Institution:
University of Cambridge

Unit of Assessment:
UoA4

Title of case study:
Using functional imaging to detect covert cognition in the vegetative state – mapping the translation from research finding to patient management framework

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

The capacity for cognitive function may be missed by clinical examination in severely disabled survivors of acquired brain injuries, resulting in individuals being mislabelled as being in the vegetative state (VS). Work from David Menon and John Pickard has shown that functional brain imaging provides a more consistent and less observer-dependent means of detecting and quantifying such cognitive capacity. As a result of this work, the use of functional imaging has been integrated into clinical protocols as the basis for: identifying patients with such covert cognition; prognosticating on outcome; defining a rational framework for patient selection in clinical trials; and exploring the use of brain-machine interfaces to improve communication with such patients.

2. Underpinning research (indicative maximum 500 words)

The research reported in this statement was led by Menon and Pickard (Professors at the University of Cambridge in Anaesthesia and Neurosciences, from 1991 and 2000, respectively), in conjunction with Dr Adrian Owen (Assistant Director, MRC Cognition and Brain Sciences Unit; MRC CBU; University of Western Ontario, from 2010). Previous work by others (Andrews et al; BMJ 1996; 313:13-6) reported that detectable cognitive capacity in could be detected in some patients with VS by expert clinical examination, raising the possibility that some patients might possess volitional capacity, clinically undetectable due to the absence of motor outputs. In 1998 Menon (then Lecturer in Anaesthesia in the University of Cambridge) and Pickard showed that functional brain imaging could demonstrate retained cognitive processing in a patient who fulfilled clinical criteria for VS,1 thus showing that functional imaging provides a means of directly addressing these concerns about covert cognition in some patients. Over the last 15 years, this use of functional imaging has been refined to communicate with patients thought to be in VS, and allow more diagnostic precision, prognostic accuracy, and management stratification in this context.

In 2005 Menon and Pickard, along with the late Dr Coleman (Clinical Neurosciences at the time) used functional magnetic resonance imaging (fMRI) to show that the cortical response to auditory stimuli is graded,2 recapitulating a hierarchical framework of language processing (sound perception, speech perception, and complex speech comprehension). In conjunction with Dr Matt Davis (MRC-CBU), they confirmed the inverse concordance of this hierarchy with worsening cognitive performance, by showing that deepening sedation in healthy volunteers recapitulated observations in patients.3 Crucially, they also showed that a patient's position on this hierarchy (determined using fMRI) predicted clinical recovery, measured six months after the functional imaging study.4

In 2006, Pickard, Owen and collaborators in Liege (Professor Steven Laureys), showed that fMRI could provide a read-out of whether a subject, when instructed to do so, chose to undertake either a motor imagery task (which activated the premotor cortex) or a mental navigation task (which activated a spatial memory network);5 this paradigm could thus be used to demonstrate volitional control of cortical activation in VS, in the absence of any behavioural responses. Pickard, with Owen and Dr Martin Monti (MRC Cognition and Brain Sciences Unit), also showed that clinically unsuspected volitional control could be detected in ~5% of patients referred to our research program with disorders of consciousness.6

Menon and colleagues have identified structural correlates of such preserved cognitive capacity, using diffusion tensor imaging (DTI),7 which shows loss of long brainstem tracts in VS secondary to traumatic brain injury, but not hypoxic ischaemic injury. These findings are important for prognostication, and for selecting and stratifying patients for clinical trials of 'arousal' interventions.

Conventional fMRI analysis cannot determine rapidly whether volitional control of cortical activation exists, or use such responses to communicate with patients. Dr Guy Williams (Wolfson Brain Imaging Centre) has recently designed and implemented a Support Vector Machine algorithm to address these needs. This resource provides robust real-time readouts of fMRI responses in healthy volunteers, and is being developed for studies in patients, following which it will allow more

efficient research design, and reduce the time that severely disabled patients have to spend in the MRI scanner. The software is being made available to other MRI users who operate on the same imaging platform through the Siemens C2P process.

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

1. Menon DK, Owen AM, Williams EJ, Minhas PS, Allen CM, Boniface SJ, Pickard JD. Cortical processing in persistent vegetative state. Wolfson Brain Imaging Centre Team. Lancet. 1998;352(9123):200. PubMed PMID: 9683212.

2. Owen AM, Coleman MR, Menon DK, Berry EL, Johnsrude IS, Rodd JM, Davis MH, Pickard JD. Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. Prog Brain Res 2005;150:457-71. PubMed PMID: 16186042.

3. Davis MH, Coleman MR, Absalom AR, Rodd JM, Johnsrude IS, Matta BF, Owen AM, Menon DK. Dissociating speech perception and comprehension at reduced levels of awareness. Proc Natl Acad Sci U S A 2007; 104(41):16032-7. PubMed PMID:17938125.

4. Coleman MR, Davis MH, Rodd JM, Robson T, Ali A, Owen AM, Pickard JD. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 2009;132(Pt 9):2541-52. PubMed PMID: 19710182.

5. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006 Sep 8;313(5792):1402. PubMed PMID: 16959998.

6. Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, Owen AM, Laureys S. Willful modulation of brain activity in disorders of consciousness. N Engl J Med 2010;362(7):579-89. PubMed PMID: 20130250.

7. Newcombe VF, Williams GB, Scoffings D, Cross J, Carpenter TA, Pickard JD, Mnon DK. Aetiological differences in neuroanatomy of the vegetative state: insights from diffusion tensor imaging and functional implications. J Neurol Neurosurg Psychiatry 2010;81(5):552-61. PubMed PMID: 20460593.

Grants where the research above has been part of the work that was funded: total funding (1993-2013): £4,260,943

Grants where the research above has been the main focus of the work that was funded:

- GB Williams GB. The Development of a Brain Computer Interface to improve the quality of life of persons with impaired consciousness following brain injury. Henry Smith Charity. 2010-2011. £ 17,600
- Owen AM & Pickard JD, and others. A collaborative study of consciousness after severe brain injury. McDonnell Foundation. 2008-2012. £482,295.
- Owen AM, Pickard JD, and others. Detecting awareness in the vegetative and minimally conscious states: novel clinical applications. MRC Translational Grant 2008-2012. £351,025.

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

The research has had clinical, scientific, policy, and societal impact

Clinical practice:

The knowledge that some patients who clinically satisfy criteria for VS are capable of complex cognition has transformed the attitude to such patients in long-stay residential homes where they are cared for, and reduced clinical nihilism regarding the condition. These changes in clinical attitudes represent a paradigm shift in the history of the condition, and have encouraged novel research (see media references and discussion below). This knowledge has been disseminated beyond the clinical centres directly involved in our research through involvement of members of our group in professional symposia and conferences, where our research results and clinical protocols are presented to practicing clinicians in neurology, neurosurgery, intensive care, and rehabilitation

medicine (see, for example, Reference 1 below). At an individual patient level, our functional imaging results already provide data that inform the management of patients who are referred to us. We see two patients per week, and of the last 100 referred for the study, approximately a fifth (20%) have shown covert cognition.

Impacts on medical research:

Since there are likely to be less than 500 patients with VS in England and Wales at any time, if research is to progress further a close collaborative relationship is essential between academic centres and NHS clinical units that care for these patients. This need was addressed by establishing strong national and international networks with common, integrated research programs. Scientific collaborators include the MRC-CBU, Liege University, Cornell University, and University of Western Ontario. National clinical collaborators include the Royal Hospital for Neurodisability; The Royal Leamington Spa Rehabilitation Hospital; The Coleman Centre, Norwich, The Jacob Centre, Sawbridgeworth; and Leicester Royal Infirmary. Apart from impacting on routine clinical care, this latter network represents a key resource for current research recruitment, and has enabled recruitment to many of the studies cited in Section 3. It also provides an essential framework for future dissemination of best practice and novel clinical management paradigms.

Impact on public policy and services:

This research has also informed the debate on national legislation. Original drafting of the Mental Capacity Bill and implementation of the Clinical Trials Directive contained highly restrictive provisions for research in people without capacity, which would have made it illegal to undertake research in diseases resulting in loss of consciousness, thereby preventing rational improvements in care for patients suffering from VS and related disorders. Menon, along with Dr Kathy Liddell (Faculty of Law, University of Cambridge) and Dr Ron Zimmern (Department of Public Health, University of Cambridge), made substantial contribution to this debate,[2] which influenced the drafting of final legislation and regulation of the Mental Capacity Act (2005) and UK implementation on the Clinical Trials Directive (2004), both of which remain current to date. This input was informed by our experience, and the narrative of Kate Bainbridge - the subject of the original Lancet paper on residual cognition in the vegetative state in 1998 who has since made a substantial cognitive recovery.[3,4] These contributions at Parliamentary committee stages of the Mental Capacity Act and during the implementation of the Clinical Trials Regulations helped convince Government that research in individuals lacking capacity was clearly ethical, and resulted in important modifications ensuring continuation of vital research in critical care and emergency medicine.

Impacts on society, culture and public understanding of medicine and science:

Our research on disorders of consciousness has already had substantial societal impact. Our contributions to national broadcast media have informed public knowledge and debate in this area. In 2010, The Neurosciences Critical Care Unit at Addenbrooke's Hospital hosted a BBC television team, who produced a programme addressing the difficult area of poor quality survival from brain injury. *Between Life and Death*[5,6,7] was broadcast on BBC1 in July 2010, and won the Royal Television Society Award[8] and the British Academy of Film and Television Arts (BAFTA) Award[9] for best single documentary. More recently a Panorama programme (*The mind reader: unlocking my voice*), recorded in Cambridge and London (Ontario) and broadcast in November 2012,[10] documented many of the scientific underpinnings of our research over the last ten years in a format that was accessible to the lay public. This received enormous public interest, with 247 comments on the programme website, and over 1000 views on 'YouTube'.

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

1. British Medical Association. Clinical scenario recorded at a major conference as part of the "Morals and Medicine" Series, available online for professional education and public information. (http://bma.org.uk/practical-support-at-work/ethics/withdraw-withhold-artificial-nutrition-and-hydration)

2. Liddell K, Menon DK, Zimmern R. The human tissue bill and the mental capacity bill. BMJ. 2004; 328 (7455):1510-1. PubMed PMID: 15217845

3. Macniven JA, Poz R, Bainbridge K, Gracey F, Wilson BA. Emotional adjustment following

cognitive recovery from 'persistent vegetative state': psychological and personal perspectives. Brain Inj 2003;17(6):525-33. PubMed PMID: 12745707.

4. Wilson BA, Gracey F, Bainbridge K. Cognitive recovery from "persistent vegetative state": psychological and personal perspectives. Brain Inj 2001;15(12):1083-92. PubMed PMID: 11712954.

5. BBC 1 Program Website: “Between Life and Death”. Broadcast 13th July 2010. (http://www.bbc.co.uk/programmes/b00t3szs)

6. “Between Life and Death”. David Menon’s program blog (http://www.bbc.co.uk/blogs/tv/2010/07/between-life-and-death-why-med.shtml)

7. Jardine C. Unlocking lives lived in limbo. Daily Telegraph online, 5th July 2010. Press report on “Between Life and Death”. (http://www.telegraph.co.uk/health/7868034/Unlocking-lives-trapped-in-limbo.html)

8. Royal Television Society Awards: Winners 2010-2011. (http://www.rts.org.uk/winners-rpa?term_node_tid_depth=193)

9. British Academy Television Awards 2011 for best single documentary: “Between Life and Death”. (http://awards.bafta.org/award/2011/television/single-documentary)

10. Panorama program website: “The Mind Reader: Unlocking My Voice”. Broadcast 13 November 2012 (http://www.bbc.co.uk/programmes/b01ny377)