clinical applicability within the NHS, was seen as a potential model for encouraging the translation of research from academic to clinical settings.

110. There are additional benefits to collaborating with the pharmaceutical industry, including the potential for opening compound libraries, providing a new basis for molecular probe development and bringing experts in drug development to the field of imaging.

111. Work in the USA, led by GE, to open up the use of novel molecular imaging techniques to academia is helping to tackle some of the challenges of conducting molecular medicine using imaging.

4.4 Bringing functional brain imaging into clinical settings

"The disappointment is that this science hasn't entered the clinic faster. I think that part of the problem is one really needs to rewrite medicine in order to make that happen. In moving forward I believe one almost has to make a choice between whether you want to drive the state of the art into the clinic, and whether you want to conduct transformative science that changes what the state of the art is. And they are two different discussions."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

112. As in many areas of basic science, a common challenge cited is the lack of interaction between clinicians and basic researchers. Functional brain imaging is also thought to suffer from this. To date, there has been only limited application of human functional brain imaging techniques in general clinical contexts. Although technologies such as MRI and fMRI have evolved at some pace, moving from the first structural imaging to dynamic structural imaging to diffusion tensor imaging (Timeline), these developments have not become commonly manifest in clinical settings.

"I think PET has certainly under achieved. Underachieved – not in oncology – but in the brain. Oncology came out of the brain, and in oncology there is only one marker. But I think there may be a lack of vision as to what we want to do with chemistry PET."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I would argue that the power of PET at the end is specificity and sensitivity. And that at the moment has not realised its full potential. That is the point we are making. We have got wonderful neurochemistry, brain imaging, and somehow that has got stuck. It is not just stuck in the pharmaceutical industry; they are using it very intelligently. But as far as the general world is concerned, and potentially the clinical application, it has got stuck. And maybe today we can look at that sticking."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

113. Our experts described the importance of clinicians sharing their requirements for brain imaging techniques with the basic neuroscience research community, so the real challenges and conundrums in the diagnosis and potential treatment of brain disorders are shared with researchers and technicians. As described earlier, clinician input should be a key ingredient to any multidisciplinary research hub. And again, the requirements of clinicians and health care providers could be part of any grand challenge forum or funding mechanism.

114. A key barrier currently inhibiting the development of functional brain imaging tools in clinical settings is that many of the diagnostic capabilities of the techniques are difficult to demonstrate across populations. The anatomical complexity and variability between human brains is massive and can often result in obscured data; people are actually very variable.

115. Conducting clinical trials and acquiring sample sizes large enough for meaningful clinical studies is traditionally difficult given the need for a range of specialist equipment and specialists. Conducting multi-centre studies would be an obvious way to address this. Again, it is possible to use parallels with the genomic community and the success of genome-wide association studies to demonstrate what can happen if research teams work together and share datasets.

"One of the other potential barriers that needs to be overcome to move forward is if you want to get large enough sample sizes to do clinical meaningful studies you need to do multi-centre studies. You have to have a body of people who understand how to do that kind of work in different centres. And to achieve that kind of level of critical mass which I think is achievable in the UK, you really have to do things on a group basis."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I think it is about having big enough populations and working with the variability rather than trying to rub it out by standardising everything."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"Rutherford's answer to this variability one was if your experiment needs statistics you did the wrong experiment. And that is all about trying to fit all patients to what we can actually currently measure."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I would like to make the point that one of the great advantages of MRI is repeatability so one can make longitudinal studies, well controlled, providing that when it becomes independent of the sequence provider the company has somebody in the group who can do it by himself so that you can keep the sequences constant. And you must not upgrade the system during a longitudinal study."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

116. Access to highly qualified clinical practitioners with protected research time is also a challenge; the Expert Group highlighted the need for research funders to consider how they might develop new strategies to secure and support the involvement of clinicians and allied professionals (such as radiographers and radiologists) in the field. As neuroimaging technology continues to advance, there is an increasing demand for academic radiologists who are also clinician scientists: they have a key part to play in bringing their observations from the bedside into the laboratory. Increasing the number of highly skilled, research-active radiologists will help bridge the gap between the bench and bedside and help enhance the quality of brain imaging research in the UK.

"Academic radiologists are not able to pick up a PhD. There is a serious policy issue there."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

4.5 More specific research required: a need for continued basic research

117. The Expert Group described several specific research questions and targets that might in themselves become a 'grand challenge'. These are summarised below.

118. Despite advances in single photon emission computed technology (SPECT), PET and fMRI, interpretation of results can still be difficult and each of these methods has their limitations; fMRI has good spatial resolution (within a few millimetres) but poor temporal precision when compared to other techniques such as MEG and EEG (although their spatial resolution is poorer). There was a general consensus across the Expert Group that there was considerable scope to further refine existing techniques, by improving the spatial resolution, temporal precision, quantification, sensitivity, specificity, and availability and cost of these techniques.

"What is coming out is that the future is largely going to be technical improvements of the existing techniques, it is particularly bringing them together and bringing them together with large scale modelling and computational power which will enable you to understand from this combination of signals, what the underlying physiology is."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"There is a lot of computing power, there are not necessarily a lot of good algorithms and new ways of analysing which will pull real signal out of bodies, not noise."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"The next big challenge...is really to develop something which has the spatial resolution of MR but actually measures the intrinsic signal. An MR technique that can actually measure local electrical activity."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

"I think for basic people like me they are really longing for a new technology that gives us high spatial resolution and high temporal resolution in one."
Wellcome Trust Expert Group on human functional brain imaging, October 2009

119. More research is required to develop fMRI quantitation. There is currently a lack of sensitivity, which is alleviated by going to higher fields. The Wellcome Trust and the Wolfson Foundation are already supporting work in this area through the York Centre for Hyperpolarisation at the University of York. In 2010, both bodies awarded the University of York a £4.36m grant to support the development of the centre. Hyperpolarisation with parahydrogen is one technique that has the potential to dramatically increase the sensitivity of MRI.

120. In addition, our industry experts particularly emphasised the continued need for imaging manufacturers to improve, and build on, existing imaging equipment, such as PET cameras and fMRI scanners. This includes the practical requirement for both research and clinical settings using smaller, more portable units of equipment (such as bench-side lightweight cyclotrons), which could be used in hospitals much more widely than they are used today.

121. Research into novel radiotracers is thought to have stalled. While PET and other scanning techniques move forward, research to yield new tracers and markers has not kept pace. The lack of intellectual property protection and economic incentives in the PET area is thought to be largely responsible for the lost interest in developing across all sectors. There is a pressing need for a new class of PET tracers as the expanding role of PET depends on the availability of these radiopharmaceuticals.

122. Our industry experts also highlighted the additional challenges facing industry such as regulatory processes and reimbursement policies. Regulatory processes delay the clinical development and utilization of novel imaging probes, which has contributed to the current lack of radiotracers in the field. This is a major limitation in terms of PET development. Reimbursement continues to pose a threat to the imaging industry. There is no common health care reimbursement policy and Europe has varied, limited reimbursement policies for high-cost medical imaging procedures.

> *"What is missing, I think, is the development of further sorts of functional imaging tracers that would elucidate brain function at a level which opens up brand new horizons."*
> **Wellcome Trust Expert Group on human functional brain imaging, October 2009**

123. Advances in probe discovery and development require new chemistry and biology. The Expert Group highlighted the need for increased chemistry and biology investment, to make clinically potential biomarkers and delivery more readily available, and highlighted the need to develop the field of neurochemistry.

> *"I would push the chemistry because if I could measure GABA concentrations, GABA release, even ionic levels, if I could measure them nicely with something close to real time changes, great. I know that the brain is full of chemical transmitters that we use to manipulate brain activity, but we don't actually pursue diseases where this is relevant."*
> **Wellcome Trust Expert Group on human functional brain imaging, October 2009**

> *"We are looking for chemistry input, biology input, biomarkers to make the delivery of it much more readily available. These are the challenges, the technology can do it, but I think we need the chemistry and biology investment."*
> **Wellcome Trust Expert Group on human functional brain imaging, October 2009**

124. The Expert Group also discussed the potential of hybrid modalities. The group emphasised that the strengths and weaknesses of functional neuroimaging techniques are complementary, so when used in combination, they offer greater potential to give new insights into human brain function. As the field is still looking at a haemodynamic effect, combining these modalities allows the anatomical, functional and molecular aspects to be studied simultaneously, giving information about the brain system and the cognitive system. The Expert Group suggested looking at potential new combinations of neuroimaging techniques, some of which could fill an important niche in future human functional brain imaging research:

- combining fMRI and EEG or MEG
- combining PET and fMRI
- combining fMRI and CT
- combining PET and SPECT.

4.6 A need to manage the social and ethical implications of brain imaging research

125. Key emerging challenges in the field of human brain imaging include reporting clinically relevant research findings to study participants and managing the increasingly large and complex datasets generated by research in this field. With regard to the former, there will be a need for funders to work with the research community to build policy principles and guidance on when, and how, findings with clinical implications are fed back to participants when they are identified during the course of research. In relation to research data, the Trust and other funding agencies are committed to ensuring that key datasets of value to the research community are preserved and shared in a way that maximises their long-term value. In neuroscience, as in other fields, much work is necessary to build and sustain the infrastructure, tools and culture that are needed to underpin this.

Professor David Gadian: Picturing the brain

Summary

Professor David Gadian studied physics and became fascinated with using the subject's techniques to aid biomedicine. His work has been instrumental in developing revolutionary brain-imaging techniques based on magnetic resonance. Today these provide vital insights into the workings of the brain and many neurological conditions, from epilepsy to developmental amnesia.

Background

Professor David Gadian read physics at the University of Oxford, where he became intrigued by the potential of using physics techniques to answer questions of biomedical importance. He joined a research group in Oxford's biochemistry department led by Sir Rex Richards, who first introduced nuclear magnetic resonance (NMR) technology to the UK. Working with Professor George Radda and colleagues, the group became the first people to use NMR to look at metabolism in intact tissue.

Professor Gadian moved to the Royal College of Surgeons of England and continued using NMR, largely spectroscopy (which looks at tissue chemistry), to study animal models of disease, primarily in the brain. Meanwhile, NMR was developed as a method of diagnostic imaging using water signals to look at pictures of the whole brain. These techniques, magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI), are now used both to understand disease processes and as a diagnostic tool. In 1990, Professor Gadian moved to the Institute of Child Health, the research arm of Great Ormond Street Hospital, to help to develop research strategy within a clinical environment. In 1992, his team received a Wellcome Trust programme grant to develop and apply non-invasive magnetic resonance methods for studies of childhood epilepsy and stroke.

Over the following years, Professor Gadian's team was able to apply the methods to a wide range of brain research projects, including studies of structure–function relationships in the developing brain. This work has placed the researchers at the forefront of establishing these techniques in children. The new imaging and spectroscopy techniques they developed have also been incorporated as standard clinical practice in the epilepsy surgery programme for children at Great Ormond Street Hospital.

Advance

Working closely with clinicians, Professor Gadian and colleagues have formed a bridge between physics and biomedicine, applying their techniques to enable clinicians to diagnose diseases and make clinical and surgical decisions on the basis of brain scans.

The development of functional MRI (fMRI) in the early 1990s, which provides a picture of the activated regions of the brain, has led to further clinical discoveries. Professor Gadian and colleagues were among the first in the UK to show that fMRI is robust and accurate, and reported the first studies using it to look at seizure activity (overactivation in certain parts of the brain) in 1994.

Epilepsy is often caused by damage to the hippocampus, a brain structure involved in episodic memory (memory for events) and navigational skills. Following on from studies of children with epilepsy, Professor Gadian and Professor Faraneh Vargha-Khadem have identified a number of children who had a profound loss of memory for events – but a surprisingly intact memory for facts (for example, they may know that Paris is the capital of France but not remember having recently been there). The work, published in *Science* in 1997, identified what appeared to be a completely new condition, which the researchers termed 'developmental amnesia'. It involves profound bilateral damage to both hippocampi, which imaging studies show to have wasted away significantly in affected children. The dissociation between the two types of memory function – and the fact that a particular structure in the brain could cause the problem – was of great interest to memory neuroscientists.

Professor Gadian's research has had a profound impact on clinical practice. In epilepsy, for example, he and his colleagues used structural and functional MRI to identify not only the parts of the brain that were damaged but also those parts activated during certain specific tasks in movement or speech. This clearer picture of brain function now helps surgical decisions in cases of intractable epilepsy, when the illness does not respond well to treatment by medication. Knowing which parts of the brain perform which critical tasks shows whether surgery would leave a patient significantly debilitated and enables doctors to make an informed decision about whether to operate, as well as the extent of surgery if they do go ahead. Great Ormond Street Hospital now uses fMRI routinely for children with epilepsy.

Professor Gadian has collaborated with scientists such as Professor Alan Lucas and colleagues at the Institute of Child Health, who have been looking at the effects of early nutrition in a large cohort of children born prematurely. This is enabling the team to build an atlas linking particular parts of the brain to particular deficits, such as impairments in calculation, visuospatial processing or memory. Again, a long-term aim is to be able to predict which children are at risk and intervene earlier. This research could have implications for childhood nutrition throughout the world.

In a further collaboration with Professor Vargha-Khadem, Professor Gadian and colleagues have explored the brain structure–function relationships associated with the speech and language impairments inherited by members of a specific family. The investigations of this family have culminated in a fascinating story linking a specific gene (the *FOXP2* gene, identified by researchers in Oxford) to speech and language acquisition and its neural correlates, attracting much scientific attention across a wide range of disciplines. Voxel-based morphometry, an image analysis technique developed at what is now the Wellcome Trust Centre for Neuroimaging, played a critical part in identifying which parts of the brain are abnormal in the affected family members.

Professor Gadian aims to develop other innovative ways of using the MRI and MRS signals, to develop increasingly clear pictures of brain structure and tissue chemistry. Another challenge is to identify differences between the brains of young children that would be predictive of the development of disorders. Ultimately, the aim is to improve the lives of at-risk children by providing earlier remediation, whether through cognitive therapies, medications, diet or other means.

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Timeline of Professor David Gadian

- **1974** Discovery that 31P NMR signals could be observed from intact tissue
- **1974–81** Series of developments leading to the first clinical applications of 31P NMR spectroscopy
- **1983** Appointed Senior Lecturer and Head of the new Department of Physics in Relation to Surgery at the Hunterian Institute, Royal College of Surgeons of England
- **1983–92** Developments in 1H NMR spectroscopy of the brain
- **1988** Appointed Professor of Physics in Relation to Surgery, Hunterian Institute
- **1990** Appointed Rank Professor of Biophysics jointly at the Hunterian Institute and the Institute of Child Health
- **1992–94** Development of MRI and MRS techniques for the identification of structural, biochemical and functional abnormalities in children with epilepsy
- **1993** Appointed Professor of Biophysics and Head of the Radiology and Physics Unit, Institute of Child Health
- **1997** Discovery of the previously unrecognised disorder developmental amnesia
- **1998** Elected Fellow of the International Society for Magnetic Resonance in Medicine
- **1998–2003** Elucidation of brain structure–function relationships in a family with an inherited (*FOXP2*) speech and language disorder
- **1999** Elected Fellow of the Academy of Medical Sciences
- **2008** Made Honorary Member, National Magnetic Resonance Society of India

Professor Tim Griffiths: Making sense of sound

Summary

Professor Tim Griffiths has been supported by the Wellcome Trust over the past 15 years. He uses novel ideas and innovative approaches to understand how the brain processes sound, particularly how it makes a 'picture' of sound.

Background

Professor Tim Griffiths trained as a neurologist. During his undergraduate studies and his postgraduate clinical training, he developed an interest in psychoacoustics – the study of the perception of sound – and functional brain imaging. He decided to try to complement clinical approaches with those based on auditory functional imaging, developing both as ways to investigate how the brain handles sound.

To make sense of complex sounds, the brain converts them to 'abstracted auditory elements' that are then processed by perceptual and cognitive systems; Professor Griffiths's work, therefore, uses several different techniques. Flexible and responsive funding from the Trust, including a Senior Research Fellowship in Clinical Science funded since 2000, has allowed him to undertake multidisciplinary research.

His longstanding collaborations with the University of Iowa and the Wellcome Trust Centre for Neuroimaging, among others, are vital to his ability to take multiple approaches to the same problem. At the whole-brain level, Professor Griffiths has developed a range of behavioural tests to elucidate how humans process complex sound in health and disease. He has also used functional brain imaging techniques – including functional magnetic resonance imaging (fMRI) and positron electron tomography (PET) – to explore this process in detail. These imaging technologies help researchers to define cortical mechanisms for sound perception, in terms of the parts of the brain involved and of the pattern of communication between them. His research team also studies human sound processing at the neuronal level.

Advance

Professor Griffiths and colleagues have probed how the brain processes various aspects of sounds, including music, and identified specific mechanisms. The team has investigated a number of sound qualities relevant to a variety of stimuli, including time perception (rhythm and meter), pitch (the perceived highness or lowness of a tone) and timbre (the quality of a sound that distinguishes between different instruments or speakers).

Another strand of research is dedicated to understanding how people's judgements of unpleasant sounds are represented in the brain. Scientists have theorised that certain acoustic properties of sound could evoke unpleasant sensations innately – perhaps tapping into an evolutionarily ancient arousal pathway in the brain. Professor Griffiths and colleagues identified specific frequency and time characteristics of sounds associated with unpleasant sensations and can now predict the unpleasantness of a sound from how it is represented in a model of the auditory system. They have also mapped the relevant acoustic features and unpleasantness within a pathway to the ancient limbic system within the brain.

In addition to these human studies, Professor Griffiths's team has recently started to apply brain imaging paradigms to macaque monkeys to establish a primate model for human auditory cognition. They have already completed the first fMRI studies and maps of the auditory areas in the brainstem and cortex. The group has also conducted several studies examining the functional organisation of those areas to allow direct comparison with those in humans.

The methods developed by Professor Griffiths are not just relevant to specific auditory disorders. His team studies people with disrupted auditory networks caused by developmental disorders such as dyslexia and also by brain lesions. Disrupted networks can also be caused by common degenerative disorders, such as dementia.

Recent work on the auditory cortex undertaken in Iowa is starting to yield direct evidence of neural bases for pitch representation. This has led to further studies looking at how this system can go wrong in tinnitus (where people perceive sounds even though there is no external stimulus). The team's work investigating unpleasant sounds is also relevant to tinnitus, in which there may be abnormal connections between the auditory brainstem and limbic system, and also to migraine, where oversensitivity to unpleasant sounds occurs.

Professor Griffiths's approaches inform current debate with other groups around the world working on central auditory processing. For example, the basis for pitch analysis is currently highly controversial: can it be explained by single neurons, groups of neurons or connected systems of neurons? Recording work and functional imaging carried out by the team support the existence of pitch representation in groups of neurons and connected systems. They also call into question suggestions of a single brain area for pitch suggested by some animal studies. The combination of human neurophysiology and functional imaging, and the use of 'generic' stimuli, make the group ideally placed to compare mechanisms for human perception with animal models.

Professor Griffiths and colleagues are now investigating how we process more complex, natural-sounding sounds rather than simple, simulated sounds such as clicks and tones. They are using syllabic-like sounds with no associated meaning – which, unlike natural sounds, can be manipulated systematically. Using this basic approach in humans and macaque models, they aim to eventually apply their findings to human conditions. This 'bottom-up' approach complements the work of the larger number of groups in the world assessing speech.

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Timeline of Professor Tim Griffiths

1995	Wellcome Trust Training Fellowship for Medical and Dental Graduates	Discovery of sound-movement deficit due to cortical damage
1997	Wellcome Trust Advanced Fellowship for Medical Graduates	
1998		Discovery of pitch mechanisms in human auditory cortex
2000	Discovery of mechanism for musical hallucinations in deaf people	Wellcome Trust Senior Research Fellowship in Clinical Science
2004	Appointed Professor of Cognitive Neurology, Newcastle University	Volkswagen Foundation grant to assess auditory size analysis in humans
2005	Renewal of Wellcome Trust Senior Research Fellowship in Clinical Science	
2008	Welcome Trust project grant to assess primate fMRI model of cognition	Appointed Academic Editor, *PLoS Biology*
2009	First macaque auditory fMRI studies completed in Newcastle	Appointed to Adjunct Faculty, University of Iowa
2010	First human neurophysiological recordings of a neural correlate of pitch in Iowa	Second renewal of Wellcome Trust Senior Clinical Fellowship

Professor Trevor Robbins: The action of drugs in the brain

Summary

Professor Trevor Robbins, of the Behavioural and Clinical Neuroscience Institute in Cambridge (funded by the Medical Research Council and the Wellcome Trust), uses brain imaging techniques and sophisticated psychological and cognitive tests to identify how and where drugs work in the brain. His team's studies are helping to clarify the precise effects of different drugs on different neurotransmitters such as dopamine and noradrenaline.

Background

Researchers at the University of Cambridge's Behavioural and Clinical Neuroscience Institute (BCNI) use imaging techniques, including magnetic resonance imaging (MRI) and positron emission tomography (PET), to explore the function of brain systems. They particularly focus on the frontal lobes and the 'reward' systems in the striatum, in humans and experimental animals. Their aim is to understand how various drugs work to produce changes in the brain, which in turn affect behaviour.

Professor Trevor Robbins is particularly interested in the beneficial effects of prescription drugs such as Ritalin that appear to 'enhance' cognition and, conversely, the long-term intellectual impairment caused by drugs of abuse, such as cocaine and amphetamines. This is helping to refine the diagnosis of psychiatric disorders and paves the way for the development of novel therapies.

He and colleagues have designed a number of sophisticated psychological tests with which to explore specific aspects of cognition, such as flexibility, addiction and self-control (or impulsivity). These include the Cambridge Neuropsychological Test Automated Battery (CANTAB), developed 20 years ago with the aid of Wellcome Trust funding.

The BCNI – of which Professor Robbins is Director and Professor Ed Bullmore Clinical Director – was established in 2005 with a joint five-year Medical Research Council–Wellcome Trust award (£4.8 million). The award has also given BCNI researchers greater flexibility, enabling them to pursue new ideas and avenues of research, without having to seek specific funding. Building on animal studies and psychological tests on humans and animals, researchers there are now able to use brain imaging to help to pinpoint precisely which parts of the brain are activated during specific cognitive operations – and what goes wrong in neurological and psychiatric disorders.

Advance

Many of Professor Robbins's studies have examined the role of the neurotransmitters dopamine, noradrenaline and serotonin in aspects of behaviour and cognition, such as addiction, impulsivity, flexibility, attention and working memory. With Dr Jeff Dalley, he has used micro-PET to show that rats with a comparatively low number of dopamine receptors in their nucleus accumbens (a brain structure at the bottom of the striatum) are more susceptible to cocaine addiction. Those same rats were more impulsive and impatient than other rats even before they had ever taken cocaine, suggesting that humans with fewer dopamine receptors may also be at risk.

In other studies, undertaken in collaboration with Professor Barbara Sahakian, Professor Robbins has demonstrated that Ritalin – a prescription drug used to treat attention deficit hyperactivity disorder (ADHD) – improved some aspects of cognitive function, including attention and working memory. Using PET and MRI imaging, his team has shown that while Ritalin improves cognition in people with fewer dopamine receptors, it actually impairs cognition in those who possess more receptors. This suggests that there is an optimal level of dopamine, different for each individual, at which performance is maximised; adding more dopamine after that point has the opposite effect.

Other research by Professor Robbins's team has cast light on the mechanisms by which Ritalin remarkably improves impulse control in healthy volunteers as well as people with ADHD. Ritalin is known to work on both noradrenaline and dopamine. The team has gained insight into how the noradrenaline pathway works by studying atomoxetine, another drug used to treat ADHD that works mainly on noradrenaline. These studies have revealed that atomoxetine improves impulse control in people with and without ADHD. The drug works in an area of the frontal cortex where, in cases of ADHD, lesions impair impulse control. These studies help to explain where and how Ritalin acts in the brain: it improves impulse control by its action on noradrenaline in the cortex and enhances cognition by its action on dopamine in the striatum.

Professor Robbins, together with Dr Roger Barker and colleagues, has further investigated the role of dopamine in cognition in Parkinson's disease, which is caused by a loss of dopaminergic neurons. Motor function is the first thing affected by the disease, with cognitive effects coming later. In light of his work showing that there is an optimum level of dopamine that can help to improve cognition, Professor Robbins hypothesised that a dose of L-DOPA (a medication that supplies dopamine to people with Parkinson's) optimised to improve motor function might be in fact be an overdose for cognitive function. His team's studies have confirmed that although L-DOPA improves motor and some cognitive functions, other aspects of cognition are impaired, explaining the risky and impulsive behaviour demonstrated by patients prescribed the drug.

Elsewhere, the team's work has provided insight into obsessive–compulsive disorder (OCD). Patients were given a learning task where they had to reverse the rules of a game, as well as a task that involved switching between visual concepts such as shape rather than specific visual objects. People with OCD were much worse than control subjects at shifting and at reversing rules, demonstrating cognitive as well as behavioural inflexibility. Further fMRI studies by Dr Sam Chamberlain and others in the team showed that both the orbital frontal cortex and the lateral frontal cortex of the brain showed reduced activity during these tasks.

Intriguingly, first-degree relatives of these patients, with no behavioural symptoms of OCD, displayed the same cognitive inflexibility in both tasks and the same localisation of underactive brain areas. This suggests OCD may be a cognitive disorder, possibly inherited through the genes, indicating that even asymptomatic family members may be at risk. Work led by Professor Bullmore and Dr Lara Menzies has also identified structural brain changes that correlate with these functional impairments.

Professors Robbins and Sahakian, Dr Ulrich Muller, Ms Natalia del Campo and colleagues are currently screening a large population of healthy adults, without drug addiction, for impulsivity (measured by various tasks) and low dopamine receptors (measured by PET scanning). Their prediction is that a subgroup with high impulsivity will have reduced dopamine receptors, suggesting they may be at risk for drug addiction. Professor Bullmore and Dr Karen Ersche are similarly investigating such candidate vulnerability factors in stimulant drug abusers.

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Timeline of Professor Trevor Robbins

- 1985: Co-invention of the CANTAB battery
- 1990: Elected Fellow of British Psychological Society
- 2000: Elected Fellow of Academy of Medical Sciences
- 2002: Appointed Professorial Head of Department of Experimental Psychology, University of Cambridge
- 2005: Development of novel theory of stimulant drug addiction (with B J Everitt), published in *Nature Neuroscience*
- 2005: Elected Fellow of the Royal Society
- 2005: Funding of MRC–Wellcome Trust Behavioural and Clinical Neuroscience Institute
- 2007/08: Discovery of impulsivity endophenotype in rodents relevant to cocaine abuse and addiction, published in *Science*
- 2009: Sixth renewal of Wellcome Trust programme grant
- 2009: President of the British Neuroscience Association

Professor Steve Williams: Imaging insight

Summary

Professor Steve Williams was the first student to obtain a PhD in magnetic resonance imaging (MRI) at the University of Cambridge. Over the following 20 years, he has advanced a wide range of brain imaging techniques and his research has provided valuable insights into numerous neurological and psychiatric disorders including motor neurone disease, stroke, depression, schizophrenia and autism. This research is leading to improved diagnosis and better predictors of response to treatment.

Background

In the 1980s, the use of MRI techniques, pioneered a decade earlier by Sir Peter Mansfield and colleagues at the University of Nottingham, was gathering pace. As bigger magnets were developed, it became possible to scan people and get an image of what was happening in their bodies.

At this time, Steve Williams was learning about magnetic resonance techniques while working as an NMR spectroscopist at Beecham Pharmaceuticals before taking up a prestigious Herchel Smith PhD Scholarship at Cambridge. He then moved to Queen Mary College in London in the late 1980s and set up an intercollegiate scanning unit shared by all London laboratories at a time when local research groups did not have the expertise or budget to develop their own facilities. He spent the next few years developing structural and metabolic imaging techniques to look at animal models of diabetes, cancer, ischaemia and multiple sclerosis. In the mid-1990s, Professor Williams took up a position at the Institute of Psychiatry at King's College London and was charged with the task of developing and applying imaging research for central nervous system disorders. Within a few short years, the institution became a world leader in psychiatric neuroimaging.

In 2002, a Joint Infrastructure Fund award from the Trust, matched by the South London and Maudsley Hospital in South London, enabled Professor Williams and colleagues to build the Centre for Neuroimaging Sciences at King's. A stream of Wellcome Trust project grants, clinical and basic research fellowships have been awarded to the Centre, helping it draw talented scientists from around the world and explore the use of imaging to help understand and treat a range of neurological and psychiatric diseases.

Professor Williams is also part of a team that, in 2009, was awarded a Wellcome Trust–EPSRC grant to advance medical engineering in the UK. The newly established Medical Engineering Centre at King's College London brings together engineers, physicists, computer scientists, chemists and clinicians to develop a range of new healthcare devices. For example, his team is particularly interested in the development of automated image analysis and classification techniques for improved patient diagnosis and prognosis.

Advance

For the past decade, Professor Williams has aimed to make brain imaging an essential clinical tool in psychiatry, which could have far-reaching effects. If imaging can provide more accurate diagnosis and visualisation of aberrant neurobiology then this will help reduce the current stigma surrounding numerous mental illnesses, as well as improve the patient's insight of their condition and compliance with treatment. With this in mind, Professor Williams and collaborators have developed and improved imaging methods to investigate several psychiatric disorders including schizophrenia, bipolar disorder, Alzheimer's disease and attention deficit hyperactivity disorder. The methods can also indicate whether a patient is likely to respond to treatment – one of the biggest problems within psychiatry. Identifying whether patients are more likely to respond to medication or to behavioural therapy could save months of wasted time, misery and frustration.

Professor Williams's team is now helping local experts in psychosis studies to investigate how brain scans could help predict whether a person might develop schizophrenia in the future. They are studying a large at-risk population of teenage males identified through family history, genetic studies, and school and behavioural reports. Early identification and treatment of these at-risk individuals may help delay – if not prevent – the onset of their first episodes.

Professor Williams and colleagues have also made major efforts to improve our understanding and assessment of neurodegenerative disorders. For example, he was part of the imaging team that first visualised the damage that occurs along the cortical spinal tract in motor neurone disease. Previously these lesions could only be detected at autopsy. He has also contributed to current strategies for the detection of multiple sclerosis in both the brain and the spinal cord and, in the area of Parkinson's disease research, the group has developed a brain scanning and analysis protocol that helps identify which particular form of the syndrome is present. The ability to distinguish between the more benign form of Parkinson's disease and more aggressive forms helps clinicians predict which patients will decline more quickly, and ultimately how they are managed. This will help make treatments more targeted and effective.

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Timeline of Professor Steve Williams

1988	First PhD in MRI awarded by the University of Cambridge	
1989		Founds University of London intercollegiate research facility for biomedical MRI
1994	Pfizer Young British Scientist of the Year	Senior Lecturer and Head of Neuroimaging Research at Institute of Psychiatry
1999	Professor of Imaging Sciences, Institute of Psychiatry, King's College London	First to propose the use of diffusion-based MRI to detect corticospinal tract damage
2002	Principal Investigator of the Wellcome Trust (JIF)-funded Centre for Neuroimaging Sciences	
2004		First fMRI studies to look at depression and drug effects on brain function
2007	Unveils homeostatic and higher brain centre interactions in regulating food intake	
2008		Receives the first King's Business Development Award
2009	Head of a new Department of Neuroimaging, Institute of Psychiatry, King's College London	
2010	GE Healthcare Thought Leader of the Year for pioneering work in psychiatric neuroimaging	Cutting-edge study on quiet MRI of infant brain maturation and myelination; NHS Innovation of the Year Award for new '90% accurate' approach to autism classification

Background

- The Wellcome Trust Centre for Neuroimaging at University College London is one of the leading brain imaging centres in the world. Established as the Functional Imaging Laboratory in 1994 with a major grant from the Trust, it was awarded Wellcome Trust Centre status in 2006.
- The Centre supports a wide range of research activities reflecting the diversity of functions the brain performs, from sensory processing to higher cognitive functioning such as decision making.

Discoveries

- Research from the Centre has helped to establish that brain function is not just isolated in single regions but involves coordinated activity integrated across many regions. The advent of brain imaging has made it possible to measure these interactions in close to real time.
- Studies have also demonstrated that the process of learning triggers changes in how different regions interact. Centre researchers have demonstrated the plasticity of the adult human brain; they have also demonstrated that this plasticity is realised not just through changes in neural activity but through physical changes in brain morphology. Professor Eleanor Maguire's studies of London taxi drivers, for example, implies that their knowledge of London streets and routes is associated with an enlarged hippocampus.
- The Centre has developed a strong underpinning methodology that has revolutionised neuroimaging analysis. Statistical Parametric Mapping (SPM) uses advanced mathematical techniques to characterise brain organisation. The software creates models of how the brain is wired and how it responds in different situations. These models are then used to interpret measured brain responses using imaging and electromagnetic studies. It provides an underlying philosophy for studying the brain that may well approximate how the organ itself actually works.

Research leaders

- The Centre has a unique environment for training with its diversity of principal investigators, the organisation of its programme, a strong mentoring system embedded in a clinical environment, and its location next to major clinical and research institutions.
- The Centre is proud to host a complement of Wellcome Trust PhD students, Clinical Training and Career Development Fellows, and intermediate and advanced fellows.
- Based in Queen Square in London, the Centre is close to a major neurological hospital, so students are regularly exposed to clinical issues and clinical demonstrations. Also next door are UCL's Institute of Cognitive Neuroscience and the Gatsby Computational Neuroscience Unit, each having their own educational programmes, which are available to Centre students.

Research environment

The Centre's principal investigators and their research groups embody the diversity of research in neuroscience:

- Professor Ray Dolan FRS (top right), Director of the Wellcome Trust Centre for Neuroimaging, studies how emotion influences cognition. A major current focus of his team's work is the influence of emotion on decision making under uncertainty across a range of contexts, and in particular a variety of emotional contexts.
- Professor Karl Friston FRS is a Wellcome Trust Principal Research Fellow whose major interest is in developing generic models of how the brain works. He is strongly associated with the development of SPM.
- Professor Jon Driver is a Wellcome Trust programme grantholder and Royal Society Anniversary Research Professor. His research focuses on attention and how the brain networks involved are affected by damage, such as that caused by stroke. He has also produced insights into unusual and striking disorders of attention such

as hemispatial neglect, in which people no longer pay attention to half of their environment.
- Professor Cathy Price is a Wellcome Trust Senior Research Fellow. She investigates how the brain processes language and what the likely effects of brain damage on this are. Her work looks not at speech but at the ability to marshal concepts and use them for thought and expression through any medium. Her research has illuminated the processes through which stroke has a devastating effect on language.
- Professor Geraint Rees FMedSci is a Wellcome Trust Senior Clinical Fellow. He studies visual awareness and consciousness. His group seeks to understand the neural basis of human consciousness and how it can be affected by neurological disease.
- Professor Eleanor Maguire aims to establish how we internally represent large-scale space and our personal (autobiographical) experiences within it, and how both types of memory can be understood within a unified framework that supports our integrated sense of who and where we are. A Wellcome Trust Senior Research Fellow, she also looks at the effects of pathology on memory representations at different points in people's lives (such as developmental disorders in children or dementia in elderly people).
- Professor Semir Zeki studies the visual brain – how we construct the visual world and how discrete aspects of vision are processed and automatically segregated to different parts of the brain. With a Wellcome Trust Strategic Award, he has also developed an interest in neuroaesthetics – how our visual brain processes aesthetic values such as beauty.
- Professor Tim Griffiths is a Wellcome Trust Senior Clinical Fellow who investigates complex sound processing by the brain ('the mind's ear'). This is not limited to speech but asks what acoustic properties of our environment are important for our brain to build up an auditory representation of our world.

Influence

- In SPM, the Centre has created a common tool and framework for brain imaging research. A freely available, open-source software package, SPM is widely used all over the world, ensuring that brain imaging researchers have a common starting point from which to compare their work and develop collaborations.
- Researchers at the Centre have produced cumulative evidence demonstrating the brain's remarkable plasticity and ability to recover. This has had an important cultural impact on clinicians and patients, creating added emphasis on rehabilitation and hope for recovery following serious brain injury.

Key publications

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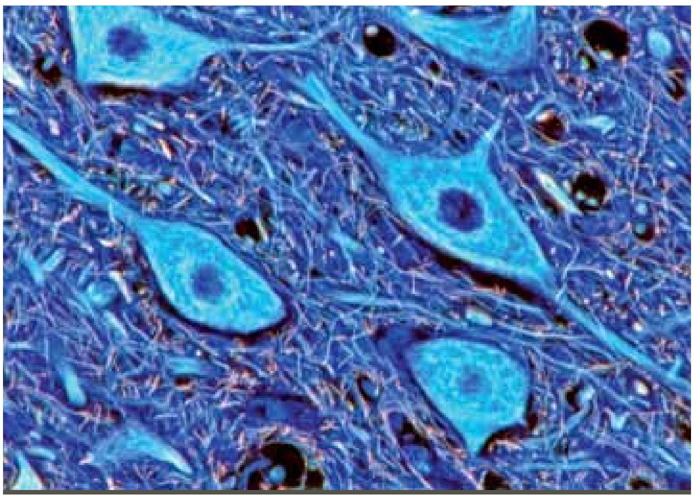


Annex A: Membership of the Wellcome Trust Expert Group

Members of the Wellcome Trust Expert Group on human functional brain imaging

Professor David Delpy (Chair)	Engineering and Physical Sciences Research Council, UK
Professor Paul Matthews	GlaxoSmithKline Clinical Imaging Centre, UK
Professor Peter Morris	University of Nottingham, UK
Professor Roger Ordidge	University College London, UK
Professor Wolf Singer	Max Planck Institute for Brain Research, Germany
Professor Arthur Toga	University of California, USA
Professor Joanna Wardlaw	Brain Research Imaging Centre, University of Edinburgh, SINAPSE Collaboration, UK
Professor Richard Frackowiak	Centre Hospitalier Universitaire Vaudois, Switzerland
Professor Terry Jones	MRC-Cyclotron Unit, Imperial College School of Medicine, Hammersmith Hospital, UK

Wellcome Trust industry experts on human functional brain imaging

Professor Paul Matthews	Head, GlaxoSmithKline Clinical Imaging Centre, UK
Dr Bengt Nielson	General Manager, General Electric Healthcare, Sweden
Mr John Jeans	Chief Operating Officer, Medical Research Council (MRC), UK

Annex B: Project background and methodology

1. As part of moves to strengthen the Wellcome Trust's review activity, in 2008, with the support of the Board of Governors, the Assessment and Evaluation team developed an approach to evaluate the impact of its funding at a subject, portfolio level. This portfolio review adopts a pragmatic, macro level approach to provide analysis of the key developments and impacts of Wellcome Trust's support and influence at a level beyond the individual grant and/or funding scheme.

2. Conducted during the second half of 2009 and 2010, this report describes the second 'portfolio' review, which focuses on the development of human functional brain imaging over the past 20 years and attempts to identify the role of the Wellcome Trust within this landscape. (The first portfolio review was entitled *Human Genetics 1990–2009*.) Human functional brain imaging is a portfolio area in which the Trust has not simply provided funding support; it has also been an active player in the formulation of international research policy and strategy in a field that has evolved radically in recent years.

3. Our portfolio review aims to be both reflective and prospective, bringing together a raft of information and viewpoints, to identify the crucial factors that have brought about the major step changes and developments in the field. Reflecting on the past also draws out learning and helps inform speculations on how we might operate in the future; by engaging our subject experts in the process, we have been able to consider future directions and whether there are opportunities for us develop our support in certain key strategic areas. By using this combination of methods, we hope this review will inform funding strategy, both in the level of future funding required to support specific scientific areas and in the selection of mechanisms – and, potentially, policies – to support research in the area.

   The specific aims of the portfolio review were three-fold:
   1. to identify the key landmarks and influences on the human functional brain imaging landscape over the past two decades (1990–2009)
   2. to consider the key features of the Wellcome Trust's impact on this human functional brain imaging research landscape
   3. to consider the future of human functional brain imaging and identify where there may be opportunities for Wellcome Trust strategy and funding.

4. Over the past two decades (1990–2009), support for human functional brain imaging has accounted for approximately 2 per cent of total Wellcome Trust funding, or £114m.

5. In performing this review of a portfolio of funding and adopting a macro approach, looking at trends across the field and bringing subject experts into the heart of the review, we also hope to test whether this approach is valuable to the Wellcome Trust and strategy more generally.

Methodology

6. Finding the optimum way to evaluate the impact of scientific research – and to use such information in strategic decision making – remains a major challenge. When attempting to assess the impact of a particular funding stream or funder over a substantial amount of time, we made the decision not to evaluate on a micro basis (by looking at individual grants) but instead to take a macro, holistic view of the development of the field over time and to consider the part that the Trust and its funding has played within the field. We know that the Trust has committed a substantial amount of its funding for brain imaging – and, specifically, human functional brain imaging-focused research – over a long period. Support for brain imaging remains a cornerstone of its research funding strategy.

7. Thus, the review involved four complementary streams:

   - a landscape analysis
   - narrative case studies
   - an Expert Group
   - semi-structured interviews with industry experts.

Landscape analysis

8. The landscape analysis had three components:

- the Wellcome Trust funding analysis
- an international scientific, policy and funding landscape analysis
- a bibliometric analysis.

Wellcome Trust funding analysis

9. A search of the Wellcome Trust's AS400 Grants System was conducted to identify human functional brain imaging-related funding provided by the Wellcome Trust from 1990 onwards. This involved a search for the specific term "medical imaging", as identified by Wellcome Trust Science Funding staff – capturing a total of 767 human functional brain imaging-related grants.

10. The full list of grants was then manually filtered by Science Funding staff to identify grants with a human functional brain imaging focus, resulting in a revised total of 218 grants. Because of limitations in the Trust's grants subject classification systems, no attempt was made to further classify grants subjects within human functional brain imaging.

International scientific, policy and funding landscape analysis

11. To provide context to the development of the field of human functional brain imaging research over the period under investigation, a Timeline of key events was produced by Trust staff. The Timeline contains key historical scientific advances that have had a major impact on human functional brain imaging-related research, focusing particularly on the period from 1990 to 2009. Each event contained on the Timeline has been classified as a 'scientific advance', a 'policy development' or a 'funding development'.

12. The Timeline was used as a prompt during the consultation with the Expert Group, and their feedback on the content was invited; the revised version of the Timeline is included in Annex E.

Bibliometric analysis

13. To identify key trends in the type, nature and location of human functional brain imaging-related research over this period, an analysis of publication outputs was conducted. This bibliometric analysis was conducted by Evidence Ltd, part of Thomson Reuters (Scientific UK), and draws on the databases underlying the Web of Science, which include comprehensive coverage of more than 10 000 journals. All research papers included within the databases are allocated by Thomson Reuters to one or more of 253 different subject categories according to which journal the paper is published in; however, it is not possible to easily identify papers concerning human functional brain imaging from these journal subject categories alone, so a subject filter based on five separate keyword searches was created (Table A).

Table A Search terms used for bibliometric analysis of brain imaging

#1 magnetoencephalograph* OR electroencephalograph* OR EEG OR fMRI
#2 (computed SAME tomograph*) SAME (brain OR cerebr*)
#3 (imag* OR positron emission tomograph* OR "magnetic resonance") SAME (brain OR cerebr*)
#4 neuroimag*
5# (PET or MRI or MEG or CAT or CT or NIRS or MRS or NMR) SAME (brain OR cerebr*)

14. As such, the final dataset is thought to be a good proximate dataset for the field of human functional brain imaging and contained 97 050 papers published over the period 1989–2008. A citation analysis was also conducted to provide insight into the quality of papers emerging over the period. To account for variation in citation practices across fields and the impact of publication date on the number of citations accumulated, Evidence Ltd rebase (or normalise) all raw citation data to the world average in the relevant subject field in the year of publication. In the context of this report, the term 'highly cited papers' refers to those papers with an average rebased impact of at least 4 (i.e. they received at least four times as many citations as the average paper published in that year in the same subject area).

15. With scientific research becoming an increasingly collaborative and multi-location activity, research papers are often linked to multiple authors based at more than one research institution. This report uses 'integer counting', meaning that any single paper counts as 'one' output for each author, institution and country contributing to its publication. For example, a paper with two authors from Harvard

University, one author from the University of Texas and one author from the University of Oxford is counted as one output for each of the four authors concerned, one output for each of the three named institutions, and one output each for the USA and the UK. The tables of top countries, institutions and authors, therefore, will feature an element of double counting.

16. Evidence Ltd are able to supply data on UK organisations with a high degree of accuracy because they ensure that organisational name variants are reconciled into one name to counter the limitations of the raw Thomson Reuters address data on the papers themselves. For non-UK data, the tables in this report rely on the raw data, so paper numbers should be considered as indicative rather than absolute, although address reconciliation was effected for 'significant' research organisations. This methodology will have most impact where major organisations have several institutions or research centres (e.g. the MRC will be split into its constituent parts, whereas papers associated with the separate institutes of the CNRS in France, CSIS in Spain or the Chinese Academy of Sciences are all indexed under the name of the parent organisation).

Narrative case studies

17. A series of case studies were compiled, to tell the story and highlight the key accomplishments associated with specific Wellcome Trust investments. These narratives were selected to reflect the range of funding types from major infrastructure and fellowship support to collaborations.

Wellcome Trust Expert Group on human functional brain imaging

18. To complement the landscape analyses and case study work, a key component of this portfolio review was the engagement of human functional brain imaging experts to provide a review of the key influences on the field and assessment of the Trust's role within this. Instead of consulting experts on an individual basis, we tested whether we could usefully employ a cohort of independent subject experts in a group setting.

19. In 1990, the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among several other initiatives, the use of Witness Seminars to promote interaction between these different groups was adopted. The Witness Seminar is a particularly specialised form of oral history, where several people (approximately 40) associated with a particular set of circumstances or events are invited to come together to discuss, debate, and agree or disagree about their memories. The Witness Seminar initiative is led by Professor Tilli Tansey at the Wellcome Trust Centre for the History of Medicine, UCL. Further information about Witness Seminars can be found in *Wellcome Witnesses to Twentieth Century Medicine*.

20. Drawing on the Witness Seminar approach to history and influence mapping, which was originally developed by the Institute of Contemporary British History in 1986, a small number of experts (n = 8, plus a Chair) were invited to debate and discuss the status of human functional brain imaging research 1990–2009 over the course of an afternoon.

21. Existing and increasing pressures on experts generated by the peer review system embedded into science funding have made it traditionally (and increasingly) difficult to involve experts in post-award review, where arguably they could play a major part in helping to consider future funding allocation at a more strategic level. Experts were selected on the basis of their expertise in the field and, to ensure the maximum relevance to the review's aims, at least half of the experts had a fairly good knowledge of the Trust over the period in question.

22. The Expert Group received a summary of the landscaping and bibliometric analysis in advance of their meeting hosted at the Wellcome Trust in October 2009. Under the Chairmanship of Professor David Delpy, the discussion was framed around the broad question areas shown in Table B. The meeting was recorded and the tapes transcribed. We found, alongside significant landscape analysis, that allowing our experts to be both retrospective and speculative enabled us to draw out learning from the past with future implications and to consider how this might link to current and potential future funding strategies.

Table B Outline agenda – Expert Review Group

Past/retrospective
Key impacts and influences on the field
What have been the key developments in the field – validation of Timeline?
What are the origins of the key developments?
What have been the key impacts within the field?
What have been the key impacts beyond the field?
Role of the Wellcome Trust and key influences on the field
What has been the role of the Wellcome Trust throughout this period?
Present
Field progression
Has field got as far as/gone in the direction you anticipated?
What are the current limiting factors?
Who is driving the agenda?
Future/prospective
Speculation and futures
What are the next big challenges in the field?
What might be Wellcome's role?
What strengths could the Wellcome Trust bring to the field?

Semi-structured interviews with industry experts

23. Given the vital part that technology and industry have played in supporting the development of functional brain imaging, semi-structured interviews were used to gain the perspectives of industry experts on how the field and the technology has progressed, particularly focusing on the period from 1990 to 2009. Three semi-structured interviews were conducted with industry experts, and their perspectives were incorporated into our analysis.

24. Specifically, the interviews probed the experts' views on the current most acute, most promising and most challenging areas for human functional brain imaging and asked for an industry perspective on where and what the next big challenges are for the field.

25. Experts were selected on the basis of their expertise in the field and represent a wide range of expertise. The interviews were structured around the broad question areas listed in Table C. The interviews were recorded and the tapes transcribed.

Table C Broad areas – semi-structured interviews

Past/Retrospective
Key impacts and influences on the field
Overall, what do you think have been the key contributions of industry during this time period?
How did these key contributions come about?
What have been the industrial impacts beyond the field ('ripple effects')?
What has been the role of funding agencies/research councils, etc., throughout this period (1990–to date) – working alongside industry?
Present
Field progression
Has the field got as far as/gone in the direction you anticipated?
In your opinion, what are the current limiting factors?
What do you see as the most important technological challenges facing the brain imaging industry (UK and overseas)?
Who is driving the brain imaging industry agenda (UK and overseas)? Who would you consider as key competitors?
What role does the UK currently play in the development of brain imaging technologies?
How are industries in the UK trying to differentiate from overseas competitors?
What role do funding agencies currently play in the brain imaging industry or do they have one?
What geographic markets do you see as a primary focus for present and future growth?
Future/prospective
Speculation and futures
What are the next challenges that you foresee in the imaging industry in the coming years?
What do you see as being the most significant commercial change in the industry during the years ahead?
Where do you see the technology moving in the future, and what do you feel is going to drive the growth of this technology and of the global imaging market?
What role can we expect industries (UK and overseas) to play in shaping the future of the market?
What role can we expect funding agencies/research councils to play in the future development of brain imaging technologies and in shaping the future of the market? Is there a role for them?
Any additional comments?

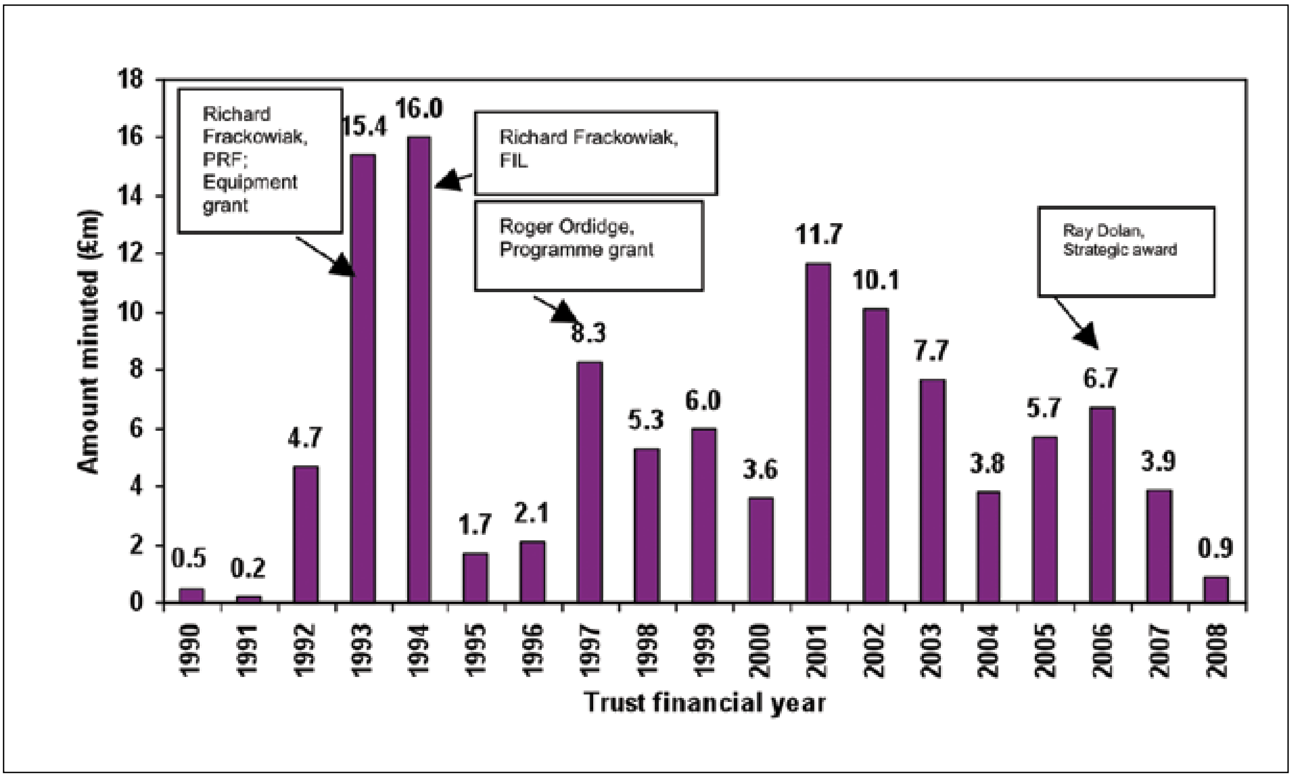
26. Between 1990 and 2008, through its funding divisions, the Wellcome Trust has awarded 218 grants associated with human functional brain imaging research, accounting for £114m (2 per cent of the Trust's funding commitment over this time), of which approximately £50m (39 grants) was allocated to the WTCN, UCL (Figure 2, Annex C).

27. One-third (32 per cent by value; £36m, or 104 grants) of this human functional brain imaging funding has been career-based, supporting individual researchers doing projects based on human functional brain imaging via personal support schemes (Figure 3, Table 2, Annex C): studentships (£2m), Early Career Fellowships (£6m), Intermediate Fellowships (£4m), and Senior and Principal Research Fellowships (£24m). Almost two-thirds of the career-based funding was made available for the Senior and Principal Research Fellowships. A feature of the Wellcome Trust portfolio is sustained and substantial funding for key players in the field (Table 5, Annex C).

28. Two-thirds of funds (69 per cent by value; £79m, or 114 grants) have been allocated to research and project support (equipment, strategic awards, buildings, Joint Infrastructure Funding and project and programme grants (Figure 3, Table 2, Annex C).

29. Over this 20-year period, most (98.6 per cent by value) Wellcome Trust human functional brain imaging research funding has been allocated to UK institutions; only 1.4 per cent of funding (£1.6m) has been committed to non-UK-based human functional brain imaging research (Figure 4, Annex C).

Figure 1 Wellcome Trust grants supporting functional brain imaging research 1990–2008

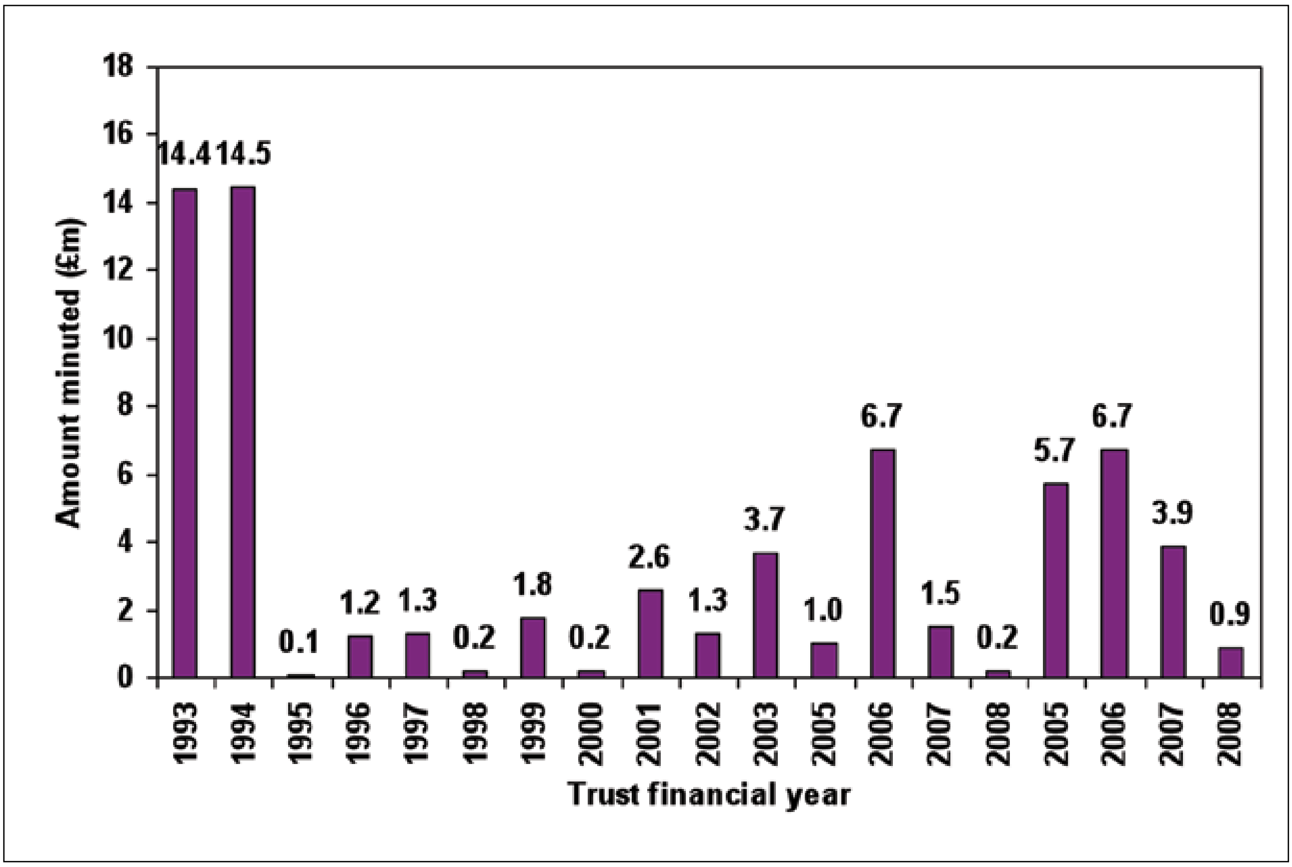


All data are commitment by the Wellcome Trust. Amounts are as awarded and have not been corrected for inflation. Renewals are counted as new grants in the Wellcome Trust grants system.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Figure 2 Spend by year on functional brain imaging research at the WTCN 1990–2008



Base: 39 Wellcome Trust grants funded to the Wellcome Trust Centre for Neuroimaging, UCL.

Source: Wellcome Trust AS400.

Table 1 **Wellcome Trust funding for human functional brain imaging research, 1990–2008**

Year	Wellcome Trust grant funding (commitment £m)	Wellcome Trust brain imaging-related research (commitment £m) (Figure 1)	WT grant funding
1990	53	0.5	1%
1991	60	0.2	0.3%
1992	86	5	6%
1993	437	15	3%
1994	193	16	8%
1995	198	2	1%
1996	168	2	2%
1997	222	8	4%
1998	212	5	2%
1999	354	6	2%
2000	480	4	1%
2001	388	12	3%
2002	419	10	2%
2003	395	8	2%
2004	258	4	2%
2005	344	6	2%
2006	325	7	2%
2007	359	4	1%
2008	525	1	0.2%
TOTALS	**5476**	**114**	**2%**

All data from the Wellcome Trust grants system are 'commitment'. Data are rounded to the nearest £m or percentage.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Table 2 Wellcome Trust funding for brain imaging by grant type 1990–2008

Grant type	number of grants	Percentage of total human functional brain imaging grants	amount (£m)[a]	Percentage of total human functional brain imaging funding
Personal funding				
Studentship	22	10%	2	2%
Early career fellowship	42	19%	6	5%
Intermediate fellowship	21	10%	4	4%
Senior/principal research fellowship	19	9%	24	21%
Total personal funding	**104**	**48%**	**36**	**32%**
Research funding				
Project	75	34%	12	11%
Programme	18	8%	25	22%
JIF/SRIF	5	2%	12	11%
Strategic award	1	0.5%	7	6%
Equipment	6	3%	9	8%
University award	1	0.5%	1	1%
Other[b]	8	4%	13	11%
Total research funding	**114**	**52%**	**79**	**69%**
TOTAL	**218**		**114**	

[a] Data are rounded to the nearest £m.

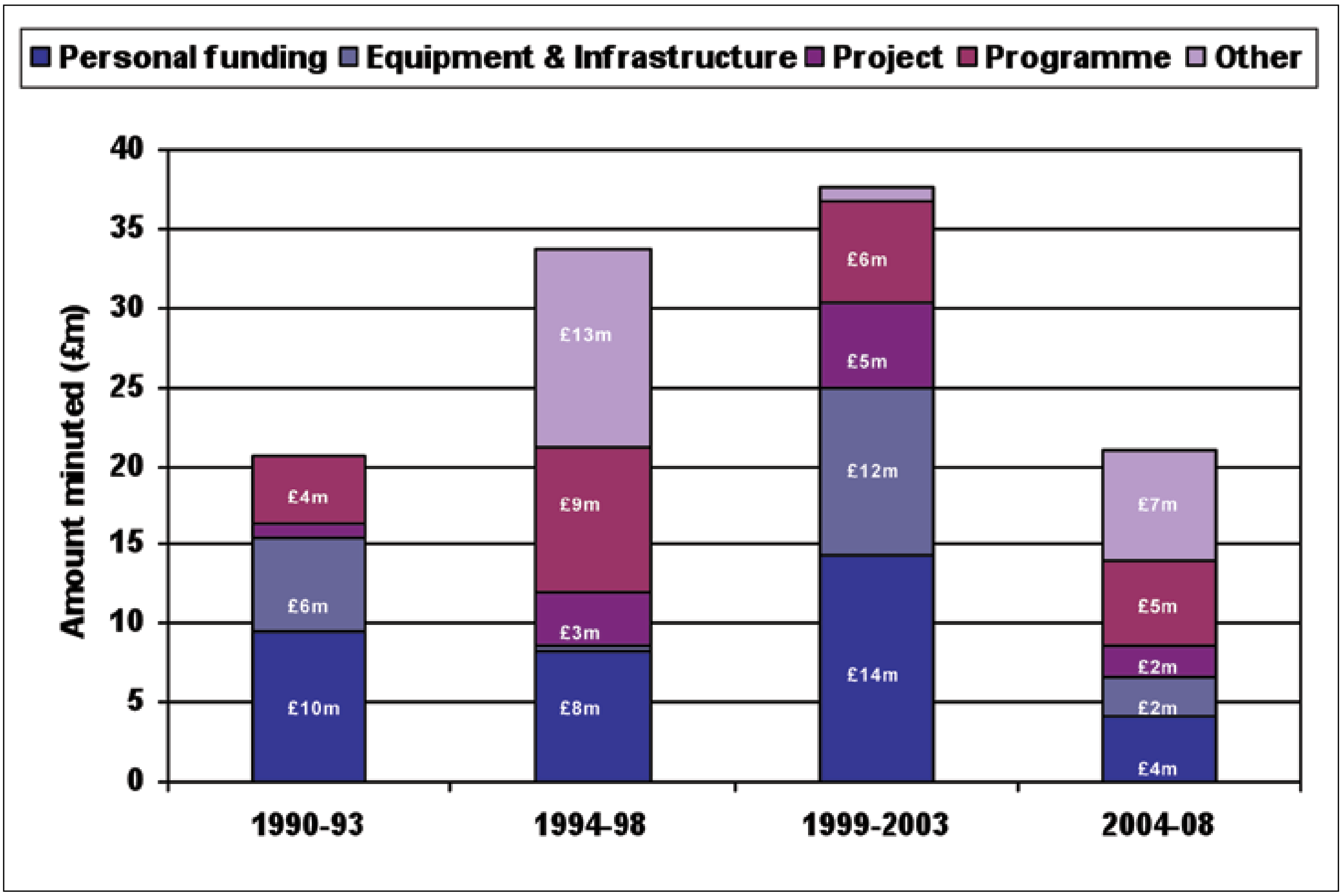
[b] 'Other' includes an Infrastructure Award (£12m), a Translational Award (£0.28m), and Travel grants, Symposium and Research Leave Awards (£0.11m).

Percentages are rounded and might not equal 100 per cent.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Figure 3 Wellcome Trust funding for brain imaging research by grant type 1990–2008 (£m)

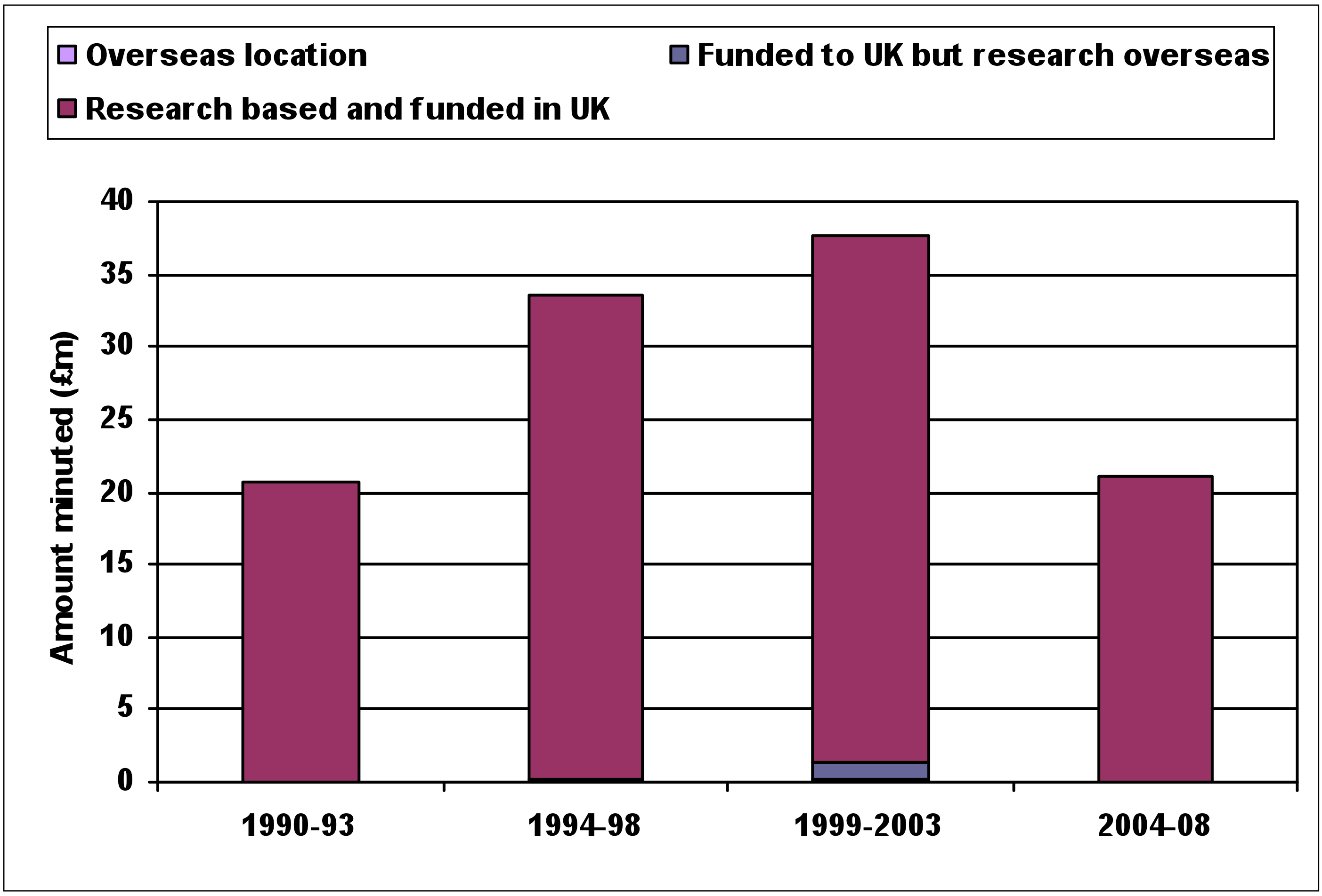


All data are commitment by the Wellcome Trust.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Figure 4 Wellcome Trust funding for non-UK-based and UK-based human functional brain imaging research 1990–2008



Base: 218 Wellcome Trust grants associated with brain imaging.
Source: Wellcome Trust AS400.

Table 3 **Institutions in receipt of most Wellcome Trust funding for human functional brain imaging, 1990–2008 (top ten)**

Institution	Amount (£m)
University College London (WTCN/FIL)	75 (51)
King's College London	11
University of Cambridge	7
Imperial College London	6
Birkbeck College London	3
University of Oxford	3
University of Nottingham	2
University of Newcastle	2
University of York	1
Aston University	0.9

All data are commitment by the Wellcome Trust.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Table 4 **Researchers in receipt of the most Wellcome Trust (research and personal support) funding for human functional brain imaging research, 1990–2008 (top ten)**

Researcher	Current host institution	Amount (£m)	Grant type
Professor Richard Frackowiak	University College London, WTCN	8	Principal Research Fellowship; programme; project
Professor Raymond Dolan	University College London, WTCN	7	Project (x2); Senior Research Fellowship; Strategic Award
Professor Roger Ordidge	University College London	6	Programme
Professor David Gadian	University College London	6	Programme (x3); Biomedical Research Collaboration Grant
Professor Trevor Robbins	University of Cambridge	5	Programme (x3)
Professor Catherine Price	University College London, WTCN	2	Senior Research Fellowship (x2)
Professor Karl Friston	University College London, WTCN	2	Senior Research Fellowship; Principal Research Fellowship
Professor John Duncan	University College London	2	Project; programme
Professor Christopher Kennard	Imperial College London	2	Programme (x2)
Professor Geraint Rees	University College London, WTCN	2	Senior Research Fellowship (x2)

Base: Senior and Principal Research Fellowships in the cohort of 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Table 5 **Wellcome Trust Senior and Principal Research Fellows focusing on human functional brain imaging-related research funded, 1990–2008**

Year	Researcher	Institution	Grant type
1993	Professor Robert Turner	University College London, WTCN	Principal Research Fellowship
	Professor Richard Frackowiak	University College London, WTCN	Principal Research Fellowship (renewed 2000)
	Professor Jeremy Hebden	University College London	Senior Research Fellowship (basic)
1994	Dr P J Grasby	University College London, WTCN	Senior Research Fellowship (clinical)
	Professor Raymond Dolan	University College London, WTCN	Senior Research Fellowship (clinical)
	Dr Richard Wise	University College London, WTCN	Senior Research Fellowship (renewed 1997 and 2000)
	Professor Karl Friston	University College London, WTCN	Senior Research Fellowship (clinical)
1996	Professor Christopher Frith	University College London, WTCN	Principal Research Fellowship (renewed 2004)
1997	Professor Catherine Price	University College London, WTCN	Senior Research Fellowship (renewed 2007)
1998	Professor Michael Rugg	University College London	Principal Research Fellowship
1999	Professor Karl Friston	University College London, WTCN	Principal Research Fellowship (renewed 2004 and 2009)
2000	Professor Timothy Griffiths	Newcastle University	Senior Research Fellowship (renewed 2005 and 2010)
	Professor Masud Husain	University College London	Senior Research Fellowship (renewed 2005)
2002	Dr Paul Fletcher	University of Cambridge	Senior Research Fellowship (renewed 2006)
2003	Professor Geraint Rees	University College London	Senior Research Fellowship (renewed 2007)
	Professor Eleanor Maguire	University College London	Senior Research Fellowship (renewed 2008)
	Professor Veena Kumari	King's College London	Senior Research Fellowship (basic)

Data are rounded to the nearest £m.

Base: 218 Wellcome Trust grants associated with brain imaging.

Source: Wellcome Trust AS400.

Annex D: Wellcome Trust bibliometric analysis for human functional brain imaging, 1989–2008

Table 1 Number of brain imaging papers published in five-year periods by country (top 20)

USA	3613	7385	10 180	15 111
Germany	818	2032	3718	5193
UK	578	1488	2774	4321
Japan	850	1980	3022	3260
France	534	1140	1666	2336
Italy	407	1027	1549	2397
Canada	432	835	1363	2379
Netherlands	266	512	926	1709
Switzerland	223	447	738	1142
Spain	118	388	752	1090
Australia	105	298	620	1046
Sweden	223	442	526	640
Finland	200	355	581	687
Belgium	135	282	468	706
Austria	160	324	486	615
China	45	78	308	1121
South Korea	20	97	349	872
Turkey	20	148	323	728
Brazil	16	125	303	620
Russia	55	280	302	333

Source: Thomson Reuters 2009. Analysis: Evidence, Thomson Reuters (Scientific UK).

Table 2 Countries (top 20) showing the fastest growth in brain imaging-focused papers

Country	Number of 'brain imaging' publications per year 1994–98	Change [a]	2004–08	Change [b]
China	78	73.33%	1121	263.96%
South Korea	97	385.00%	872	149.86%
Turkey	148	640.00%	728	125.39%
Brazil	125	681.25%	620	104.62%
Netherlands	512	92.48%	1709	84.56%
Canada	835	93.29%	2379	74.54%
Australia	298	183.81%	1046	68.71%
UK	1488	157.44%	4321	55.77%
Italy	1027	152.33%	2397	54.74%
Switzerland	447	100.45%	1142	54.74%
Belgium	282	108.89%	706	50.85%
USA	7385	104.40%	15 111	48.44%
Spain	388	228.81%	1090	44.95%
France	1140	113.48%	2336	40.22%
Germany	2032	148.41%	5193	39.67%
Austria	324	102.50%	615	26.54%
Sweden	442	98.21%	640	21.67%
Finland	355	77.50%	687	18.24%
Russia	280	409.09%	333	10.26%
Japan	1980	132.94%	3260	7.88%

Source: Thomson Reuters 2009. Analysis: Evidence, Thomson Reuters (Scientific UK).

[a] Percentage change 1989–93 and 1994–98 (ten years).

[b] Percentage change 1999–03 and 2004–08 (ten years).

Table 3 Subjects showing the fastest growth in 'brain imaging' publications

Subject field	Number of publications per year 1994–98	Change[a]	2004–08	Change[b]	Change[c]
Computer science, artificial intelligence	94	3033.33%	462	36.69%	15 300.00%
Psychology, experimental	206	390.48%	1352	94.81%	3119.05%
Computer science, theory and methods	62	181.82%	483	189.22%	2095.45%
Neurosciences	1994	173.53%	6363	93.88%	772.84%
Behavioural sciences	95	72.73%	460	134.69%	736.36%
Engineering, electrical and electronic	148	362.50%	252	11.01%	687.50%
Psychology, clinical	125	165.96%	284	34.60%	504.26%
Radiology	2586	106.38%	6354	43.82%	407.10%
Clinical neurology	3735	127.19%	7761	21.11%	372.08%
Ophthalmology	141	95.83%	310	21.09%	330.56%
Physiology	260	94.03%	496	47.62%	270.15%
Surgery	1102	132.49%	1708	3.89%	260.34%
Paediatrics	988	111.11%	1478	22.66%	215.81%
Neuroimaging	418	176.82%	469	75.00%	210.60%
Psychiatry	1329	98.95%	1923	35.61%	187.87%
Anaesthesiology	330	97.60%	478	20.10%	186.23%
Endocrinology and metabolism	242	96.75%	285	19.75%	131.71%
Medicine, general and internal	472	55.26%	646	5.73%	112.50%
Pharmacology and pharmacy	553	40.71%	589	-3.60%	49.87%
Engineering, biomedical	674	48.13%	498	72.32%	9.45%

Source: Thomson Reuters 2009; Analysis: Evidence, Thomson Reuters (Scientific UK).

[a] Percentage change 1989–93 and 1994–98 (ten years).

[b] Percentage change 1999–03 and 2004–08 (ten years).

[c] Percentage change 1989–93 and 2004–08 (20 years).

Table 4 Organisations producing highly cited papers[a] in brain imaging, 1989–2008

World organisation (ranked by highly cited papers over 2004–2008 period)	Highly cited papers			
	1989–1993	1994–1998	1999–2003	2004–2008
University College London	28	111	194	175
Harvard University	26	110	138	147
University of California Los Angeles	30	47	72	102
Stanford University	13	46	65	92
University of Pittsburgh	9	48	56	76
Massachusetts General Hospital	10	64	76	74
University of Oxford	5	19	67	73
National Institute of Mental Health (NIMH)	10	62	76	71
University of California San Diego	21	29	51	63
Columbia University	0	16	28	61
King's College London	4	21	54	57
Washington University, St Louis	12	43	58	56
University of Pennsylvania	8	40	46	56
New York University	3	18	23	55
Yale University	19	36	51	55
Duke University	5	15	33	53
Johns Hopkins University	14	35	50	50
McGill University	14	47	47	48
University of Toronto	6	18	35	47
University of Cambridge	0	9	39	46
University of California Davis	2	14	30	46

[a] Highly cited papers refers to those papers with an average rebased impact of at least 4 (i.e. they have received at least four times as many citations as the average paper published in that year in the same subject area).

Base: 21 organisations producing the most highly cited papers in human functional brain imaging in the 2004–2008 period.

Source: Thomson Reuters 2009; Analysis: Evidence, Thomson Reuters (Scientific UK).

Table 5 Authors of highly cited papers in brain imaging, 1989–2008, worldwide

Author	Number of highly cited papers
Karl Friston	100
Ray Dolan	94
Richard Frackowiak	89
Chris Frith	69
Alan Evans	67
David Miller	61
Bruce Rosen	57
Daniel Weinberger	55
Gary Glover	47
Steven Williams	46
Michael Brammer	42
John Gabrieli	42
Mark D'Esposito	41
Massimo Filippi	41
Ferenc Jolesz	41
Marcus Raichle	41
Alan Thompson	41
Ed Bullmore	40
Frederik Barkhof	39
Randy Buckner	39

Base: 20 authors producing the most highly cited papers in brain imaging, 1989–2008.
Source: Thomson Reuters 2009. Analysis: Evidence, Thomson Reuters (Scientific UK).

Table 6 Wellcome Trust-funded researchers in receipt of awards and prizes for human functional brain imaging-related research

Researcher	Awards and Prizes
Professor Chris Frith	• European Latsis Prize (2009) awarded to Professors Chris and Uta Frith for their contribution to understanding the human mind and brain
FIL Group	• Pittsburgh Brain Activity Interpretation Competition (2007) awarded to the FIL Methods group for applying Pattern Recognition approaches to MRI
Professor Eleanor Maguire	• Royal Society Rosalind Franklin Award (2008) for outstanding contributions to cognitive neuroscience • Feldberg Foundation Prize (2011)
Professor Ray Dolan	• Kenneth Craik Research Award (2006) • Minerva Foundation Golden Brain Award (2006) • Max Planck Research Award (2007) • Fellow of the Royal Society, FRS (2010)
Professor Karl Friston	• Medal, Collège de France (2008) • Fellow of the Royal Society, FRS (2006)
Professor Semir Zeki	• Erasmus Medal, Academia Europaea (2008) • Doctorate Honoris Causa, University of Aberdeen (2008) • Segerfalk Award, Segerfalk Foundation, Sweden (2009)
Professor Cathy Price	• Editors Choice Award, Human Brain Mapping (2006); • Justine et Yves Sergent Award, University of Montreal (2008)
Professor Jon Driver	• Member of Academia Europaea (2006) • President's Award of the British Psychology Society (2009) • Royal Society Anniversary Research Professorship (2009) • Fellow of the British Academy, FBA (2008)
Professor Geraint Rees	• Royal Society Francis Crick Lecture and medal (2007) • Experimental Psychology Society Prize (2007) • Royal College of Physicians Goulstonian Lecturer (2009)
Professor Richard Passingham	• Fellow of the Royal Society, FRS (2009)
Professor Richard Frackowiak	• Wilhelm Feldberg Prize awarded by the Feldberg Foundation (1996) • Ipsen Prize for neuroplasticity (jointly with M Merzenich and A Damasio) from the Foundation Ipsen citing "studies on the organization of cortical maps and their plasticity" (1997) • Docteur honoris causa University of Liege (1999) • Klaus Joachim Zulch Prize (jointly with N Logothetis) from the Max Planck Society and Gertrude Reemtsma Foundation citing "broad influence on the field of neuroimaging" (2004) • Member of the Institute of Medicine of the American Academies of Science (2009)

Source: Wellcome Trust Science Funding

Annex E: Human functional brain imaging research timeline

The Timeline displays an overview of historical events including key scientific, policy and funding developments that have influenced the field of human functional brain imaging. In the past two decades, the emphasis is on the contribution of the Wellcome Trust – where the Wellcome Trust has had a key role or a contributory role alongside others in the field.

Key landmarks in human functional brain imaging (Wellcome Trust-associated post-1990 shaded)

Date	Key	Summary	Description	People and place
1868	Scientific advance	Mental chronometry introduced	Mental chronometry introduced.[1]	Frans Cornelius Donders
1878	Scientific advance	Blood flow and brain function linked	Blood flow in humans first associated with human brain function.	Charles Sherrington
1924	Scientific advance	Hans Berger records the first human electroencephalogram		
1928	Scientific advance	Paul Dirac theoretically predicts the positron	Paul Dirac at Cambridge theoretically predicted the existence of the positron in 1928; Carl Anderson at CalTech demonstrated it in 1932.	Paul Dirac, Cambridge, UK
1931	Scientific advance	Ernest Lawrence at Berkeley, California, invents the cyclotron	Ernest Lawrence at Berkeley, California, invented the cyclotron, for which he was awarded the Nobel Prize for Physics in 1939.	Ernest Lawrence, Berkeley, California
1931	Funding development	Mallinckrodt Institute of Radiology, Washington University, founded[2]		Washington University Medical Center, St Louis
1932	Scientific advance	Cockcroft, Walton and Rutherford split the atom	Cockcroft and Walton in Cambridge split the atom, thereby demonstrating the ability to produce radioactivity with particle accelerators.	Cockcroft, Walton and Rutherford
1938	Funding development	Commissioning of the first cyclotron solely for medicine and biology		Berkeley, California
1944	Funding development	MRC Applied Psychology Unit established		MRC, Cambridge, UK
1946	Scientific advance	Magnetic resonance phenomenon discovered		Bloch and Purcell, awarded a Nobel Prize in 1952
1948	Funding development	UK MRC decides to establish the world's first hospital-based cyclotron at Hammersmith Hospital	The UK MRC decided to establish the world's first hospital-based cyclotron at Hammersmith Hospital to produce radioisotopes, such as the positron emitters that eventually came to be used for positron emission tomography (PET).	Hammersmith Hospital, London
1950	Scientific advance	First positron imaging device developed		Gordon Brownell and William Sweet, Massachusetts General Hospital (MGH)
1953	Scientific advance	Brownell and Sweet at MGH, Boston, publish the use of positron coincidence counting for imaging the distribution of the positron emitter to delineate brain tumours		Brownell and Sweet, MGH, Boston
1955	Scientific advance	Brain blood flow studied with radioisotopes	Regional blood flow in animals correlated with behaviour using radioisotopes.	

Date	Key	Summary	Description	People and place
	Funding development	Hammersmith cyclotron established to produce radioisotopes and to undertake neutron therapy of cancer and radiobiology research		Hammersmith Hospital, London
1956	Scientific advance	Infrared imaging introduced	The first application of infrared imaging in medicine, using indocyanine green as a fluorophore.[3,4]	
1961	Scientific advance	First single-plane PET instrument, the 'headshrinker', developed at Brookhaven		James Robertson and associates at Brookhaven National Laboratory (BNL), NY
1963	Scientific advance	Brain blood flow linked with behaviour	Regional blood flow in man correlated with behaviour.	Neils Lassen and David Ingvar
1965	Funding development	Medical cyclotrons installed in USA	Medical cyclotrons installed at MGH and Mallinckrodt Institute of Radiology, Washington University.	MGH, Boston, and Mallinckrodt Institute of Radiology, Washington
1968 onwards	Scientific advance	Single photon emission computed technology (SPECT) developed for brain imaging		David Kuhl and his group at the University of Pennsylvania, Philadelphia
1968–72	Scientific advance	Magnetoencephalography (MEG) introduced	The measurement of brain activity with MEG.[5,6]	
1970	Scientific advance	St Louis group measures regional cerebral blood flow and oxygen utilization using carotid artery administrations of $^{15}O_2$ and $H_2{}^{15}O$		Washington University, St Louis
1970S	Scientific advance	Boston Positron Camera came online		
1970S	Scientific advance	Sokoloff develops the use of tritiated deoxyglucose for autoradiographic studies of regional glucose metabolism in animal brains		Sokoloff
1971–72	Scientific advance	X-ray computed tomography (CT) introduced	MRC supported the testing of head and body scanners. Rapidly commercialised over the next few years[7] and awarded a Nobel Prize in 1979.	Godfrey Hounsfield (EMI Laboratories) and Allan McLeod Cormack (Tufts University, Massachusetts)
1972	Scientific advance	CT scanning introduced in patients		Atkinson Morley's hospital
1972	Policy development	Society for Neuroscience (SfN) Committee on Social Responsibility established[8]		
1972	Scientific advance	Tomographic images reported using the Boston Positron Camera		Chesler
1973	Scientific advance	PET invented[9]		Michel Ter-Pogossian, Edward J Hoffman and Michael Phelps developed the first human PET scanner at Washington University, St Louis
1973	Scientific advance	First images of metabolism of the human brain recorded	Jones et al recorded the first images of metabolism of the human brain using inhaled $^{15}O_2$ and the Boston Positron Camera (July; published 1976). Early tomographic images were also recorded (September; unpublished).	Jones et al

Date	Key	Summary	Description	People and place
1973	Scientific advance	MRI principles first described		Mansfield, Lauterbur and Damadian
1973	Scientific advance	Whole-body CT scanner marketed	ACTA, a whole-body CT scanner,[10] was marketed.	Robert Ledley
1973–74	Scientific advance	St Louis group develop quantitative PET		
1974	Funding development	Fifteen cyclotrons worldwide	Fifteen cyclotrons had been installed worldwide by this date.	
1975	Scientific advance	Next-generation CT scanners marketed	Second-generation Delta CT scanners were marketed, and GE's third-generation CT scanners were marketed.	GE
1975	Policy development	Radiopharmaceuticals regulated in USA	The Food and Drug Agency (FDA) began to regulate the clinical use of radiopharmaceuticals.[11]	
1975–78	Scientific advance	Qualitative gamma camera imaging of inhaled $^{15}O_2$, $H_2{}^{15}O$ and $C^{15}O_2$ used in a range of brain disorder patients	This provided the case for installing a PET scanner at Hammersmith in 1979 and initiated collaborations with the Institute of Neurology at Queen Square, London.	Jones et al, Hammersmith Hospital, London
1976	Scientific advance	^{18}FDG imaged in human brain using SPECT	The ^{18}FDG was synthesized at Brookhaven National Lab on Long Island by Ido and Wolf and transported to Philadelphia.	The Philadelphia group of Reveich, Kuhl, Alavi, Phelps and Hoffman
1977	Scientific advance	FDG used as PET ligand	Radiography with ^{18}FDG to demonstrate functional neuronal activity in animals.	M Reivich and L Sokoloff, Philadelphia
1977	Scientific advance	Echo-planar imaging (EPI) developed	Peter Mansfield developed EPI, which sped up MRI.	Peter Mansfield
Late 1970s–early 80s	Scientific advance	First modified EPI sequences applied to image animals and limbs		Peter Mansfield and Roger Ordidge
1978	Scientific advance	Functional imaging with PET introduced		
1978	Scientific advance	Commercial PET scanner available: EGG ORTEC, based on St Louis designs		
1979	Scientific advance	Clinical magnetic resonance imaging (MRI) introduced	Mansfield was funded by the MRC and the Wolfson Foundation.[12] Awarded a Nobel Prize in 2003.	Paul Lautbauer (University of Illinois) and Peter Mansfield (University of Nottingham)
1979	Scientific advance	Quantitative regional cerebral oxygen utilization and blood flow demonstrated using PET and inhaled $^{15}O_2$ and $C^{15}O_2$		Hammersmith
1980	Scientific advance	Quantification in PET	PET was used for the quantification of myocardial infarction in dogs.[13]	
1980s	Scientific advance	MRI applied routinely to clinical diagnostics		
1980s	Funding development	Imaging centre established in Aberdeen	An imaging centre was established in Aberdeen, with a focus on the clinical applications of PET and MRI.	Aberdeen, Scotland
1981	Scientific advance	^{18}FDG brain tumours – forerunner of today's clinical PET for oncology		
1981	Scientific advance	Brain activation demonstrated with ^{18}FDG at Los Angeles		

Date	Key	Summary	Description	People and place
1982	Scientific advance	Functional imaging with PET and bloodflow introduced		
1982	Scientific advance	MRI used to measure oxygen utilisation *in vivo*		Thulborn et al
1983	Scientific advance	PET for brain receptor imaging first demonstrated		Wagner et al, The Johns Hopkins
1983	Scientific advance	Demonstration of PET imaging of ^{18}F-L-dopa in striatum of humans		Garnett, Firnau and Nahmias at McMaster
1983	Scientific advance	First commercial MRI scanner in Euprope installed[14]		University of Manchester Medical School
1983	Policy development	SfN Social Issues Roundtable initiated		
1983	Funding development	Laboratory of Neuroimaging founded (St Louis)	This moved to UCLA in 1987.[15]	University of Washington School of Medicine, St Louis
1984	Funding development	McConnell Brain Imaging Centre (McGill, Montreal) founded		McConnell Brain Imaging Centre, McGill University, Montreal[16]
1984	Scientific advance	Pioneering PET-based tumour pharmacokinetic study measuring the uptake and time course of 11-BCNU in gliomas		Diksic, Yamamoto, Feindel and others, Montreal
1986	Policy development	EU Biotech Directive	EU Directive: High Tech – Biotech (87/22), updated as 93/41.	
1986	Scientific advance	Neuroleptic dose/D2 receptor occupancy measured using PET		Farde et al, Karolinska Institutet
1986	Scientific advance	MRI of intravoxel incoherent motion: applications to diffusion and perfusion in neurologic disorders[17]		
1986	Funding development	New cyclotron installed at Hammersmith for PET		Hammersmith Hospital, London
1987	Scientific advance	High axial resolution PET introduced		
1987	Scientific advance	First brain SPECT tracer, Ceratec™ (Amersham), developed		Amersham
1988	Scientific advance	Early image processing techniques developed	Task analysis by subtraction, stereotactic image normalisation and image averaging in PET.	P T Fox, Raichle laboratory, Washington University, St Louis
1988	Scientific advance	PET applied to cognitive studies		
1988	Scientific advance	Statistical parametric mapping (SPM) developed to analyze PET data	The first SPM was used to establish functional specialization for colour processing in 1989 by Luek et al.[18] The methodology and underpinning of SPM were described in two papers in 1990[19] and 1991.[20]	Karl Friston, Frackowiak Laboratory at the MRC Cyclotron Unit
1989	Funding development	Human Frontier Science Program established		
1990	Scientific advance	Blood oxygenation level dependent (BOLD) contrast in MRI identified		Ogawa, AT&T Bell Laboratories

Date	Key	Summary	Description	People and place
1990	Scientific advance	Introduction of diffusion imaging	Michael Moseley initiated the use of diffusion in MRI. Basser and Le Bihan jointly filed and were both granted a patent for diffusion tensor imaging (DTI) between 1992 and 1996. Filler and his colleagues were also granted a patent for DTI in the same period.	Michael Moseley, Peter Basser, Denis Le Bihan and Aaron Filler
1990	Policy development	EU Radiopharmaceuticals Directive	EU Directive: radiopharmaceuticals (89/343)[21] extended the existing rules of medicinal compounds to include radiopharmaceuticals (previously exempt), due for implementation in two years. This required manufacturers to file the registration of products. Protocols had to be reduced to fit the time frame.	
1990	Scientific advance	Early detection of regional cerebral ischaemia in cats: comparison of diffusion and T2-weighted MRI and spectroscopy[22]		
1990–2000	Policy development	US Decade of the Brain[23]		
Early 1990s	Scientific advance	SPECT used routinely in clinic	SPECT was an established technique – for example, in the detection of ischaemia, the presurgical detection of seizure foci and the detection of amyloid beta in Alzheimer's diagnosis.[24]	
1991	Scientific advance	Functional MRI (fMRI) in humans introduced[25]		
1991	Scientific advance	High-sensitivity 3D PET developed		
1991	Scientific advance	EPI time course MRI of cat brain oxygenation changes[26]		
1992	Scientific advance	fMRI imaging using BOLD introduced		Several groups, including Ken Kwong et al, MGH Ogawa and Tank, AT&T Bell Laboratories, Ugirbil, and Menon, University of Minnesota
1992	Funding development	MRC cease funding MRI at Cyclotron Unit		
1992	Funding development	PET centre established (Guy's and St Thomas's)	A commercial PET centre, focusing on the clinical use of PET, was established at Guy's and St. Thomas's.	
1992–2002	Policy development	EU Decade of the Brain		
1992–95	Scientific advance	Sensitivity of commercial MRI scanners improved	Fluid-attenuated inversion recovery (FLAIR) and diffusion MRI achieve higher sensitivity than conventional MRI.[27]	
1992	Scientific advance	Experimental design advanced	Development of parametric and factorial experimental design. Allowed, for example, pharmacological challenge, plus cognitive response.	Karl Friston
1993	Policy development	International Bioethics Committee established	UNESCO founds the International Bioethics Committee (IBC).	
1993	Policy development	EU Medical Devices Directive		

Date	Key	Summary	Description	People and place
1993	Policy development	European Board of Nuclear Medicine (EBNM) founded	EBNM, part of the European Association of Nuclear Medicine, was founded.	
1994	Scientific advance	First intraoperative use of MRI	Brigham and Women's Hospital, Boston, introduced a 0.5-Tesla MRI scanner to the operating theatre.	
1994	Scientific advance	Image-guided surgery introduced	The development of computer systems allowed the registration of imaging results to instruct brain surgery.[28]	Wayne State University and Stealth Technologies
1994	Scientific advance	DuPont Merck Pharmaceutical's brain SPECT tracer Neurolight® approved		DuPont Merck Pharmaceutical
1994	Funding development	Functional Imaging Laboratory (FIL) founded (UCL)	FIL at UCL was founded by a core group of researchers from the MRC Cyclotron Unit at Hammersmith Hospital, funded by a £20m grant from Wellcome Trust.	
1994–95	Scientific advance	Functional connectivity measures of evoked and intrinsic activity demonstrated		Karl Friston (effective connectivity) and Biswal (seminal demonstration of intrinsic activity)
1995	Scientific advance	Image normalisation	Spatial registration and normalisation of images.[29]	Karl Friston, FIL
1995	Scientific advance	Spontaneous brain activity noted	The presence of spontaneous, spatially coherent activity in the fMRI BOLD signal was noted.[30]	
1995	Policy development	FDA introduces PET guidelines	The FDA introduced three sets of regulations and guidelines on the manufacture and use of PET. They were considered burdensome and resulted in strong lobbying from manufacturers.	
1995	Funding development	Wolfson Brain Imaging Centre founded, Cambridge	Wolfson Brain Imaging Centre (WBIC) founded (Cambridge).[31] Collaboration between several funders including GSK, MRC, BHF and Wolfson foundation.	
1995	Funding development	John Hopkins Center for Imaging Science founded, Baltimore	John Hopkins Center for Imaging Science, Baltimore, founded by the Army Research Office.[32]	
1996	Scientific advance	Combined CT/SPECT imaging	CT/SPECT devices juxtaposed to allow simultaneous imaging.[33]	Blankespoor et al
1996	Scientific advance	First direct demonstration that the human amygdala is crucial to the perceptional analysis of fear	J S Morris, C D Frith and R J Dolan of the Wellcome Department of Cognitive Neurology, Queen Square, were supported by the Wellcome Trust.	Morris et al
1996	Policy development	Report on ethical implications of neuroscience	IBC developed a report on the ethical implications of developments in neuroscience.	
1996	Policy development	First Brain Awareness Week	Brain Awareness Week was launched in the USA. It became international in 1998.	
1996	Funding development	Oxford Centre for Functional MRI of the Brain (FMRIB) founded	The FMRIB, funded by the MRC, was established on the John Radcliffe Hospital site.[34]	FMRIB, Oxford, UK

Date	Key	Summary	Description	People and place
1996	Funding development	Institute of Medical Science founded (Aberdeen)	Institute of Medical Science founded (£50m) with major contributions from the Wellcome Trust.[35] This included the Aberdeen Biological Imaging Centre.	
1996–98	Scientific advance	Event-related MRI developed		Dale and Butler, MGH[36]
1997	Policy development	1995 FDA PET guidelines retracted	The FDA retracted their 1995 guidelines under the FDA Modernisation Act.	
1997	Scientific advance	Development of MRI-compatible PET scanner		Y Shao et al
1997	Funding development	RIKEN Brain Science Institute founded, Japan	RIKEN Brain Science Institute established (US$61m), as part of a wider US$125m initiative.[37]	Japan
1997	Scientific advance	Multi-modal imaging	Combination of transcranial magnetic stimulation (TMS) and PET used to study connectivity in the brain.[38]	
1997	Scientific advance	Multi-modal imaging	Measurement of BOLD MRI responses induced by TMS.[39]	
1998	Scientific advance	MEG used for epilepsy lesion identification	MEG identified as a suitable technique for non-invasive presurgical identification of lesions in epilepsy.	
1998	Policy development	Medicare approve use of PET	Centres for Medicaid and Medicare Services approve reimbursement for use of PET in diagnosis of some cancers.	
1998	Policy development	Scottish Funding Council (SFC) Brain Imaging Research Centre founded (Edinburgh)	Funded by the Scottish Higher Education Funding Council (now the SFC), the MRC, the University of Edinburgh and industrial collaborators (GE, Boehringer Ingelheim, Novartis and Schering Health Care), and supported by Lothian University Hospitals NHS Trust and substantial donations from the public.	Edinburgh, UK
1998	Funding development	MRC Cognition and Brain Sciences Unit (CBU) extended and refurbished (Cambridge)	The MRC Applied Psychology Unit, Cambridge, was renamed the MRC Cognition and Brain Sciences Unit and extended and refurbished. It reopened in 2001.[40]	Cambridge, UK
1998	Scientific advance	Integration of images from different modalities	Computers used to integrate imaging results from different modalities to give a single image.[41]	So et al, Department of Neurology, Mayo Clinic, Rochester, Minnesota
1998	Scientific advance	Software package Brain Voyager developed[42]	BrainVoyager QX is a highly optimized and user-friendly software package for the analysis and visualization of functional and structural MRI data sets.	Brain Innovation BV, Maastricht, The Netherlands
1999	Policy development	MRC Cyclotron Unit separates clinical and non-clinical research	The MRC decided to develop the Cyclotron Unit into a public–private partnership, separating clinical and non-clinical research.	
1999	Funding development	Wellcome Trust MEG lab at Aston University, Birmingham, established	Aston received a Wellcome/HEFCE infrastructure grant to set up the MEG facility in collaboration with GI sciences in Manchester.	Aston University, Birmingham

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1999	Scientific advance	Disconnection theory proposed as cause of schizophrenia	The neural network disconnection hypothesis proposes that schizophrenia arises from dysfunctional integration of a distributed network of brain regions or a misconnection syndrome of neural circuitry, leading to an impairment in the smooth coordination of mental processes.[43]	Karl Friston, FIL
1999	Scientific advance	The involvement of visual cortex in processing of visual imagery	Repetitive TMS in combination with PET imaging identified that activation of area 17 in the visual cortex is causally linked to processing of visual imagery.[44]	
1999	Funding development	Remaining groups from Cyclotron Unit merge with MRC Clinical Sciences Centre	Some remaining groups from MRC Cyclotron Unit incorporated into MRC Clinical Sciences Centre.	
2000	Scientific advance	Longitudinal BOLD scanning introduced		McGonigle (PhD Thesis) and Frackowiak, FIL
2000	Scientific advance	Voxel-based morphometry developed[45]		John Ashburner and Karl Friston, Queen Square, London
2000	Scientific advance	Hybrid PET/CT scanner	Combined PET/CT scanner developed.	T Beyer et al
2000	Policy development	FDG and other PET ligands announced safe by FDA	FDA release new notices on PET radiopharmaceuticals. ^{18}F-FDG, ^{18}F-NaF and ^{13}N-NH_3 considered safe and effective. New guidelines for new PET radiopharmaceuticals.	
2000-	Scientific advance	Brain–computer interface technology developed		
2000	Scientific advance	Voice-selective areas identified in the superior temporal sulcus (STS) in the auditory cortex	Greater activation of STS (shown by fMRI) in response to vocal sounds than to non-vocal environmental sounds.[46]	
2000	Scientific advance	SPECT imaging agent DatSCAN™ (GE Healthcare) is approved in Europe		GE
2001	Funding development	New cyclotron at Hammersmith	The MRC formed a public–private partnership with Amersham (now GE Healthcare)[47] – funding a new cyclotron at Hammersmith.	Amersham (GE) and the MRC; Hammersmith Hospital, London
2001	Scientific advance	Neurophysiological basis of the fMRI signal investigated[48]		Nikos Logothetis et al, Max Planck Institute for Biological Cybernetics, Tubingen, Germany
2001	Scientific advance	Cross-disciplinary work on the prefrontal cortex (PFC)[49]		John Duncan, MRC CBU, Cambridge
2000–03	Scientific advance	New fluorophores developed for near infrared (NIR) imaging, including quantum dots[50]		Including Frangioni et al, Beth Israel Deaconess Medical Center, Boston, MA
2002	Policy development	Neuroethics conference	Neuroethics: Mapping the Field conference.	
2002	Policy development	New FDA guidelines on PET ligands	The FDA released new guidance on good practice for PET radiopharmaceuticals.	
2002	Policy development	ACR produces paper on magnetic resonance (MR) safety	American College of Radiology released *White Paper on MR Safety* (updated in 2004).	
2003	Scientific advance	Multivariate pattern classification developed[51]		David Cox and Robert Savoy

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2003	Scientific Advance	Reinforcement learning (TD) models applied to fMRI		Ray Dolan, Peter Dayan and John Doherty, FIL
2003	Scientific advance	Dynamic causal modelling developed		Karl Friston, FIL
2003	Funding development	High Field Magnetic Resonance Centre founded, Tubingen	High Field Magnetic Resonance Centre founded at Max Planck Institute for Biological Cybernetics, Tubingen, for the methodical enhancement of imaging techniques (focusing on MR) and the development of contrast agents.[52]	Tubingen, Germany
2003	Policy development	SfN launches annual neuroethics lecture		
2004	Funding development	PET decommissioned at the FIL		FIL, Queen Square, London
2004	Funding development	UK's first 7-Tesla MR whole body system established in Nottingham University	The 7-Tesla scanner was funded by the Joint Infrastructure Scheme (The Wellcome Trust, the Office of Science and Technology and the Higher Education Funding Council for England).	Wellcome Trust, Office of Science and Technology, and the HEFCE, Nottingham University
2004	Scientific advance	First human study of a novel amyloid-imaging PET tracer, Pittsburgh Compound-B. Pittsburgh Compound-B associated with areas of amyloid accumulation	Pittsburgh Compound-B used to image amyloid plaques.[53]	Klunk et al, Pittsburgh and Sweden
2004	Policy development	EU Physical Agents (electromagnetic fields) Directive	Implementation due by 2008 but postponed until 2012. Policy Impact Report due September 2009.	
2004	Funding development	GSK establishes first clinical imaging centre at Hammersmith Hospital for PET/MRI in drug development	Imperial, GSK and MRC funded £76m medical imaging centre at Hammersmith Hospital site, to focus on cancer, stroke, neurological diseases (such as Parkinson's and multiple sclerosis), and psychiatric diseases.[54] Opened 2007.	Hammersmith Hospital, London
2004	Funding development	Centre for Neuroimaging Sciences founded (KCL Institute of Psychiatry and Maudsley)	The Centre for Neuroimaging Sciences established as a collaboration between the KCL Institute of Psychiatry and the South London and Maudsley NHS Trust at King's College London. Designed to provide world-class neuroradiological services and research and to facilitate translation to the clinic.[55]	
2004	Scientific advance	Activity in premotor cortex underlies feeling of ownership of body limbs	BOLD-fMRI signal revealed that multisensory integration in the premotor cortex provides a mechanism for bodily self-attribution.[56]	
2004	Funding development	Alzheimer's Disease Neuroimaging Initiative launched	Alzheimer's Disease Neuroimaging Initiative launched to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).[57] The $60m initiative is funded by the National Institute on Aging (NIA) in conjunction with other Federal agencies, private companies and organizations.	NIA and the National Institute of Bioimaging and Bioengineering (NIBB), both part of the National Institutes of Health (NIH)

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2004	Funding development	Foundation of the Brain Imaging Center (BIC), Frankfurt[58]		Frankfurt, Germany
2004	Scientific advance	Human brain mechanism for perceptual decision making	Activation of dorsolateral prefrontal cortex (shown by fMRI) is involved in human perceptual decision making.[59]	
2005	Policy development	SfN initiates Dialogues between Neuroscience and Society		
2005	Funding development	fMRI scanner commissioned at MRC CBU		MRC CBU, Cambridge, UK
2005	Scientific advance	Theoretical work on inference in neuroimaging[60,61]		Rik Henson, MRC CBU, Cambridge, UK
2006	Scientific advance	First fMRI longitudinal studies of stroke recovery		N Ward and Frackowiak, FIL
2006	Funding development	FIL becomes Wellcome Trust Centre for Neuroimaging (WTCN)	FIL awarded Wellcome Trust Centre status and becomes the WTCN at UCL.	Ray Dolan, founding Director, WTCN at UCL, Queen Square, London
2006	Scientific advance	Neural correlates of corrective behaviour after sensory discrepancies in lifting task	fMRI study identified brain regions activated after discrepancies in predicted and actual sensory input.[62]	
2006	Scientific advance	Somatosensory decision making in human brain	Human fMRI studies revealed increased activity of the primary somatosensory cortex during the encoding phase of tactile decision making.[63]	
2007–08	Scientific advance	Characterisation of neuronal interactions in schizophrenia	Dynamic causal modelling and other techniques used to characterise neuronal interactions in schizophrenia, including the effect of neuromodulatory influences.	Corlett et al, Honey et al and Murray et al
2007	Scientific advance	MEG used to identify disorders	MEG used to differentiate patients with disorders (multiple sclerosis, Alzheimer's disease, schizophrenia, Sjögren's syndrome, chronic alcoholism and facial pain) from healthy patients.[64]	
2007	Scientific advance	High-resolution fMRI of the medial temporal lobe[65]		C Brock Kirwan and Craig E L Stark, John Hopkins University, Baltimore, Maryland
2007	Scientific advance	Simultaneous MR/PET	Simultaneous MR/PET demonstrated in prototype.[66]	Siemens
2007	Scientific advance	Correlation of resting state with individual behaviour	Demonstration that individual differences in resting-state correlation patterns relate to individual variability in behaviour.[67]	
2007	Policy development	American College of Radiology (ACR) guidelines on MR	The ACR guidelines for safe MR practices were released.[68]	
2007	Policy development	Medicines and Healthcare products Regulatory Agency (MHRA) guidelines on MRI	MHRA produced *Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use*.	
2007	Funding development	Oxford MEG Center founded	Oxford MEG Centre opened[69] for neurodevelopment studies including autism.	Oxford, UK

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2007	Funding development	SINAPSE initiative founded[70]	New initiative formed: SINAPSE (Scottish Imaging Network – A Platform for Scientific Excellence) to help move the collaboration of imaging throughout Scotland forward, introducing a new phase in the life of the SFC Brain Imaging Research Centre. Funding from the Scottish Funding Council, the Chief Scientific Office and the six Universities.	Scotland
2008	Scientific advance	Automatic classification of Alzheimer's with MRI	Support vector machines successfully used to separate patients with AD from healthy ageing subjects and perform well in the differential diagnosis of two different forms of dementia.[71]	Kloppel and Frackowiak, FIL
2008	Policy development	EU radiopharmaceutical manufacturing regulations	European Medicines Agency produced new good manufacturing practice regulations for radiopharmaceuticals, for compliance by March 2009.[72]	
2008	Policy development	US Joint Commission issue patient safety advisory on MR	The Joint Commission, a US healthcare accrediting organization, issued a Sentinel Event Alert #38,[73] their highest patient safety advisory, on MRI safety issues.	
2008	Funding development	Ernst Strüngmann Institute (ESI)[74] founded (Max Planck Institute for Brain Research, Frankfurt)	Ernst Strüngmann Institute (ESI) created to promote cognitive neuroscience, housed in Max Planck Institute for Brain Research.	ESI, Frankfurt, Germany
2008	Funding development	New MRI scanner at WBIC, Cambridge	New scanner installed at WBIC, funded by MRC and Wellcome Trust.	
2008	Funding development	New MRI scanner funded at FMRIB, Oxford	FMRIB awarded £4.2m by the MRC and the Engineering and Physical Sciences Research Council to purchase a 7-Tesla state-of-the-art MRI system.	Oxford, UK
2008	Funding development	Donders Institute for Brain, Cognition and Behaviour (DCCN) established[75]		DCCN, Nijmegen, The Netherlands
2009	Scientific advance	Review of non-independent analysis of images in top journals	Concerns raised over quality of brain imaging analysis in top journals[76] through 'non-independent selected analysis'.	Kriegeskorte et al
2009	Scientific advance	Quantification of incidental findings in MRI	Study found that incidental findings on brain MRI are common, with prevalence increasing with age, raising issues for consent for healthy research volunteers.[77]	
2009	Scientific advance	Functional connectivity between auditory cortex and visual cortex underlies generation of auditory occipital activation	BOLD-fMRI signals used to identify activation of peripheral regions of visual cortex in response to auditory attention stimuli and not in response to passive exposure to sounds.[78]	
2009	Scientific advance	Role of amygdala in regulating interpersonal distance in humans	Activation of amygdala (shown by fMRI) may be responsible for the strong emotional response to personal space violation.[79]	
2009	Funding development	Max Planck Institute for Brain Research moves to new site (Frankfurt)	Max Planck Institute for Brain Research occupied new buildings on the Riedberg campus, Frankfurt, initially in and in proximity to the MPI for Biophysics. The new building is due to open in 2012.	

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2010	Funding development	NIH Human Connectome Project established[80]	Supported by the NIMH and other leading NIH institutes.	UCLA-MGH, Washington University-University of Minnesota
2011	Funding development	Core infrastructure support for WTCN is renewed by the Wellcome Trust		WTCN at UCL, Queen Square, London

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