Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Novel brain imaging methods improve neurosurgical treatment for epilepsy

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

Recent advances in MRI brain scanning developed at the UCL Institute of Neurology have underpinned major improvements in the surgical treatment of epilepsy. Information about the location of critical brain structures, such as the optic radiation that carries visual signals, and language areas of the brain, are used to identify the risks of neurosurgery in specific individuals. This helps to inform patient choice and to reduce the risk of loss of any part of the visual field or language when performing the surgery. UCL's pioneering use of these imaging techniques during surgery, with correction of the movement of the brain that occurs during surgery, showed that this approach reduced the occurrence of serious loss of vision to zero. This information is now used in epilepsy surgery every week at the National Hospital for Neurology and Neurosurgery and is being rolled out to other centres.

2. Underpinning research (indicative maximum 500 words)

Epilepsy is one of the most common serious brain disorders, affecting over 450,000 people in the UK. One third of these individuals continue to have seizures despite anti-epileptic drug treatment. For those in whom the source of epilepsy can be pinpointed in the brain, neurosurgical treatment can be curative. Over the last 20 years, research at the UCL Institute of Neurology, led by Professor John Duncan, has optimised brain imaging applied to epilepsy surgery, with numerous publications on qualitative and quantitative imaging, and the application of automated voxel-based analytical techniques to increase the yield of detection of abnormalities. In the last decade, we developed methods to quantitatively analyse scans that show increased sensitivity to subtle abnormalities that are not evident on traditional visual inspection by radiologists **[1]**.

We have further optimised the clinical utilisation of fMRI for the visualisation of brain activations related to language, motor and sensory functions and memory. For example, we developed the use of fMRI to determine non-invasively which side of the brain processes language, as this area has to be preserved in surgery **[2]**. Previous procedures required an invasive carotid amytal test, in which a short-acting barbiturate was injected into the artery, with associated risk of complications.

The most common surgical treatment for epilepsy is called anterior temporal lobe resection. A common adverse effect of this surgery is blindness in part of the visual field, which can prevent driving, even if the epilepsy is cured. Since 2003, we have implemented MR tractography, with the first demonstration of seeding a tract from activation maxima with functional MRI. We have used tractography to visualise the optic radiation and corticospinal tracts, and have combined these visualisations with 3-dimensional multimodal data to provide a comprehensive depiction of individual structural and functional neuroanatomy. Since 2004, we have used MR tractography to delineate white matter pathways on magnetic resonance images acquired from patients prior to the surgery, publishing the first paper on this topic **[3]**. We subsequently showed the variability of the anatomy of this part of the brain, and how the extent of surgical damage was related to the severity of loss of vision **[4]**. We have used this information to help plan the surgery and reduce the risk of damage to this critical white-matter structure during the operation **[5]**. We have also used those methods to determine the risks of neurosurgery to language function **[6, 7]**.

In 2012, we introduced the use of tractography during neurosurgical operations using an interventional MRI suite to assist in the planning and ongoing conduct of the surgical procedures and further minimise the risk of damaging critical pathways. Most recently, we have pioneered the display of tractography of the visual pathway during surgery, with correction of the movement of the brain that occurs during surgery, showing that this approach reduced the occurrence of serious loss of vision after surgery to zero. The 3D multimodal datasets we have developed to facilitate this approach now combine structural and functional MRI, tractography and representation of arteries and veins, and also maps of abnormalities of cerebral blood flow, glucose utilisation and visual representations of electrical (electrical source imaging, ESI) and magnetic (magnetic source imaging, MSI) abnormalities that permit us to infer the location of epileptic foci in the brain. The end result is a 3-dimensional map of the brain that visualises critical structures that must not be damaged, and highlights abnormal areas the removal of which is needed to cure epilepsy. This allows optimal decisions to be made regarding the surgical approach and trajectory to give the best chances of a good outcome and with minimum risk to the individual patient.

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

[1] Rugg-Gunn FJ, Boulby PA, Symms MR, Barker GJ, Duncan JS. Whole brain T2-mapping demonstrates occult abnormalities in focal epilepsy. Neurology 2005: 64(2):318-325. http://dx.doi.org/10.1212/01.WNL.0000149642.93493.F4

[2] Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koepp MJ, Duncan JS. Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study. Neuroimage. 2006 Aug 1;32(1):388-99.

[3] Powell HWR, Parker GJM, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CAM, Barker GJ, Koepp MJ, Duncan JS. MR tractography predicts visual field defects following temporal lobe resection. Neurology. 2005 Aug; 65(4):596-599. http://doi.org/dws9jb

[4] Yogarajah M, Focke NK, Bonelli S, Cercignani M, Acheson J, Parker GJ, Alexander DC, McEvoy AW, Symms MR, Koepp MJ, Duncan JS. Defining Meyer's loop-temporal lobe resections, visual field deficits and diffusion tensor tractography. Brain. 2009 Jun;132(Pt 6):1656-68. http://doi.org/dccwtg

[5] Winston GP, Yogarajah M, Symms MR, McEvoy AW, Micallef C, Duncan JS. Diffusion tensor imaging tractography to visualize the relationship of the optic radiation to epileptogenic lesions prior to neurosurgery. Epilepsia. 2011 Aug;52(8):1430-8. http://doi.org/c6j38m

[6] Powell HWR, Parker GJM, Alexander DC, Symms MR, Boulby PA, Barker GJ, Thompson PJ, Koepp PJ, Duncan JS. Imaging language pathways predicts postoperative naming deficits. J Neurol Neurosurg Psychiatry 2008;79:327-330 http://doi.org/b63q3p

[7] Winston GP, Daga P, Stretton J, Modat M, Symms MR, McEvoy AW, Ourselin S, Duncan JS. Optic radiation tractography and vision in anterior temporal lobe resection. Ann Neurol. 2012 Mar;71(3):334-41. http://doi.org/ffp3xn

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

Use of approach in clinical practice

The underpinning research described above has enabled clinicians to reveal abnormalities causing refractory epilepsy that were not previously identifiable, presenting a target for surgical treatment. This results in increased access to potentially curative neurosurgery. Functional MRI and tractography approaches that we pioneered are now used by neurosurgeons throughout Europe (particularly Zurich and Bonn) to identify the risks of surgery in individuals, and to plan the surgery so that risks may be reduced **[a]**.

Surgeons use tractography to visualise pathways of white matter fibres in the brain in the pre-operative MRI scans. The system is used on roughly one patient a week and it has been fully operational since mid-2012, although a preliminary version was in clinical use for about a year prior to that. The system helps surgeons avoid damaging nerve fibre pathways, which can otherwise lead to visual deficits that would, for example, prevent driving. An early evaluation of the system demonstrated its impact by using the system in 21 patients undergoing anterior temporal lobe resection. The outcomes were compared to a control group who underwent the same surgery without the system. None of those who had their visual pathway displayed to the surgeon via the tractography system had a visual field deficit that would prevent driving, compared to 13% in the control group. The experiment shows preservation of vision in the patients operated on using the system **[ref]**.

As of mid-2013, around 140 patients have benefited from surgery at NHNN performed using tractography, which has been of critical importance for improving the precision and safety of neurosurgical treatment **[b]**.

As well as informing decisions about whether to undertake surgery or not, scans are also used in the interventional MRI operating theatre during surgery. A 3-dimensional map of critical brain areas can now be visualised and presented to the surgeon as the operation proceeds, to enable the guiding of the surgery away from critical areas that must be avoided. This enhancement is already used in clinical practice at the National Hospital for Neurology and Neurosurgery, resulting in safer surgery with reduced risk of causing new deficits.

Individual patient benefit and public engagement

A specific example of the dramatic impact of this technology was of a 28-year-old man with severe epilepsy that was not controlled by medications. The nature of the epileptic seizures and the EEG recordings suggested that their source was on the left side of the brain, towards the front. Standard MRI scans were unremarkable, but a computerised analysis identified an abnormal area approximately 2cm by 1cm in the middle frontal gyrus. Functional MRI scans showed that this was a few millimetres above areas involved in language, and abutted parts used to control the use of the right upper limb. Tractography showed that the corticospinal tract, which carries command and control information to the limbs, ran within a few millimetres of the abnormal area. Large veins were directly over the abnormal area. These data allowed the precise positioning of recording electrodes in and around the abnormal area to pinpoint the site of seizure onset. This led to precise surgical removal of the part of the brain that was giving rise to the seizures, with the consequence that no further seizures have occurred, medication has been withdrawn, and the patient is going to college **[c]**. For these individuals, the impact of our research is thus immediate and life changing.

A further example is that the 3D representation of the optic radiation, which carries visual information from the eye to the brain, can be displayed in the eyepiece of the operating microscope, so the surgeon knows where this structure is, and the surgery can be designed to avoid this pathway, and the risk of damaging vision averted.

Our improvements to surgery have had a huge impact on the lives of patients treated. One such example was featured on the 2010 BBC One programme “How Science Changed Our World” **[d]**. Emma, an 18-year-old girl, had surgery to treat epilepsy that had previously meant she suffered from up to eight seizures per day. After the surgery she no longer suffered from seizures and her quality of life was immeasurably improved.

New clinical procedures

The use of fMRI for testing language retention has entirely replaced the carotid amytal test at the National Hospital for Neurology and Neurosurgery, with benefits to patients and health providers. The old, more expensive test could be dangerous, involved radiation and required a two-day hospital stay. The hospital used to carry out around four such procedures per month, but have done none since 2004, with the benefits to patients continuing throughout the REF impact period. The fMRI method has been widely adopted in epilepsy surgery centres around the world **[e]**.

NICE guidelines

The Institute of Neurology’s focus on MRI applied to epilepsy contributed to the development of epilepsy imaging protocol guidelines by the International League against Epilepsy, between 1998 and 2011 **[f, g, h]**. These underpinned the imaging guidelines for epilepsy that were used in the

NICE epilepsy guidelines of 2004 and 2012 **[i]**, which recommended that neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. MRI is particularly important in those in whom seizures continue in spite of first-line medication. In both 2004 and 2012, Duncan was a member of the NICE guideline development group.

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

[a] See for example, the following papers:

- Doelken MT, Mennecke A, Huppertz HJ, Rampp S, Lukacs E, Kasper BS, Kuwert T, Ritt P, Doerfler A, Stefan H, Hammen T. Multimodality approach in cryptogenic epilepsy with focus on morphometric 3T MRI. J Neuroradiol. 2012 May;39(2):87-96. http://dx.doi.org/10.1016/j.neurad.2011.04.004
- House PM, Lanz M, Holst B, Martens T, Stodieck S, Huppertz HJ. Comparison of morphometric analysis based on T1- and T2-weighted MRI data for visualization of focal cortical dysplasia. Epilepsy Res. 2013 Oct;106(3):403-9. http://dx.doi.org/10.1016/j.eplepsyres.2013.06.016
- Pascher B, Kröll J, Mothersill I, Krämer G, Huppertz HJ. Automated morphometric magnetic resonance imaging analysis for the detection of periventricular nodular heterotopia. Epilepsia. 2013 Feb;54(2):305-13. http://dx.doi.org/10.1111/epi.12054
- Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. Brain. 2011 Oct;134(Pt10):2844-54. http://dx.doi.org/10.1093/brain/awr204

[b] Data can be verified by the epilepsy surgery database manager. Contact details provided.

[c] Rodionov R, Vollmar C, Nowell M, Miserocchi A, Wehner T, Micallef C, Zombori G, Ourselin S, Diehl B, McEvoy AW, Duncan JS. Feasibility of multimodal 3D neuroimaging to guide implantation of intracranial EEG electrodes. Epilepsy Res. 2013 Nov;107(1-2):91-100. http://dx.doi.org/10.1016/j.eplepsyres.2013.08.002.

[d] Featured in BBC One at 21:00, 23 December 2010: "How Science Changed Our World". Clip available on YouTube: http://www.youtube.com/watch?v=N8VZkoJAZz0 (from 03:27 onwards)

[e] Janecek JK, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, E Rozman M, Binder JR. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. Epilepsia. 2013 Feb;54(2):314-22. http://doi.org/p8p

[f] ILAE Neuroimaging Commission. ILAE Neuroimaging Commission Recommendations for Neuroimaging of Patients with Epilepsy. Epilepsia 1997;38:S10 http://dx.doi.org/10.1111/j.1528-1157.1997.tb00084.x John Duncan was a member of this commission.

[g] Neuroimaging Subcommision of the International League Against Epilepsy. Commission on Diagnostic Strategies: recommendations for functional neuroimaging of persons with epilepsy. Epilepsia. 2000 Oct;41(10):1350-6. http://dx.doi.org/10.1111/j.1528-1157.2000.tb04617.x John Duncan was a member of this commission.

[h] Gaillard WD, Cross JH, Duncan JS, Stefan H, Theodore WH; Task Force on Practice Parameter Imaging Guidelines for the International League Against Epilepsy, Commission for Diagnostics. Epilepsy imaging study guideline criteria: Commentary on diagnostic testing study guidelines and practice parameters. Epilepsia. 2011 Sep;52(9):1750-6. 2011 Jul 8. http://dx.doi.org/10.1111/j.1528-1167.2011.03155.x.

[i] NICE CG137, Epilepsy Clinical Guidelines. Corroborates John Duncan's membership of the guideline development group. See section 8.3 for the guidelines on the use of neuroimaging: http://www.nice.org.uk/nicemedia/live/13635/57784/57784.pdf