Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Economic and health benefits of a new method of assessing atrophy progression in Alzheimer's disease: the Boundary Shift Integral technique

1. Summary of the impact

Our research has had a major impact on the way pharmaceutical trials in Alzheimer's disease are conducted. The Boundary Shift Integral technique, which we developed and validated, has changed commercial practice and has become the industry standard for measuring atrophy progression. Our methods have largely replaced previous manual measures and in 2008-13 were used in over 20 large international trials. This had significant economic benefits for several companies providing image analysis services. For UCL alone they generated over £5m of industrial contracts. Additionally, through licensing and collaboration, UCL's research contributed to IXICO establishing a significant market share in this important commercial area.

2. Underpinning research

Research at UCL led by Professors Nick Fox and Martin Rossor (both Department of Neurodegeneration) since the mid-1990s has had a particular focus on improving diagnosis and the measurement of disease progression in Alzheimer's disease (AD) and related disorders. Cerebral atrophy had long been recognised as characteristic of AD. The initial interest was in describing brain changes to improve diagnosis. Detailed volumetric work showed that certain cerebral regions (e.g. the hippocampus) were reduced in volume very early in AD. The diagnostic utility of these measurements was, however, confounded by the wide natural variation between individuals. Rates of atrophy, using each individual as their own control, provided a means of reducing the effect of this wide between-individual variability. Measurement of within-individual change requires a high level of precision and our research then aimed to address this problem. We (Fox and Rossor) showed that registration-based measures allowed sensitive assessment of change **[1]**. We then developed a novel technique (the Boundary Shift Integral) for quantifying changes in brain volume from rigid-body registration of serial MRI. We were able to show that the method had a very high level of precision (10x greater than previous methods) **[2, 8]**.

In a decade of subsequent research we refined, developed and validated the techniques. In collaboration with Dr Kelvin Leung and Professor Sebastien Ourselin (UCL Centre for Medical Image Computing) we introduced methods to deal with potential artefacts and differences between scanners that are an inevitable feature of multi-centre international commercial trials **[8]**. Not only have these methods found diagnostic clinical use they have been adopted for use in monitoring disease progression and assessing therapeutic effects in trials designed to show disease modification **[1, 7]**.

Rates of atrophy measured with our techniques have been shown to correlate with cognitive decline in AD **[3]**. Sample size estimates for disease progression trials have been estimated and shown to provide significantly greater power than alternative manual measures **[4, 8]**. Our Boundary Shift Integral measures were chosen as one of the reference methods for the large open-access Alzheimer's Disease Neuroimaging Initiative (ADNI) study (800 subjects, several thousand MR brain scans); using this data-set we (Fox, Leung, Ourselin) showed the method to produce competitive sample size estimates **[8]**. The sensitivity and power of our techniques has been recognised in European (EFNS) guidelines and consensus statements on neuroimaging and in several review articles. More importantly these techniques have had a major impact on natural history studies and on the way clinical trials of potential disease modifying therapies for Alzheimer's disease have been conducted **[5, 6, 8]**.

We continue to develop and extend the methods and now have fully automated measures of rates of whole brain or regional atrophy (e.g. hippocampus) from serial MRI and can accommodate

differences in MRI acquisition inherent in different scanners. We have shown that we can detect (with high sensitivity) and correct important scanner artefacts such as voxel scaling errors. This has added robustness to precision and allowed MRI clinical trial data to be used when previously it may have been discarded **[8]**.

3. References to the research

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[4] Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain MRI to measure disease progression in Alzheimer's disease: power calculations & estimates of sample size to detect treatment effects. Arch Neurol. 2000 Mar;57(3):339-44. http://dx.doi.org/10.1001/archneur.57.3.339

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[8] Leung KK, Clarkson MJ, Bartlett JW, Clegg S, Jack CR, Weiner MW, Fox NC, Ourselin S. ADNI. Robust atrophy rate measurement in AD using multi-site serial MRI: tissue-specific intensity normalization and parameter selection. NeuroImage. 2010 Apr 1;50(2):516-23. http://dx.doi.org/10.1016/j.neuroimage.2009.12.059

Peer-Reviewed Funding

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2005-15: US National Institute on Aging. Funding totaling c.£0.8m

2007-10: DTI (previously TSB) grant to Hawkes (UCL), Hill (UCL & IXICO) and Fox (UCL): Imaging to assess efficacy and safety of new treatments for Alzheimer's disease - £736,000

4. Details of the impact

UCL's impact on the way that international trials in Alzheimer's disease use brain imaging has been considerable. Our Boundary Shift Integral method has provided a precise, regulatory-compliant means of assessing whether a potential treatment for Alzheimer's disease could modify the disease course by slowing the rate of atrophy. It has therefore had a significant impact on clinical trial protocols across phases 2-3 by reducing the number of patients needed for imaging outcomes, thus reducing costs and reducing participant exposure to potential side effects. Additionally the techniques have been shown to be useful clinically – individuals with very early

Alzheimer's disease show increased rates of brain atrophy relative to healthy controls.

Adoption of our methods in clinical trials: Historically, image analysis for trial outcomes involved relatively crude and expensive manual measurements of brain volumes or regions from imaging at baseline and end of study to try to show an effect of the therapy on the progression of atrophy. The method of choice was manual tracing of regions of interest on a brain scan. These measures were limited to those areas easy to define (e.g. hippocampus) but more importantly were manual, and therefore both labour intensive and error prone. Our image analysis methods removed the need for these manual measurements and at the same time also greatly improved the precision and reliability of the measures (5 times lower variance on scan-rescan testing) **[a]**. This led to its increasing uptake as the method of choice for AD trials (and now other diseases).

The Boundary Shift Integral has become the most widely used method of analysing brain atrophy in trials in Alzheimer's disease and in related disorders. Trials using UCL's techniques include most recently the largest international immunotherapy trials in AD led by Elan/Janssen and Pfizer/Wyeth **[b]**, **[c]**. The method provides a biomarker that can be used as a clinical trial endpoint to establish whether a candidate drug can slow brain atrophy (a long established downstream effect of the disease). Many trial protocols (including from Pfizer, Wyeth, Elan, Janssen, Roche, BMS) have used this analysis as a secondary endpoint. Lundbeck chose to use the Boundary Shift Integral measure as their primary outcome to assess whether memantine had any disease-modification effects in Alzheimer's disease **[d]**. (The study showed no benefit of memantine on rates of brain atrophy.)

Furthermore, the European Medicines Agency has recently issued draft opinion indicating that magnetic resonance imaging (MRI) of hippocampal volume is a valid approach for selecting people in the early, pre-dementia, stages of Alzheimer's disease (AD) for clinical trials **[e]**.

Economic benefits to pharmaceutical companies: The use of image analysis allows trials to be conducted using far fewer subjects than would have been needed to power a study using clinical outcomes. The memantine trial described above was conducted in fewer than half as many subjects as would have been needed otherwise (power calculations conducted by Lundbeck – see **[e]**). This effectively reduced the cost to the company of this study by several million dollars. Furthermore, trial participant exposure to potential side-effects was reduced.

Economic benefits to companies providing services to the pharmaceutical industry: Introduction of our techniques has also had a significant benefit to the UK economy, through the provision of image analysis services to foreign companies. The image analysis unit at the Dementia Research Unit has provided ~£5m in image analysis services to Janssen, Elan, Pfizer, Wyeth, and Lundbeck in the 2008-13 period **[f]**. IXICO (an Imaging CRO providing end to end imaging solutions for clinical trials) uses our boundary shift integral technique under licence and has attracted a number of large contracts **[g]**. They report that:

> "*Between January 2008 and July 2013, we used the BSI with three of the world's top 10 pharmaceutical companies and small biotechs, including on high-profile pivotal trials of potential treatments for mild-moderate Alzheimer's Disease, and prodromal Alzheimer's disease. We have processed 10s of thousands of patient images in this period… IXICO's ability to offer BSI to pharmaceutical companies enabled UCL technology to continue to have high impact in clinical trial market at a time when many pharmaceutical companies were reducing their use of academic groups for image analysis in large clinical trials… Involvement of IXICO in pivotal trials in which the Boundary Shift Integral was one of the services we offered contributed to IXICO's significant growth in revenue and reaching profitability during the 2008-2013 period*."

Furthermore, in the US, our techniques have been used in a large number of studies by image analysis companies e.g. Bioclinica **[h]** and Synarc **[i]**, who report that:

> "*The development, validation and introduction of the Boundary Shift Integral (BSI) was*

widely recognized as a major advance for the field. The BSI subsequently established itself as one of the most important techniques for the measurement of rates of atrophy in AD clinical trials. The BSI has been employed in many of the most high profile international clinical trials including several of those analysed by Synarc. In the period January 2008 – July 2013 Synarc has used this technique in 12 clinical trials. The contribution of the BSI along with the broader work by Professor Nick Fox is widely recognized as being very important in the industry. His work in developing registration-based methods or measuring brain changes and the use of the BSI to quantify atrophy measurements has been seen as a standard against which other techniques are compared. These developments have had a major commercial impact well beyond academia."

Use in investigating other diseases: The Boundary Shift Integral technique is not simply applicable to Alzheimer's disease. Its use has now begun to spread to the investigation of other diseases, including Huntington's disease **[j]**, frontotemporal dementia and MS **[k]**.

5. Sources to corroborate the impact

[a] Ezekiel F, Chao L, Kornak J, Du AT, Cardenas V, Truran D, Jagust W, Chui H, Miller B, Yaffe K, Schuff N, Weiner M. Comparisons between global and focal brain atrophy rates in normal aging and Alzheimer disease: Boundary Shift Integral versus tracing of the entorhinal cortex and hippocampus. *Alzheimer Disease & Associated Disorders.* 2004 Oct-Dec;18(4):196-201.

[b] Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M; Bapineuzumab 201 Clinical Trial Investigators. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology. 2009 Dec 15;73(24):2061-70. http://dx.doi.org/10.1212/WNL.0b013e3181c67808

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[d] Wilkinson D, Fox NC, Barkhof F, Phuld R, Lemminge O, Scheltens P and the Study 10112 investigators. Memantine and Brain Atrophy in Alzheimer's Disease: A 1-Year Randomized Controlled Trial. Journal of Alzheimer's Disease 29 (2012) 459–469 http://doi.org/n8s

[e] Commentary on European Medicines Agency draft opinion: http://www.alzforum.org/new/detail.asp?id=2934

[f] Details available on request. Contact details provided.

[g] IXICO website http://www.ixico.com/clinical-trials. Letter of testimony provided by CEO of Ixico. Copy available on request.

[h] Bioclinica information leaflet, giving details of how they use the BSI technique in imaging: http://www.bioclinica.com/assets/Uploads/alzheimer-capabilities.pdf

[i] Synarc website: http://www.synarc.com/ta/neuro/alzheimersdisease.html. Letter of testimony provided by Vice President Neurology, Synarc. Copy available on request.

[j] Tabrizi et al. (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. Lancet Neurology. Volume 10, Issue 1, January 2011, Pages 31–42

[k] Chataway J, Schuerer N, Alsanousi A et al. THE MS-STAT TRIAL: High Dose Simvastatin Slows Brain Atrophy and Delays Disability in Secondary Progressive Multiple Sclerosis: A Phase II Placebo-Controlled Trial. Lancet Neurology In Revision. http://www.neurology.org/cgi/content/meeting_abstract/80/1_MeetingAbstracts/PL02.001