Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Research-driven advances in surgical techniques lead to improved patient outcomes after Deep Brain Stimulation

1. Summary of the impact

The clinical research of the UCL Unit of Functional Neurosurgery has led to improvements in the operative technique of Deep Brain Stimulation (DBS) with clear and demonstrable impact on patient outcomes with respect to efficacy, safety, and adverse event profiles. Our published data have been described by an independent editorial as a new "Benchmark for Functional Neurosurgery". Our Unit's excellent safety record has led to an ever-growing number of referrals, has allowed us to trial DBS for new indications, and has prompted visits from a succession of international specialists who seek to learn and disseminate our practice in their centres.

2. Underpinning research

There are an estimated 120,000 people affected by Parkinson's disease (PD) in the UK. Medication improves the symptoms of PD in the early stages but with disease progression, patients develop fluctuations in their symptoms, and involuntary movements in response to medication. The motor symptoms of PD, as well as the complications of medical treatment for PD, can be improved using high-frequency-stimulation delivered to precise targets deep within the brain, such as the subthalamic nucleus (STN). This technique is known as Deep Brain Stimulation. The placement of electrodes requires invasive brain surgery, and therefore must be performed only by experienced teams. The major concerns surrounding DBS are intracranial haemorrhage, imprecise placement of electrodes, and uncertainty regarding the anatomical origin of stimulation-related adverse effects such as deterioration in speech and cognition.

Our group has improved the operative methods used in DBS surgery to minimise the number of brain penetrations required to accurately site electrodes and thus avoid the inevitable increased risks associated with multiple electrode trajectories. This has been achieved by developing optimised pre-operative imaging protocols, ensuring that brain-shift during surgery is minimised, and that electrodes do not traverse the cerebral ventricles en route to their targets, thus enabling electrodes to be placed using a completely image-guided and image-verified approach to the surgery **[1]**.

Furthermore we have made improvements to our imaging techniques in order to better understand the connectivity of the STN and thus inform on the sub-regions of this structure that are involved in motor pathways rather than cognitive functions, enabling us to modify the chosen surgical target accordingly **[2]**. Additionally we have used a range of functional imaging techniques (both PET and fMRI) to identify which brain regions change their activity in response to clinically effective stimulation. This has identified the brain networks that are involved in normal movement and that are disrupted in PD and opens up further avenues for future neuromodulation techniques **[3]**. Recordings from the brains of our patients with their stimulation switched off and on, using a range of neuro-physiological tools, have led to discoveries of the details of the abnormal brain function that underlies PD, and the mechanisms through which DBS can lead to its improvements. These findings are paving the way for the development of a closed-loop stimulation device that can detect abnormal brain activity and deliver therapeutic stimulation in precise spatial and temporal distributions **[4]**. (This work was done in collaboration with Peter Brown, University of Oxford and formerly UCL, where much of his early work on this project was completed.)

We have performed a systematic evaluation of patient outcomes, including motor aspects of PD, as well as examining the relationship between DBS and speech disturbance using validated methods to document speech intelligibility and volume. We have successfully identified important aspects of the relationship between electrode position, patient phenotype and stimulation-related

adverse events (electrodes are now targeted away from both the fasciculus cerebellothalamicus and the internal capsule, two areas which can both lead to deterioration in speech intelligibility) **[5]**. We have confirmed that by applying this summed knowledge, the complications of DBS surgery can be avoided, while still providing efficacy in terms of motor outcomes as good as, if not better than, any other centre worldwide **[6]**.

3. References to the research

[1] Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012; 116(1):84-94. http://dx.doi.org/10.3171/2011.8.JNS101407

[2] Lambert C, Zrinzo L, Nagy Z, Lutti A, Hariz M, Foltynie T, Draganski B, Ashburner J, Frackowiak R. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. Neuroimage. 2012;60(1):83-94. http://dx.doi.org/10.1016/j.neuroimage.2011.11.082

[3] Kahan J, Mancini L, Urner M, Friston K, Hariz M, Holl E, White M, Ruge D, Jahanshahi M, Boertien T, Yousry T, Thornton JS, Limousin P, Zrinzo L, Foltynie T. Therapeutic subthalamic nucleus deep brain stimulation reverses cortico-thalamic coupling during voluntary movements in Parkinson's disease. PLoS One. 2012;7(12):e50270. http://dx.doi.org/10.1371/journal.pone.0050270

[4] Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, Foltynie T, Limousin P, Ashkan K, Fitzgerald J, Green AL, Aziz TZ, Brown P. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol. 2013 Sep;74(3):449-457. http://dx.doi.org/10.1002/ana.23951

[5] Tripoliti E, Zrinzo L, Martinez-Torres I, Tisch S, Frost E, Borrell E, Hariz MI, Limousin P. Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. Mov Disord. 2008 Dec 15;23(16):2377-83. http://dx.doi.org/10.1002/mds.22296

[6] Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, Aviles-Olmos I, Jahanshahi M, Hariz M, Limousin P. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. J Neurol Neurosurg Psychiatry. 2011 Apr;82(4):358-63. http://dx.doi.org/10.1136/jnnp.2010.205542

4. Details of the impact

The research described above has had immediate impact on the clinical outcomes of over 420 patients who have undergone DBS in the UCL Functional Neurosurgery Unit since November 2002. As a result of the success of the procedure, the number of referrals is increasing year on year. During the period January 2008 to July 2013, 243 new DBS implantation procedures were performed with a year-on-year increase in number. (By the end of 2013, 98 new procedures will have been performed compared with 68 in 2012, 46 in 2011 and 43 in 2010) **[a]**.

The benefits for patients of our improved surgical techniques are considerable. We have demonstrated that we can improve the underlying severity of PD using DBS by ~55%, with accompanying improvements in quality of life (equal to any other series in the world), while the risks associated with the surgery at our centre are lower than those seen anywhere worldwide. Indeed, in our ongoing audit of adverse events, we have not detected a single symptomatic intracerebral haemorrhage in comparison with symptomatic haemorrhage rates of 2% worldwide **[b]**. Compared to traditional methods, we have achieved a low rate of adverse events through the use of an image-guided and image-verified surgical methodology that provides the ability to accurately and precisely place electrodes with the use of a single brain penetration. Reduced haemorrhage rates translate to reduced patient disability, paralysis or death. In our centre, 97% of electrodes are placed with a single brain penetration. This approach has the additional advantage

that the whole procedure can be performed under general anaesthesia which is far better tolerated by patients. Furthermore, we can now avoid stimulation-induced speech disturbance through better placing of electrodes. An independent expert in the field described our work as "*a new benchmark for all centres involved in PD surgery*" **[c]**.

Our excellent safety record with DBS for PD has provided the reassurance and confidence necessary to embark on pioneering clinical trials using DBS as an experimental treatment for other disabling conditions, in which the potential benefits of the surgery are less certain and therefore the known risks of the operation must be minimised. Following initial success and publication of treating five patients **[d],** we have recruited a further 10 patients to date, to a double blind crossover trial of DBS for severe, treatment-refractory Tourette syndrome **[e]**. We have also recruited and operated on two patients in an MRC-funded double blind crossover trial of DBS for severe treatment-refractory Obsessive Compulsive Disorder and a single patient to a Brain Research Trust-funded double blind crossover trial of DBS for Parkinson's disease dementia **[f]**, all of which are led by our team and continue recruitment in our Unit.

Further testimony to the impact that DBS performed in our Unit has on patients can be seen in a number of media features on our work:

- In May 2013, an episode of *Keeping Britain Alive: The NHS in a Day* on BBC2 featured two patients undergoing DBS in our hospital **[g]**.

- In December 2011, Sky News featured a woman who was treated with DBS for the symptoms of Tourette syndrome. The patient stated that "*It is absolutely amazing. I do not feel I am the same person. I have had three years of getting worse. Now I have got my life back*" **[h]**.

- The website of the Brain Research Trust features the story of one of our patients, a 62 year old woman with a genetic form of dystonia (DYT-1). She describes the results of the surgery as follows: "*the improvement I feel in my walking is beyond my wildest expectations: it's actually 95%*" **[i]**.

The clinical activity of our Unit and academic output has attracted a large number of visitors from around the UK and overseas. The neurosurgical techniques, patient selection process and post-operative management pathways developed through our research have been used for the instruction of over 75 visiting neurosurgeons, neurologists and clinical trainees over 2009-13. The research-evidenced standard of care in place at NHNN has disseminated to multiple other centres throughout the world including European centres (Groningen and the Karolinska Institute), and in the United states (Atlanta and UCLA) where the local functional neurosurgical teams have changed their surgical approach following visits to, or publications by our Unit **[j].** Furthermore, attendance in our Unit with instruction in patient selection, surgical procedure and DBS programming techniques have enabled colleagues from Sweden and Portugal to perform surgery and publish their own results of DBS for patients with Tourette syndrome **[k]**.

5. Sources to corroborate the impact

[a] UCLH Clinical data repository accessed August 2013. Details available from the unit. Contact details provided.

[b] Videnovic A, Metman LV. Deep brain stimulation for Parkinson's disease: prevalence of adverse events and need for standardized reporting. Mov Disord 2008; 23(3):343-349.

[c] Krack P. Subthalamic stimulation for Parkinson's disease: a new benchmark. J Neurol Neurosurg Psychiatry 2011; 82(4):356-357.

[d] Martínez-Fernández R, Zrinzo L, Aviles-Olmos I, Hariz M, Martinez-Torres I, Joyce E, et al. Deep brain stimulation for Gilles de la Tourette syndrome: A case series targeting subregions

of the globus pallidus internus. Mov Disord. 2011 Apr 29. doi: 10.1002/mds.23734.

[e] http://www.clinicaltrials.gov/ct2/show/NCT01647269

[f] http://www.clinicaltrials.gov/ct2/show/NCT01701544

[g] www.bbc.co.uk/programmes/b01s5ftf

[h] http://news.sky.com/story/911236/deep-brain-op-ends-womans-tourettes-tics

[i] www.brt.org.uk/sandra-david

[j] Zrinzo L, van Hulzen AL, Gorgulho AA, Limousin P, Staal MJ, De Salles AA et al. Avoiding the ventricle: a simple step to improve accuracy of anatomical targeting during deep brain stimulation. J Neurosurg. 2009; 110(6):1283-1290. http://doi.org/dtfxzn
This paper includes data from three centres: NHNN, Groningen and Los Angeles, demonstrating the advantage of avoiding the ventricle in DBS surgery. Both these other centres have changed their practice as a result.

[k] Massano J, Sousa C, Foltynie T, Zrinzo L, Hariz M. Vaz R. Successful pallidal deep brain stimulation in 15-year old with Tourette syndrome: 2-year follow up. J. Neurol. 2013 Sep;260(9):2417-9. http://dx.doi.org/10.1007/s00415-013-7049-1.
Email from the Karolinska Institute stating their intention to change practice as a result of their visit to the unit also available on request.