Institution:
ASTON UNIVERSITY

Unit of Assessment:
3: ALLIED HEALTH PROFESSIONS, DENTISTRY, NURSING AND PHARMACY

Title of case study:
6) DEVELOPMENT OF MAGNETOENCEPHALOGRAPHY (MEG) FOR CLINICAL SERVICE PROVISION

1. Summary of the impact (indicative maximum 100 words)

Early diagnosis of major brain diseases, especially in children, is a crucial yet largely unmet clinical need. Since 1996 Aston University researchers have pioneered the development and clinical application of Magnetoencephalography (MEG). The team's research now supports the UK's first and largest clinical pre-surgical evaluation programme in partnership with leading neurosurgery centres. This work has had the following impacts (2008 - date) on health services, patient welfare and commerce:

1. Practitioner adoption of clinical MEG techniques to inform surgical intervention.
2. Improved patient outcomes through earlier surgical intervention.
3. Overseas industry investment secured for technological development of benefit to the global neuroimaging market.

2. Underpinning research (indicative maximum 500 words)

Background: Over the last ten years, the gold standard for neuroimaging has been functional Magnetic Resonance Imaging (fMRI), an indirect measure of neuronal activity requiring a high degree of participant compliance and limited in its clinical application. On the other hand, electroencephalography (EEG) is a well-established clinical tool for direct measurement of neuronal activity, but has been limited by its ability to localise abnormalities. Clinical neurophysiologists at Aston University sought to integrate and develop new technologies to combine the high spatial resolution of MRI with the exquisite temporal resolution of EEG. This new technology was magnetoencephalography (MEG).

Key Science Faculty conducting the research during review period 1993-2013

The core scientific team leading the research and a multi-disciplinary group comprised:

Harding GF: 1963 - 2003, Professor of Clinical Neurophysiology.

Furlong PL: 2000 - to date. Lecturer, Senior Lecturer in Psychology, Professor of Clinical Neuroimaging.

Holliday IE: 2005 - to date, Reader Psychology, Professor of Vision Science.

Seri S: 2004 - to date, Chair in Clinical Neurophysiology

Witton, C: 2001 - date, Lecturer Senior Lecturer in Psychology, Reader in Neuroscience.

Research insights: Using custom designed and built systems (1993 - 1996), research was undertaken to characterise the value of MEG to answer questions that neither MRI nor EEG could do alone; namely to accurately localise changes in neuronal oscillations with high spatial accuracy

(S3.1). As a consequence of this work, a Wellcome Trust grant secured the purchase of the first whole brain MEG system in the UK (1999). In 2004 the group became one of the first in Europe to combine high resolution MEG with the new generation of 3Tesla MRI facilities. Subsequent publications were amongst the first to report comparative findings of cortical source localisation techniques, including the development at Aston of a novel 'beamformer' method known as Synthetic Aperture Magnetometry (SAM). The advantage of the beamformer approach has been that closely similar paradigms could be integrated across neuroimaging modalities for the first time, allowing close comparison of similarities and differences in the techniques that could be used to enhance them for clinical application. Thus, Aston publications included the first reports of MEG measures integrated with MRI and fMRI measures (S3.2), and adaptations of statistical methods for comparative analyses (S3.3). Proof of concept publications (1996 - 2005) demonstrated the effectiveness of MEG for fundamental neuroscience research (S3.2) and for clinical use (S3.4). Importantly the MEG beamformer approach and its integration with MRI has proved a valuable tool in the clinical application of pre-surgical evaluation, where evidence of neuronal abnormality and its association with anatomical abnormalities can now readily be made.

Since 2005 we have applied MEG to the study of pharmacokinetics and produced one of the first reports characterising the ability of the technique to dynamically model changes in cortical oscillations associated with GABAergic intervention (S3.5). Furthermore in 2009, a Wellcome Trust grant (2009) led to technological optimisation of MEG systems for use in paediatrics (see S5.3). Since this award, several publications have characterised the use of MEG for objective psychometric and psychophysical evaluations in paediatric age, with important implications for enhanced diagnostic application (S3.6).

3. References to the research (indicative maximum of six references)

Vision science

1. Anderson S.J., Holliday I.E, Singh K.D. and Harding G.F.A. (1996). Localisation and functional analysis of human cortical area MT (V5) using magneto-encephalography. Proceedings of the Royal Society of London, Series B, 263, pp. 423-431. doi:10.1098/rspb.1996.0064 [Impact factor, IF, 5.415, 104 citations].

MEG methodologies

2. Hillebrand, A. Singh, K.D., Furlong P.L., Holliday, I.E., Barnes, G.R. A new approach to neuroimaging with magnetoencephalography. (2005). Human Brain Mapping. 25(2):199-211. doi: 10.1002/hbm.20102 [IF 5.880, 143 citations].

3. Brookes, M, Gibson, A. Hall, S.D., Furlong, P.L., Barnes, G.R., Hillebrand, H., Singh, K.D., Holliday, I.E., Francis, S., Morris. P. A. (2005). GLM-beamformer method demonstrates stationary field, Alpha ERD and gamma ERS co-localisation with fMRI BOLD response in visual cortex. Neuroimage. 15; 26 (1):302-8. doi.org/10.1016/j.neuroimage.2005.01.050 [IF 5.880, 91 citations].

Pre-surgical evaluation using MEG

4. Agirre-Arrizubieta, Z., Thai Ngoc, J., Valentín, A., Furlong, P.L., Seri, S., Selway, R.P., Elwes, R.D.C., Alarcón, G. (2013) The value of magnetoencephalography to guide electrode implantation in epilepsy. Brain Topography doi: 10.1007/s10548-013-0330-x [IF 3.671].

Pharmacokinetics

5. Hall SD, Barnes GR, Furlong PL, Seri S, Hillebrand A. Neuronal network Pharmaco-dynamics of GABAergic modulation in the human cortex determined using pharmaco-

magnetoencephalography. Hum Brain Mapp. 2010 Apr;31(4):581-94. doi: 10.1002/hbm.20889. [IF 6.878, citations 20]

Neurodevelopment

6. Witton C, Patel T, Furlong PL, Henning GB, Worthen SF, Talcott JB. Sensory thresholds obtained from MEG data: Cortical psychometric functions. Neuroimage. 2012 Aug 11;63(3):1249-1256. doi: 10.1016/j.neuroimage.2012.08.013. [IF 5.880]

4. Details of the impact (indicative maximum 750 words)

Background: Research conducted at Aston (1996 - date) had a pioneering role nationally and internationally by characterising the value and sensitivity of the technique for the study of brain physiology. Notably, by rigorous evaluation of the novel beamformer approach which allowed direct integration and comparison of the technique with other neuroimaging modalities, the technique has become broadly accepted into every main neuroscience centre in the UK. Further, as the first Centre in the UK to apply MEG to clinical diagnostic and pre-surgical evaluation with leading surgical teams in the UK, the value of the technique in the treatment pathway for intractable epilepsy is exploited. This research has further led to a commercial partnership with the world leaders in MEG system development, to optimise MEG technology for paediatric application with enhanced clinical value.

Practitioner and Clinical Service: The most notable impact of our research is in its clinical application. The latest Wellcome Trust Laboratory for MEG Studies is located in a £4.4 million state-of-the-art neurosciences facility, the Aston Brain Centre. The facility, operational from July 2011, is the only Care Quality Commission approved MEG facility for diagnostic service provision in paediatric age in the United Kingdom. The facility is providing research-led diagnostic services directly benefitting health trusts and their clients across the United Kingdom.

Clinical research collaborations with several health trusts across the country have been active for 8 years. Since 2008, a total of 226 referrals have been received. MEG investigations have revealed no abnormality (36 patients 16%), provided new and important clinical evidence (172 patients, 76%) with 44 patients (23%) progressed to surgery. 29 of these patients have significant lasting improvements (Engel class I outcome). Since 2010, we have provided a contracted tertiary referral service for Kings College London (KCL; 64 adult referrals), Great Ormond Street London (GOSH; 22 child referrals) and Birmingham Children's Hospital (18 referrals). Clinical leads in the epilepsy surgery teams from GOSH have reported that 'notable success has been achieved through pre-surgical evaluation of patients where existing methods failed to provide unequivocal evidence of focal epileptiform activity or the characterisation of eloquent cortex close to lesions for excision' (S5. 1). Four key MEG groups supporting clinical research activity are now being led by Aston trained staff (Barnes, Functional Imaging Lab, University College London in 2009; Singh CUBRIC Cardiff in 2005; Hillebrand, VuMC Amsterdam in 2009; Brookes, Sir Peter Mansfield MRI Centre, Nottingham PhD at Aston 2003 (S5.2).

Health and Welfare: Intractable epilepsy is debilitating at any age as frequent uncontrolled seizures have physical, social, and cognitive implications. Successful intervention affords significant benefit for all patients. However, early successful intervention for children affords important cognitive and educational advantages as the ability to succeed in main stream education has lifelong implications. The child brain is also very adaptable so recovery from surgery is usually optimal. However, conventionally there are two major limitations to progressing to surgery. First, conventional techniques need to establish that there is a focal abnormality amenable to resection. Second, resecting the identified area must not lead to debilitating consequences such as loss of mobility or loss of speech and language capability. Children struggle to comply with conventional testing at an early age to establish these criteria. Our work to optimise MEG to address these questions in paediatric age have led to many patients, but notably children, progressing to early surgery when otherwise such a decision would have been deferred. Thus, our MEG research is directly affording significant patient benefit (S5.1; S5.2).

Commercial Investment in Technological Developments: Principal investigators Furlong, Holliday, Seri, Talcott and Witton further developed a strategy based on our research to enhance both the fundamental science and clinical value of MEG in the field of paediatric neuro-development. Having characterised significant limitations of current MEG technologies for clinical measurements in paediatric age, and through collaboration with a commercial partner (Elekta Corporation), one of the world's first paediatric compliant MEG system is being developed with Wellcome Trust funding, together with investment from the commercial partner (S5.3). This collaborative partnership has had an impact on the roadmap for the commercial partner, with a focus on clinical application and optimisation, with important implications for the future development of the technology (S5.4). The technological developments resulting from joint research with Elekta are of benefit to the global clinical neuroimaging market.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Statement from Consultant Paediatric Neurologist & CESS Epilepsy Lead, Great Ormond Street Hospital for Children, London WC1N 3JH.

2. Statement from the Director, The Sir Peter Mansfield Magnetic Resonance Imaging Centre, University Park, Nottingham, NG7 2RD.

3. Wellcome Trust grants in support of MEG development at Aston University
Wellcome Trust Equipment Grant Ref: 088314/Z/09/Z **'**Development of a paediatric MEG system' Prof P.L. Furlong, Dr I.E. Holliday, Prof S Seri, Dr J.B. Talcott, Dr C Witton. £1,000,000 Commencing 01/11/09 for three years.

4. Statement from the Director of MEG Business, Elekta Oy, Siltasaarenkatu 18-20FI-00530 Helsinki, Finland.