Institution: University of Nottingham (UoN)		
Unit of Assessment: 9		
Title of case study: OPM-MEG: Commercialisation of an optically pumped magnetometer magnetoencephalography (OPM-MEG) system for human brain imaging		
Period when the underpinning research was undertaken: 1 Jan 2007-31 Dec 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed:**
Richard Bowtell	Professor	1987 – present
Matthew Brookes	Professor	2005 – present
Mark Fromhold	Professor	1991 – present
Peter Morris	Professor	1990 – present
Paul Glover	Dr	2000 – present
Period when the claimed impact occurred: 1 January 2015 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Magnetoencephalography (MEG) measures human brain function via the assessment of magnetic fields generated by neuronal current flow. It is used for neuroscientific research and clinical diagnosis. However, current systems are expensive (>GBP2M), require cryogenic cooling, and have low sensitivity. Further, the scanning environment (in which subjects must remain still for long periods) cannot always be tolerated, limiting uptake and utility. Research by the UoN OPM-MEG team, part of the Sir Peter Mansfield Imaging Group (SPMIG) in the School of Physics and Astronomy, has enabled the development of a new type of MEG scanner based on Optically Pumped Magnetometers (OPMs). This offers a 'wearable' (head-mounted) system that removes the limitations of conventional MEG, providing better performance and more flexible operation at substantially lower cost (price range of GBP375K-GBP1.5M dependent on whether a basic or advanced system is sought, with a lower cost device easily upgraded). This research has stimulated the development of improved miniaturised OPMs by QuSpin Inc., increasing sales and providing new product lines. OPM-MEG requires a zero magnetic field environment, and the UoN OPM-MEG team have developed novel magnetic field control technology which has been commercialised by Magnetic Shields Limited (MSL). In 2020, this research and related intellectual property led to the formation of a spin-out company, Cerca Magnetics Limited, selling integrated OPM-MEG brain imaging systems. The clinical impact of this technology is evidenced by the recent installation of the world's first clinical OPM-MEG scanner at Young Epilepsy – a charity providing world-leading care for epilepsy patients.

2. Underpinning research

MEG detects magnetic fields generated close to the scalp by current flow in neuronal assemblies. Mathematical analysis of these fields yields 3D images showing changes in brain activity in response to controlled stimuli. This provides a powerful method to investigate brain function, with millisecond temporal accuracy and high spatial precision (~ 5-8 mm). MEG is used in neuroscientific research, and clinically – for example to map abnormal brain activity in epilepsy. Conventional MEG employs Superconducting Quantum Interference Devices (SQUIDs) to detect the weak (~100 fT) magnetic fields from the brain. Whilst highly sensitive (~5-10 fT/√Hz), SQUIDs require cryogenic cooling which imposes significant limitations; MEG systems (see Fig.1a) are rigid, making them 'one-size-fits-all' with inhomogeneous brain coverage (due to variation in head shape/size) and little sensitivity in infants (due to their small heads). They also require subjects to remain still for long periods (sometimes hours), are expensive (>GBP2M) and have high operating costs (GBP150k PA) due to rising costs of liquid helium.

Since 2015, the UoN OPM-MEG team have worked on the development of a novel MEG scanner based on Optically Pumped Magnetometers. OPMs exploit the spin properties of alkali atoms and optical pumping to generate a measure of local magnetic field with a sensitivity rivalling that of SQUIDs (~7 fT/√Hz). OPMs do not require cryogenic cooling and so can be placed closer to the head, providing improvements in signal strength and spatial resolution. OPMs are small and lightweight, facilitating the development of a wearable scanner which can be adapted to any head shape/size and allows subject movement during scanning. For the first time, individuals such as infants who simply cannot tolerate conventional scanning environments can be scanned. We developed OPM-MEG in collaboration with the Wellcome Centre for Human Neuroimaging at University College London (UCL), who have a duplicate

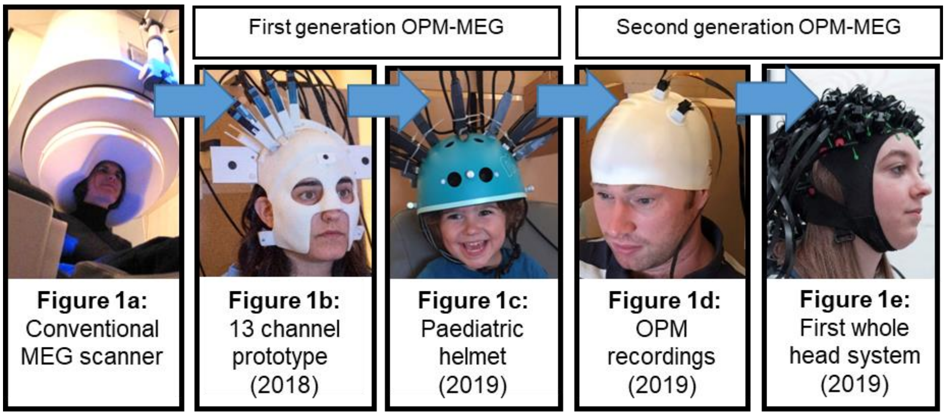

Figure 1: Development timeline of the first whole head OPM-MEG system.

UoN system for neuroscientific and clinical translation (such as epilepsy evaluation) **[a]**. In initial simulations **[1]**, we outlined the advantages afforded by OPM-MEG compared to cryogenic MEG. Since OPM sensors can be placed within ~6 mm of the scalp, a multi-channel whole-head OPM-MEG system offers (on average) a 5-fold improvement in sensitivity as well as improved spatial resolution (~2 mm). These improvements were confirmed in our first experimental measurements made using a single OPM sensor placed over different locations on the scalp during sensory stimulation **[2]**. A Wellcome Collaborative Award in Science **[i]** allowed us to develop a 13-channel prototype wearable scanner (Fig.1b) which provided the first MEG measurements of brain activity in moving subjects **[3]**.

To acquire OPM-MEG measurements during subject movement, it was necessary to control the magnetic field in the region through which the subject's head moved. Experiments were performed inside a Magnetically Shielded Room (MSR) formed from multiple layers of high-permeability (mu-metal) and high-conductivity material. However, even within this room, the static magnetic field was too large (~30 nT) for OPM operation. To overcome this, we devised a bi-planar nulling coil system **[4, 5]**, comprising multiple coils confined to two (1.6x1.6 m^2) planar surfaces positioned on either side of the subject. These coils (which were designed using an approach derived from *Bowtell's* work on Magnetic Resonance Imaging (MRI) **[6]**) generate uniform fields, directed along three orthogonal directions, to which constant field gradients can be added to shape the overall field profile. By adjusting currents in the coils, it is possible to reduce the background magnetic field to less than 0.3 nT over a 50x50x50 cm^3 volume. In further research, we have updated this system to null dynamic field changes **[5]** and developed new coil designs that account for the effect of the mu-metal on the fields generated. This approach to the design and optimisation of active magnetic shields is now being used across the UK National Quantum Technology (QT) Hub in Sensing and Timing, and also the wider UK National QT Programme **[ii, iii]** to fabricate miniaturised shields for applications including chip scale magnetometers **[iv]** and gravity gradiometers.

The 13-channel prototype was used for the first demonstration of OPM-MEG alongside virtual reality stimulation and paediatric OPM-MEG in children as young as 2 years old (Fig.1c) **[7]**. Conventional MEG measures in children are extremely challenging due to the one-size-fits-all (adult) scanner design and increased subject movement; OPM-MEG solves both problems. We have made direct comparisons to measures acquired using the closest competitor in wearable imaging technology, electroencephalography (EEG), showing the major advantages OPM-MEG brings in superior spatial resolution (~2mm for OPMs; >10 mm for EEG), and a 10-fold reduction in sensitivity to artifacts from non-brain sources **[8].** Recently, we have used new lightweight sensors (no larger than a Lego brick, Fig.1d) to expand the prototype to 50-channels, providing whole brain coverage (Fig.1e). Initial results **[9]** show that this system offers equivalent or better performance compared to a state-of-the-art cryogenic MEG system, with significantly improved practicality, enabling previously impossible neuroscientific research and clinical applications. This 50-channel whole brain system is the basis for commercialisation of OPM-MEG technology by Cerca Magnetics Limited.

3. References to the research

Publications: *Academic staff* and PDRAs working in the UoN OPM-MEG team.

[1] **Boto, E.**, ***Bowtell, R.***, Kruger, P., ***Fromhold, T.M.***, ***Morris, P.G***., Meyer, S.S., Barnes, G.R., ***Brookes, M.J.***, 'On the Potential of a New Generation of Magnetometers for MEG: A Beamformer Simulation Study', *PLOS One*, Vol. 11, No. 8, e0157655, 2016; DOI: 10.1371/journal.pone.0157655.

[2] **Boto**, **E.,** Meyer, S.S., Shah, V., Alem, O., Knappe, S., Kruger, P., ***Fromhold, T.M.***, Lim, M., ***Glover, P.M.***, ***Morris, P.G.***, ***Bowtell, R.***, Barnes, G.R., ***Brookes, M.J.***, 'A new generation of magnetoencephalography: Room temperature measurements using optically-pumped magnetometers', *Neuroimage,* Vol. 149, 404-414, 2017; DOI: 10.1016/j.neuroimage.2017.01.034.

[3] **Boto, E**., **Holmes, N**., **Leggett, J**., **Roberts, G.**, Shah, V., Meyer, S.S., Munoz, L.D., ***Mullinger, K.J***., Tierney, T.M., Bestmann, S., Barnes, G.R., ***Bowtell, R***., ***Brookes, M.J***., 'Moving magnetoencephalography towards real-world applications with a wearable system', *Nature,* Vol. 555, No. 7698, 657-661, 2018; DOI: 10.1038/nature26147.

[4] **Holmes, N**., **Leggett, J.**, **Boto, E.**, **Roberts, G**., **Hill, R.M**., Tierney, T.M., Shah, V., Barnes, G.R., ***Brookes, M.J***., ***Bowtell, R***., 'A bi-planar coil system for nulling background magnetic fields in scalp mounted magnetoencephalography', *NeuroImage*, Vol.181, 760-774, 2018; DOI: 10.1016/j.neuroimage.2018.07.028.

[5] **Holmes, N**., Tierney, T.M., **Leggett, J**., **Boto, E**., Mellor, S., **Roberts, G**., **Hill, R.M**., Shah, V., Barnes, G.R., ***Brookes, M.J.***, ***Bowtell, R.***, 'Balanced, bi-planar magnetic field and field gradient coils for field compensation in wearable magnetoencephalography', *Scientific Reports*, Vol.9,14196, 2019; DOI: 10.1038/s41598-019-50697-w.

[6] **Poole, M**., ***Bowtell, R***., 'Novel gradient coils designed using a boundary element method, Concepts in Magnetic Resonance Part B-Magnetic Resonance', *Magnetic Resonance Engineering*; Vol.31B, No.3,162-75, 2007; DOI: 10.1002/cmr.b.20091.

[7] **Hill, R.**, **Boto, E**., **Holmes, N**., Hartley, C., **Seedat, Z**., **Leggett, J**., **Roberts, G**., Shah, V., Tierney, T., Woolrich, M., Stagg, C., Barnes, G., ***Bowtell, R***., Slater, R., ***Brookes, M***., 'A new tool for functional brain imaging with lifespan compliance', *Nature Communications*, Vol.10, 4785, 2019; DOI: doi.org/10.1038/s41467-019-12486-x.

[8] **Boto, E**., **Seedat, Z.A**., **Holmes, N**., **Leggett, J**., **Hill, R.M**., **Roberts, G**., Shah, V., ***Fromhold, T.M***., ***Mullinger, K.J***., Tierney, T.M., Barnes, G.R., ***Bowtell, R***., ***Brookes, M.J.***, 'Wearable neuroimaging: Combining and contrasting magnetoencephalography and electroencephalography', *Neuroimage*, Vol.201, 116099, 2019; DOI: 10.1016/j.neuroimage.2019.116099.

[9] **Hill, R.M.**, **Boto, E.**, **Rea, M**., **Holmes, N.**, **Leggett, J**., Coles, L,A, Papastavrou, M., Everton, S.K., Hunt, B.A.E., **Sims, D.**, Osborne, J., Shah, V., ***Bowtell, R.***, ***Brookes, M.J***. 'Multi-channel whole-head OPM-MEG: Helmet design and a comparison with a conventional system', *Neuroimage*, Vol.219, 116995, 2020; DOI: 10.1016/j.neuroimage.2020.116995.

Grants:

[i] 'Moving functional brain imaging into the real world: A wearable, cryogen-free, magnetoencephalography (MEG) system', Barnes, G. R., Brookes, M. J., Bowtell, R., (203257/Z/16/Z and 203257/B/16/Z), Wellcome Collaborative Award in Science, (Apr 2017 – Apr 2022), GBP1.6M (GBP0.8M to Nottingham).

[ii] 'UK Quantum Technology Hub for Sensors and Metrology', PI: Bongs, UoN Co-Is: Brookes, M. Fromhold, T. M., Bowtell, R., (EP/M013294/1), EPSRC, (Dec 2014 – Nov 2019), GBP35.5M (GBP6M to Nottingham).

[iii] 'UK National Quantum Technology Hub in Sensing and Timing', PI: Bongs, K., UoN Co-Is: Brookes, M. J, Bowtell, R., Fromhold, T.M., (EP/T001046/1), EPSRC, (Dec 2019 – Dec 2024), GBP24.0M.

[iv] 'MAG-V: Enabling Volume Quantum Magnetometer Applications through Component Optimisation & System Miniaturisation'. PI: Wotherspoon, T., UoN PI: Fromhold, T. M., (106172), Innovate UK, (Jun 2020 – Dec 2022), GBP1.9M.

[v] 'SMART SHIELD', Brookes, M. J., Bowtell, R., Fromhold, T. M., Sims, D. R., Woolger, D., EPSRC (QT Hub for Sensors and Metrology, ATEP), (Oct 2018 – Apr 2020), GBP423k.

[vi] 'Lightweight and compact, high performance magnetically shielded rooms for biomagnetic measurements – LightMuRoom'. Woolger, D., Bowtell, R., Barnes, G. R., Brookes M. J., (104604), Innovate UK, (Apr 2019 – Mar 2021), GBP970k.
[vii] 'Active and Passive Shielding for OPM MEG', Bowtell, R., (2275234), EPSRC Case studentship, (Oct 2019 – Sept 2023), GBP18k.

Prizes and Recognition:

Professor Matthew Brookes, BIOMAG 2018 Mid-Career Prize 'in recognition of sustained and devoted contributions to the field, and exemplary impact on the field.'
Professor Richard Bowtell, Institute of Physics (IoP) James Joule Medal and Prize (2020) for 'his outstanding application of physics to the innovative development of new hardware and techniques for biomedical imaging, and their application in medicine and neuroscience.'

4. Details of the impact

This research has, to date, had significant commercial impact on two well-established companies, **QuSpin Inc.** and **Magnetic Shields Limited (MSL)**. In addition, it has led to the formation of **Cerca Magnetics Limited**, a new spin-out company selling integrated OPM-MEG systems. It has also had clinical impact through the installation of the first clinically dedicated OPM-MEG system at **Young Epilepsy's Neville Childhood Epilepsy Centre**.

The UoN OPM-MEG team have worked closely with the US-based atomic devices company **QuSpin Inc. [b]** (USD2.5M annual revenue) in evaluating and optimising the performance of the QuSpin Zero Field Magnetometers (QZFMs). UoN performed a full characterisation of the first-generation (QZFM-Gen-1) product for MEG, identified its limitations, and collaborated with QuSpin to develop the intellectual property required to integrate their second-generation sensor (QZFM-Gen-2) into a MEG array. This resulted in the development of the world's first wearable OPM-MEG scanner (this development is outlined in Figure 1). This work has transformed the trajectory of QuSpin in terms of product development and sales, enabling the company to grow **[b]**. Specifically, (i) the UoN team provided QuSpin with critical technical inputs related to limitations of their early generation of sensors, allowing them to advance the performance and usability of their latest hardware; (ii) high impact research and publications by the UoN OPM-MEG team '*generated tremendous enthusiasm for QuSpin sensors, stimulating worldwide demand*' as stated by the Founder & Chief Scientist of QuSpin Inc. '*This resulted in substantial growth in sales and expanded QuSpin Inc. through the creation of new highly paid jobs (USD50k to USD125k per annum)*'. Analysis of sales figures by QuSpin Inc. confirm '*~60% of their USD2.5M sales revenue in 2019 can be directly attributed to UoN research*' **[b];** (iii) UoN OPM-MEG team members provided QuSpin with training and expertise in MEG technology, allowing them to connect quantum physics with imaging physics, brain electrophysiology and neuroscience. QuSpin confirm the impact of UoN's research '*the Nottingham team's truly ground-breaking work has affected our business in terms of product development and sales, enabling us to grow as a company*' **[b]**.

From 2016, we have collaborated with **MSL [c]**, a UK-based SME (annual turnover GBP7M) specialising in magnetic shielding technologies. Collaboration has centred on the development of Magnetically Shielded Rooms that provide the environment needed for OPM-MEG **[v]**. Our initial OPM-MEG papers generated *'new orders for these rooms, totalling £2M in value to date with an additional £6M worth of active enquiries*' **[c]**. This is because MSL's passive shield design outperforms competitors' products in terms of reducing the background static magnetic field values, a critical factor for the successful operation of OPMs. Subsequent work with MSL (supported by the EPSRC-funded UK National Quantum Technology Hub in Sensing and Timing **[iii]**) focused on improving magnetic field control by uniquely combining passive (mu-metal and aluminium/copper) and active (coils) shielding. This approach led to improvements in MSR performance. Using passive shielding alone, the lowest magnetic fields achieved are ~2 nT; by incorporating passive and active shielding fields one can routinely reduce this value to <0.3 nT. The initial coil design was commercialised by MSL, generating orders of GBP160k and live quotes of GBP500k within the assessment period **[c]**. More recently, the development of a lighter MSR, based on a combination of a matrix of coils and a single layer of mu-metal, has been supported by Innovate UK **[vi]**. An output of this grant is the construction of a demonstrator lightweight MSR, another new product line for MSL. Further knowledge exchange between MSL and UoN, for example an EPSRC CASE studentship on

'Active and Passive Shielding for OPM MEG' **[vii]**, has led to a better understanding of the interaction between electromagnetic fields and mu-metal. The Managing Director of MSL states '*research taking place at UoN is having significant impact on our company; it has led to increased sales, new product lines, new jobs, and new expertise*' **[c]**.

Over the past two years there has been a growing worldwide demand for a fully integrated (turnkey) OPM-MEG system. Funded by Wellcome and the UK National Quantum Technologies programme, we have developed OPM-MEG from prototype to commercialisation. In collaboration with QuSpin and MSL, we have formed a new joint-venture spin-out company, **Cerca Magnetics Limited**, registered on 24 July 2020 and publicly launched on 7 December 2020 **[c,d].** Cerca Magnetics Limited has licenced unique IP from UoN to form an integrated OPM-MEG system; this IP includes hybrid active/passive shielding technology, integration of shielding with OPM arrays, newly patented array designs (Patent Application No. 2015427.4 **[e]**) and OPM helmet technology. At the end of the assessment period Cerca Magnetics Limited had over GBP800k of orders and >GBP1M of live quotes for the sale of MEG equipment to flagship laboratories in the USA, Canada and Europe **[c]**. This includes the first order for a complete commercial OPM-MEG system which will be installed at the Hospital for Sick Children, Toronto, Canada in mid-2021.

The clinical impact of OPM-MEG for epilepsy is also evidenced by the changing strategy of **Young Epilepsy (YE)**, a UK-based Charity dedicated to the diagnosis, assessment and rehabilitation of children and young people with epilepsy. In 2020, YE (in collaboration with UoN, UCL and Great Ormond Street Hospital) made the strategic decision to install the world's first clinically dedicated OPM-MEG system within their Neville Childhood Epilepsy Centre, with clinical trials due to commence mid-2021. The Director of Integrated Care at YE states '*installation of this new OPM-MEG system, built to the Nottingham design, will facilitate new and improved diagnostic capability and ultimately a means to map epileptogenic as well as eloquent cortex which will provide vital information to neurosurgeons… Over 112k children and young people below the age of 25, in the UK alone, are affected by epilepsy. Therefore, it is easy to understand just how vital this OPM-MEG project is*' **[f]**.

In addition to the commercial and clinical impact, OPM-MEG research has led to numerous outreach and public engagement activities. For example, OPM-MEG underpinned our '*Quantum sensing the brain'* exhibit at the 2018 Royal Society Summer Exhibition (RSSE) **[g]**. This exhibit has subsequently been used at other exhibitions (including New Scientist Live, the Cheltenham Science Festival, Going Global conference (Berlin), The British Embassy in Berlin, and the UK Quantum Showcase (London)), and has been used by QuSpin Inc. on their commercial stand at scientific meetings. The UoN OPM-MEG project has been recognised through commendations by Times Higher Education **[h]**, and the Institute of Physics (IoP) publication Physics World as '*one of the top ten breakthroughs of 2019*' **[i]**, as well as prizes to *Bowtell* and *Brookes* by the IoP and BIOMAG, respectively (**Section 3**).

5. Sources to corroborate the impact that has occurred:

[a] Letter from Director, Wellcome Centre for Human Neuroimaging, UCL.
[b] Letter from Founder & Chief Scientist of QuSpin Inc.
[c] Letter from Managing Director of MSL and CEO of Cerca Magnetics Limited.
[d] Companies house record for Cerca Magnetics Limited Company number 12766132 https://find-and-update.company-information.service.gov.uk/company/12766132/
[e] Patented OPM array designs: Patent Application No. 2015427.4
[f] Letter of support from Director of Integrated Care, Young Epilepsy.
[g] Royal Society Summer Exhibition (RSSE) *Quantum sensing the brain* exhibit review.
[h] 'Highly commended' by Times Higher Education Awards 2019. https://www.timeshighereducation.com/news/times-higher-education-awards-2019-winners-announced
[i] Institute of Physics 'breakthrough of the year' finalists 2019: https://physicsworld.com/a/physics-world-announces-its-breakthrough-of-the-year-finalists-for-2019/