Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Statistical Parametric Mapping

1. Summary of the impact

Research by Professor Karl Friston at UCL has led to the development of Statistical Parametric Mapping (SPM), a statistical framework and software package. By providing a way to analyse signals measured from the human brain in MRI scanners, SPM triggered the creation of an entirely new field of imaging neuroscience. Beneficiaries include: commercial manufacturers who provide imaging equipment; healthcare practitioners and patients, where SPM is used to deliver new treatments; pharmaceutical industries using SPM to deliver clinical trials; the IT industry developing new software based on SPM; and entirely new industries such as neuromarketing that could only have been created once SPM had been invented.

2. Underpinning research

Statistical Parametric Mapping (SPM) is both the name of a statistical framework for analysing brain images and the name of a software package now standard in the field of imaging neuroscience. SPM is used for analysing brain imaging data and was originally conceived by Karl Friston when working at the MRC Cyclotron Unit at the Hammersmith Hospital in 1991. The initial application was to data from Positron Emission Tomography (PET) and, in the spirit of open science, Friston shared his SPM code with colleagues in the nascent brain imaging community. A new era began in 1994 when Friston and colleagues opened the Wellcome Trust Centre for Neuroimaging (WTCN) at UCL, and re-invented SPM to analyse functional Magnetic Resonance Imaging (fMRI) data **[1, 4, 5]**. At the time functional MRI was a new approach to brain imaging and there were no principled frameworks in which to analyse the data produced by MRI scanners. The underpinning research carried out by Friston provided such a framework, together with accompanying software.

At the heart of SPM is the simple idea of fitting a general linear model (GLM) at every location in a time series of functional brain images measured using an MRI scanner while a subject lies in it. Parametric statistical models are assumed at each location, using the GLM to describe the data in terms of experimental and confounding effects, and residual variability. Corrections for multiple dependent statistical comparisons are then made using Random Field Theory. The output of SPM is an image, or a 'statistical parametric map', indicating statistically significant changes in brain activity. This allows neuroscientists to relate brain activity to human behaviour and has led imaging neuroscientists to a mapping of the human brain, identifying specific areas for sensory, emotional and decision-making processes. Without SPM, there would be no principled framework for undertaking such analyses and thus no easy way to undertake imaging neuroscience. The underpinning research carried out by Friston and colleagues is now the basis for all brain imaging data analysis (and all brain imaging software packages) throughout the world.

In 2000, further research by Friston and Ashburner at UCL significantly extended the SPM approach to apply not just to functional brain images but also to structural MRI data. This allowed statistical characterisation and localisation of differences in grey matter density among or between different groups of patients (or healthy humans) using a procedure known as Voxel-Based Morphometry (VBM) **[2]**. Such an approach has now been used, for example, to map the loss of grey matter in dementia by pharmaceutical companies.

In 2005, further research by Friston and Penny at UCL permitted the extension of the SPM framework and software to the analysis of magnetoencephalographic (MEG) and electroencephalographic (EEG) data **[6]**. This allows neuroscientists to study brain activity as it evolves on a fast time scale, and creates new beneficiaries in this emerging area.

Finally, research led to additional enhancements to the software to allow neuroscientists to study interactions among brain regions using a technique called Dynamic Causal Modelling (DCM) **[3]**. DCM fits biologically realistic differential equation models to brain imaging data, using Bayesian inference. It allows neuroscientists to detect changes in brain pathways, rather than brain regions. It has been used, for example, to show that connections from frontal to temporal regions were altered in patients in a vegetative state, whereas other pathways remained intact.

3. References to the research

[1] Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith C, Frackowiak RSJ. Statistical Parametric Maps in Functional Imaging: A General Linear Approach. Hum Brain Mapp. 1995;2:189-210 http://dx.doi.org/10.1002/hbm.460020402

[2] Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000 Jun;11(6 Pt 1):805-21. http://dx.doi.org/10.1006/nimg.2000.0582

[3] Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage. 2003 Aug;19(4):1273-302. http://dx.doi.org/10.1016/S1053-8119(03)00202-7

[4] Friston KJ, Ashburner J, Kiebel SJ, Nichols TE, Penny WD, editors. Statistical Parametric Mapping: The Analysis of Functional Brain Images. Academic Press; 2007. http://www.sciencedirect.com/science/book/9780123725608

[5] Ashburner J. SPM: a history. Neuroimage. 2012 Aug 15;62(2):791-800. http://dx.doi.org/10.1016/j.neuroimage.2011.10.025

[6] Litvak V, Mattout J, Kiebel S, Phillips C, Henson R, Kilner J, Barnes G, Oostenveld R, Daunizeau J, Flandin G, Penny W, Friston K. EEG and MEG data analysis in SPM8. Comput Intell Neurosci. 2011;2011:852961. http://dx.doi.org/10.1155/2011/852961

4. Details of the impact

Before SPM there was no principled framework or easily usable software that could be used to analyse and report functional brain images in the scientific literature or elsewhere. By creating that ability in a principled and extensible theoretical framework, the underpinning research led to the establishment and dramatic growth of an entirely new scientific field, **imaging neuroscience**. Establishing a new scientific field has created a wide range of beneficiaries, including commercial manufacturers (such as Siemens, Phillips and GE Healthcare) who provide the brain scanners to such a new field.

SPM is used by academic neuroscientists, healthcare professionals and neuroimaging consultants to analyse brain-imaging data. The basic operations, of describing the imaging experiment in the form of a GLM and interrogating the statistical results, are usually implemented via a simple Graphical User Interface. Maps showing regions of significant change can then be surfed in an interactive viewer.

The SPM software is released under a General Public Licence (GPL), meaning that users are free to run the software, as well as to share (copy, distribute), study and modify it. This greatly simplifies code transparency and provides a software platform for the brain imaging community to develop new technologies. A broad community of academic neuroscientists and healthcare professionals has adopted SPM which is disseminated using a proven delivery pipeline comprising (I) release of open source software (II) delivery of specialised short courses (III) collaborative research (IV) email support **[a]**. SPM is currently the most widely used software package globally for brain imaging analysis and now has 4,500 subscribers on its mailing list. A recent systematic study of methods used to analyse brain imaging data showed SPM to be the most popular software worldwide, used in 64% of studies (compared to 13.9% for each of its two nearest rivals) **[b]**.

Clinical Applications

SPM has been used by the neuroimaging company **Imagilys** to develop a commercial product, BrainMagix, for use in brain surgery **[c]**. People with brain tumours, for example, may require surgery to remove malignant tissue. The goal of surgery is to remove cancerous tissue without damaging important parts of the brain. If structural imaging shows damage close to language areas, for example, then patients will have fMRI scans prior to surgery to map more precisely which regions that person uses when speaking or understanding language. Surgeons will make reference to the resulting SPM images before surgery to ensure these critical regions will not be excised. Such presurgical planning has been used to deliver impact in many neurological disorders including drug-resistant epilepsy (as illustrated in case study UCL04-DUN).

New approaches to drug development in the pharmaceutical industry

All pharmaceutical companies use medical imaging in the drug development process and recent years have seen attempts to develop drugs for many of the major health issues today, from depression and dementia to epilepsy and schizophrenia. Brain imaging is used here as a 'biomarker' – if drugs are effective they will change activity in specific brain regions. The SPM software is used to assess whether this change is statistically significant.

A factor in the transfer of SPM technology to industry has been the role of two SPM co-authors, Dr Tom Nichols and Dr Andrew Holmes, who have had extended periods working in the pharmaceutical industry (at **GSK** and **AstraZeneca** respectively). Along with the fact that SPM is distributed under GPL, this has resulted in SPM being widely used in global drug research. Dr Nichols became the Director of Imaging Research at GSK's Clinical Imaging Centre that used SPM approaches to measure brain activity and structural changes associated with disease and the neural effects of pharmacological agents in drug development **[d]**. Imanova Ltd was established as a spin-out imaging provider company in 2011 and now owns and manages the renowned Clinical Imaging Centre; this state of the art facility was developed by GSK, and has benefitted from £47m of investment in equipment and infrastructure since opening in 2007. SPM approaches are used routinely throughout Imanova **[d]**.

SPM's use has now spread to many other companies involved in the drug development process. These include other major pharmaceutical companies, such as **Eli Lilly** and consultancies such as **Mango Solutions [e]**.

New software products

SPM has contributed to the development and use of commercial software packages. SPM is built on the commercial programming language 'MATLAB' developed by **MathWorks.** SPM is one of MATLAB's core applications **[f]**. Each of the thousands of SPM users requires a MATLAB licence to run SPM with significant commercial benefit to MathWorks. Several companies have developed commercial software products based, in part, on the ideas and framework underlying SPM. This includes software installed on all the major MRI scanners now sold globally, for instance the inline BOLD imaging software of the **Siemens** MAGNETOM Tim Trio (a commonly sold MRI scanner) that provides basic real-time analysis of fMRI data **[g]**. Brain Innovation BV has developed **BrainVoyager** QX based on SPM for fMRI, MEG and EEG data analysis **[h]**. It is now being used by approximately 2,000 scientists and clinicians and a single licence is currently available for about €5,000. These developments would not have been possible without the SPM framework.

Creation of new sectors and companies

The emerging field of neuromarketing, an approach in which Professor Read Montague (jointly appointed between Virginia Tech and UCL) was a pioneer, proposes that the decisions people make are influenced by subconscious brain activity, for example in brain regions dealing with emotional responses, and this activity can be accessed using fMRI. SPM is used as the basis of such an industry to detect, for example, which sets of advertising stimuli produce significantly larger responses in these brain regions. This approach has been developed commercially by **Neurosense [i]**. Statistical parametric mapping approaches have also enabled the creation of commercial companies that seek to detect deception such as No Lie MRI (http://www.noliemri.com), and those that support investigators such as Neurometrika **[j]**. SPM has also been used to help provide part of the new evidence base to evaluate illegal drugs (as illustrated in case study UCL04-CUR).

Training of non-academic professionals

UCL researchers have facilitated the development of a range of short courses held over three days that explain SPM's main theoretical concepts, and provide hands-on tuition in small groups to academic and non-academic end users, which is now delivered across the world. Most of these courses are run by universities, but some also by commercial enterprises such as Neurometrika, who run several SPM courses primarily in the US but also Brazil, Canada and China, for training academic neuroscientists and healthcare professionals **[j]**. UCL run courses every year (two in 2008, and three per year since then), organised by academics from the WTCN. There is one course per year in Zurich, Lausanne, Hamburg, Utrecht and Edinburgh organised by local academics but including UCL faculty. These courses have ~40 students each and fees vary from £100 to £1,000 **[k]**.

5. Sources to corroborate the impact

[a] http://www.fil.ion.ucl.ac.uk/spm/software/spm8/

[b] Carp J. The secret lives of experiments: Methods reporting in the fMRI literature. NeuroImage 2012;63(1):289-300. http://dx.doi.org/10.1016/j.neuroimage.2012.07.004

[c] Provision of the BrainMagix system for surgical planning can be corroborated by the Founder, Imagilys; contact details provided. See also:
http://www.imagilys.com/brainmagix-neuroimaging-fmri-software/

[d] Use of SPM in drug development at GSK and at Imanova can be corroborated by the former Director of the Clinical Imaging Centre and currently Vice President in Medicines Discovery and Development, GSK; contact details provided.

[e] http://www.mango-solutions.com/mangoimaging/index.html

[f] SPM's status as a core application of the MATLAB technology can be seen in the keynote 'Embracing Complexity' talk at MathWorks 2013 Virtual Conference

http://www.mathworks.co.uk/company/events/conferences/matlab-virtual-conference/2013/proceedings/embracing-complexity.html?sec=keynote see 4:50-10:36

[g] Details of clinical software packages based on the SPM approach used by Siemens can be corroborated by their Scientific Officer - Research Partnerships and Innovation; contact details available. See also: http://www.healthcare.siemens.com/magnetic-resonance-imaging

[h] Details of the Brainvoyager QX software can be corroborated by the CEO, Brain Innovation BV; contact details provided. See also http://www.brainvoyager.com/products/brainvoyagerqx.html

[i] The use of SPM fMRI analysis in neuromarketing can be corroborated by the Managing Director, Neurosense; contact details provided. See also for example
http://www.neurosense.com/docs/Hakuhodo_press_release_2009.pdf

[j] Neurometrica training provision: http://www.neurometrika.org/Courses

[k] UCL Training provision: http://www.fil.ion.ucl.ac.uk/spm/course/