Institution: The University of Nottingham

Unit of Assessment: 9

Title of case study: Catalysing the Clinical Application of High-Field Magnetic Resonance Imaging (MRI)

1. Summary of the impact

Nottingham researchers constructed the world's first 3T MRI scanner, thus demonstrating the viability and benefits of high-field MRI. This provided a stimulus for magnet and MRI system manufacturers to develop 3T scanners, which have now become established as the standard platform for high-end clinical MRI studies. We estimate that since 2008: 2500 3T scanners have been installed, representing a global investment of $5 billion; and 30-40 million patient examinations have been performed with 3T MRI scanners. Technical advances which underpinned the Nottingham 3T scanner also impacted on the development of functional MRI, thus opening up a new field of medical research and clinical application. In a subsequent phase of research, the Nottingham group developed ultra-high (7T) magnetic MRI in partnership with Philips; forty 7T MRI scanners (current unit cost >$10M) have now been installed across the world.

2. Underpinning research

The early development of MRI through the late 1970s and 1980s brought an increase in the operating magnetic field strength, from the 0.05-0.15T of the first systems, to 1.5T, which was considered to be high field at that time. Despite the clear theoretical advantage of still higher fields, namely improved signal-noise ratio resulting in higher spatial and temporal resolution, attempts to introduce 4T systems were not successful (see Section 4). The major manufacturers (Siemens, Philips and GE) produced just a handful of these systems in the late 1980s and then abandoned the project since the anticipated improvements were not realised, primarily due to limitations in the performance of the scanner hardware and software. A field of 1.5T then remained the clinical standard for most of the next two decades.

It was against this background that the Nottingham MRI group commissioned and took delivery of the world's first 3T whole-body magnet in October 1991. In a project funded by the Department of Health, British Technology Group and the University of Nottingham (1991-1994), we developed a unique MRI scanner around this magnet. This involved designing and building our own control electronics, radio-frequency and gradient systems, as well as developing our own scanner control software. The aim, and successful outcome, of the project was to produce a high-field system with the ability to run echo-planar imaging (EPI). EPI is a technique that was developed in Nottingham, and whose importance was recognised in the award to Sir Peter Mansfield of the 2003 Nobel Prize for Physiology or Medicine. The extremely high quality that we demonstrated in our 3T EPI images was particularly noteworthy [1,2;i,ii], given that at that time commercial manufacturers were struggling to implement EPI even at 1.5T.

The application of EPI at 3T provided an important enabling technology for the field of functional MRI (fMRI) [iii] in which brain function is monitored through the detection of changes in local blood flow. fMRI is heavily reliant on high temporal and spatial resolution, and our 3T scanner was ideally suited to research in this area. From 1994 onwards, fMRI formed a major focus of our research, and we made several significant contributions to its early development including the first paper on Single Event MRI, and indeed coined the term 'Single (cognitive) Event' [3]. In a series of highly cited papers [4-5], we then demonstrated how fMRI could be used to investigate the cortical encoding of sensory responses in the auditory [4], somatosensory and olfactory cortices [5]. Our work, funded by the MRC in a series of special project and programme grants which have run continuously since 1993, was a major factor contributing to the establishment of 3T MRI as the new clinical standard for neuroimaging and functional neuroimaging (see Section 4).

We continued with our strategy of delivering higher sensitivity through increased magnetic field strength when, in 2005, we acquired one of the first 7T scanners in the world (the first in the UK and the first to be supplied by Philips) through a £3M award from the HEFCE Joint Infrastructure Fund [iv]. This field strength posed new challenges as the wavelength in tissues at 300MHz is commensurate with the dimensions of the human head, leading to significant interference effects. Our work at 7T, demonstrating the increased sensitivity of fMRI, the increased spatial resolution of anatomical images, and the improved access to new contrast (including chemical exchange saturation transfer sensitisation and quantitative susceptibility maps), has demonstrated that these effects are surmountable [6,7;v-viii]. Indeed we have used the improved susceptibility contrast to develop a reliable method for differential diagnosis of multiple sclerosis (MS) [6; vi,vii]. Moreover, the quality and robustness of our 7T data have played a significant role in stimulating the growth of the 7T MRI market worldwide.

The following members of our MRI group contributed to the development of the world's first 3T scanner: *Bowtell*, *Francis*, *Glover*, *Gowland*, *Mansfield*, *Morris*; this group together with *Brookes* and *Mullinger* contributed to the 7T work.

3. References to the research * denotes papers best indicating quality of research

1) ***P. Mansfield, R. Coxon, P. Glover**, *'Echo-planar imaging of the brain at 3.0T - first normal volunteer results.'* J. Comput. Assist. Tomogr. **18**, 339 (1994).
DOI:10.1097/00004728-199405000-00001

2) **P. Mansfield, R. Coxon, J. Hykin**, *'Echo-volumar imaging (EVI) of the brain at 3.0 T - first normal volunteer and functional imaging results',* J. Comput. Assist. Tomogr. **19**, 847 (1995).
DOI:10.1097/00004728-199511000-00002

3) ***M. Humberstone, G. V. Sawle, S. Clare, J. Hykin, R. Coxon, R. Bowtell, I. A. Macdonald, P. G. Morris,** *'Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area',* Ann. Neurol. **42**, 632 (1997).
DOI:10.1002/ana.410420414

4) **D. Hall, M. P. Haggard, M. A. Akeroyd, A. R. Palmer, A. Q. Summerfield, M. R. Elliott, E. Gurney, R. W. Bowtell, '***Sparse temporal sampling in auditory fMRI',* Human Brain Mapping **7**, 213 (1999).
DOI:10.1002/(SICI)1097-0193(1999)7:3<213::AID-HBM5>3.0.CO;2-N

5) **S. Francis, E.T. Rolls, R. Bowtell, F. McGlone, J. O'Doherty, A. Browning, S. Clare, E. Smith**, '*The representation of pleasant touch in the brain and its relationship with taste and olfactory areas',* Neuroreport **10**, 453 (1999).
DOI: 10.1097/00001756-199902250-00003

6) ***E.C. Tallantyre, M.J. Brookes, J.E. Dixon, P.S. Morgan, N. Evangelou, P.G. Morris,**
'Demonstrating the perivascular distribution of MS lesions in vivo with 7-tesla MRI', Neurology **70**, 2076, (2008).
Listed in REF2; DOI: 10.1212/01.wnl.0000313377.49555.2e

7) **W. van der Zwaag, S. Francis, K. Head, A. Peters, P.A. Gowland, P.G. Morris, R. Bowtell,** *'fMRI at 1.5, 3 and 7 T: Characterising BOLD signal changes'*, Neuroimage **47** 1425 (2009).
Listed in REF2 DOI: 10.1016/j.neuroimage.2009.05.015

Grants in support of MRI at high and ultra-high field

i. *'Ultra High Speed Echo-Planar Imaging at 3.0T'*, P. Mansfield, R. Bowtell, P.A. Gowland and B.S. Worthington, MRC Special Project Grant, (1993-1996) £534,000
ii. *'Techniques of functional MRI/S: Application to dystonia, hearing and recovery from stroke',* P.G. Morris, R.W. Bowtell, P.A. Gowland, A. Moody, G.V. Sawle and B.S. Worthington, MRC, Special Project Grant, (1996-1999) £599,242
iii. '*Fundamental improvements to functional MRI and their application to hearing, movement disorders and stroke',* P.G. Morris, R.W. Bowtell, P.A. Gowland, G.V. Sawle and A. Sunderland, MRC, Programme Grant, (1999-2004) £1,280,844
iv. '*An ultra-high frequency facility for functional magnetic resonance',* P.G. Morris, R.W. Bowtell, P.A. Gowland, P.M. Glover, S. Francis, S.R. Jackson and P.F. Liddle., Joint Infrastructure Fund, (2001-2004) £2,478,124
v. '*Functional neuroimaging at ultra-high field',* P.G. Morris, R.W. Bowtell, P.A. Gowland, S.T. Francis, P.M. Glover, S. Jackson, C. Rorden, P. Liddle, D. Hall, A.R. Palmer, MRC Programme Grant, (G9900259), (2005-2010) £1,860,084
vi. '*Investigation of MS lesion heterogeneity in vivo using high field (7Tesla) MRI',* P.G. Morris and P. Morgan, MS Society, (01/04 /08 – 31/03/09) £39,745
vii. '*Potential use of newly detected MRI features of lesions to diagnose MS',* N. Evangelou and P.G. Morris, MS Society, (02/08/09 – 02/08/11) £127,792
viii. '*Realising the benefits of structural and functional MRI at ultra-high-field',* P.G. Morris, R.W.

Bowtell, P.A. Gowland, S.T. Francis, W.A. Kockenberger, P.M. Glover, D. Auer, S.R. Jackson, P.F. Liddle, T. Paus, A.R. Palmer, K. Krumbholz, MRC Programme Grant, (G0901321), (01/01/2010 – 31/12/2015) £2,424,424

4. Details of the impact

Using the world's first 3T MRI scanner we demonstrated, in papers from 1994 onwards [1,2], that it was possible to generate high resolution, artefact-free images. These results played a significant role in convincing magnet and system manufacturers that the move to high field was not only technically feasible, but could herald the new state-of-the-art for clinical MRI systems.

The primary impact of high-field MRI on patient care has been through the improvement in the quality of clinical diagnostic scans that high field provides (see estimate of the number of patient examinations below), but high field has also underpinned the new field of functional MRI (fMRI). As described in section 2, the work of the Nottingham group was critical in this development through their demonstration of EPI at 3T [1], and this technique has subsequently been implemented in all commercial high-field scanners. The stimulus to the new field of fMRI arose since EPI offers the fastest mode of image acquisition, and was rapidly adopted as the functional neuroimaging method of choice. EPI offered a viable alternative to 'FLASH', the fastest imaging technique then (mid-1990s) commercially available (FLASH proved inadequate to deal with the confounding effects of motion on the small signal changes due to brain activity that must be detected in fMRI).

The move to 3T gathered momentum and, by the mid-2000s, sales of 3T MR scanners by all three major manufacturers (GE, Philips and Siemens) were beginning to grow. At first, it was major MRI research centres who installed 3T scanners (for example, in 1998 Oxford University's fMRIB Laboratory were the first to follow the Nottingham example in the UK), then clinical research facilities, and eventually larger hospitals, both increasing capacity and replacing some of their older 1.5T systems.

The growth of high-field MRI has been sustained through the assessment period (2008 onwards). Figures provided by a leading industrial source [A] provide some key indicative data:

- The number of new scanner installations per annum (high- and low-field) grew from approximately 2000 in the year 2003, to approximately 3000 in 2010 (global figures);
- The fraction of these new installations designated as high field (3T) grew from less than 2% before 2003, to 20% in 2010;
- The typical cost of a 3T MRI scanner is $2M [B]; the value of global sales of high-field scanners in 2010 (the last year for which data are available to us in a relevant form) was $1 billion;
- In the first half of the REF assessment period (2008-2010; data were available only for this period) approximately 1400 high-field scanners were sold.

Extrapolating these data [A] we estimate that over 2500 high-field scanners were installed from January 2008 – July 2013 (this is almost certainly an underestimate since the rising trend in sales is neglected), representing a global investment of $5 billion.

To evaluate the impact on patient care over the assessment period we estimate the number of high-field examinations as follows: (i) the average number of scans per scanner per year (averaged over both low- and high-field scanners) in England is 6500 (using figures of 300 installed scanners [C] and two million patient examinations [C]); the average number of operational high-field scanners during the assessment period is taken as 2250 (1000 installed prior to 2008 [A], plus half of the newly installed scanners). This gives a global estimate of the capacity for 80 million patient examinations using high-field MRI from January 2008 to July 2013. Taking into account the use of some of the high-field scanners for research, and their application in more complex cases, we estimate that 30 - 40 million high-field patient examinations were performed during this period.

The role of the Nottingham research in underpinning these developments is confirmed by leading industrialists:

'The development of a prototype 3T scanner at the Sir Peter Mansfield Magnetic Resonance Centre in Nottingham demonstrated that the theoretical benefits of high field could be realised in practice.' Joint written statement from the Premium & Portfolio MR Manager and the 7T & High Field MR Product Segment Marketing Manager, GE Healthcare [D];

'*The 3T scanner constructed at the Sir Peter Mansfield Magnetic Resonance Centre (SPMMRC)* *demonstrated that ……. the high speed imaging technique of echo-planar imaging, developed in Nottingham by Sir Peter Mansfield, could be implemented at high field. The combination of high field and imaging speed was crucial in the development of functional MRI, now the mostly widely used functional neuro-imaging technique.'* MRI Clinical Science Director, Philips Healthcare [E].

The success of the Nottingham group also led to a change in the strategy of magnet manufacturers such as Oxford Instruments and motivated a decision to re-invest in the manufacture of wide-bore superconducting 3T magnets. *Morris* (Director of the Sir Peter Mansfield Magnetic Resonance Centre (SPMMRC), part of the School of Physics & Astronomy) held a consultancy with Oxford Instruments during the period when the first 3T scanner was built (early 1990s – 1998) and provided advice regarding the technical challenges of implementing MRI at 3T and the new market opportunities for high-field scanners. His contact at Oxford Instruments was a senior magnet designer who was a member of the main Board during this period and states:

'*The failure of 4T systems to 'take off' had made the Board of Oxford Instruments nervous about investment in high field systems, but you helped to convince us that there would be a new market for such systems,…*' ex-Board Member of Oxford Instruments now working as a consultant [F].

In addition, fMRI, which was initially used primarily as a research tool in basic neuroscience and clinical studies, now supports clinical and commercial applications which impact directly on the diagnosis and treatment of patients. Clinically, fMRI is used in pre-surgical mapping of the eloquent cortex, and in some institutions this has become standard procedure [G]. It is also contributing to the diagnosis of neurodevelopmental, psychiatric and neurodegenerative disorders. In addition, fMRI provides a basis for monitoring the actions of new therapeutic agents, enabling their mechanisms of action to be identified and/or confirmed. It is also being taken up by companies offering diagnostic and other services, including the elucidation of pain pathways [H].

The same drivers that led to the development of high-field 3T MRI systems apply *a fortiori* to the development of ultra-high field (7T) MRI systems. However, the barriers to delivering the additional improvements were substantial, and it was unclear whether such systems were a viable proposition, even in a purely research environment. In 2005, we took delivery of the first 7T MRI system to be supplied by Philips. Our work in developing structural and functional MRI on this system stimulated take-up by several prestigious research institutions, as confirmed by a statement from Philips:

'*The SPMMRC was one of the first in the world to undertake human studies at ultra-high field (7T). It took delivery of the first 7T MRI system to be constructed by Philips Healthcare and the pioneering work of the SPMMRC at 7T encouraged investment in this technology and rapid uptake by the user community.'* MRI Clinical Science Director, Philips Healthcare [E].

It is estimated that forty 7T instruments have now been sold [I], with further growth anticipated. The current cost of a 7T scanner is over $10M.

5. Sources to corroborate the impact (available on request)

A. MR Business Manager, Philips Healthcare.
B. 'Advances in Whole-Body MRI Magnets', T. C. Cosmus and M. Parizh, IEEE Trans. On Appl. Supercond. **21** 2104 (2011); see top of page 3.
C. National Audit Office report 'Managing High Value Equipment in the NHS in England' http://www.nao.org.uk/report/managing-high-value-capital-equipment-in-the-nhs-in-england/; Figure 2, page 13 for number of MRI scans, for number of scanners see Figure 1e on page 5.
D. Letter signed jointly by the Premium & Portfolio MR Manager and the 7T & High Field MR Product Segment Marketing Manager GE Healthcare.
E. Letter from MRI Clinical Science Director, Philips Healthcare.
F. Letter from ex-Board Member of Oxford Instruments.
G. 'The Evolution of Clinical Functional Imaging during the Past 2 Decades and its Current Impact on Neurosurgical Planning', J.J. Pillai, Am. J. Neuroradiol. **31** 219 (2010); DOI: 10.3174/ajnr.A1845
H. See for example the services offered by Chronic Pain Diagnostics, http://chronicpd.com/.
I. Reference B gives a figure of 30 units installed by 2010; the estimate of 40 comes from the DOTmed online publication http://www.dotmed.com/news/story/17820.