Institution:
University of Cambridge

Unit of Assessment:
UoA4

Title of case study:
Touch screen based cognitive testing for rats and mice

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

In 2009 Tim Bussey and Lisa Saksida commercialised novel apparatus and control software for computer-automated behavioural testing of rats and mice, reducing the time and user-hours required to generate data; and yielding improved performance levels and opportunities for translation whilst also reducing variability. The apparatus is sold with a battery of purpose-designed cognitive tests that parallel those used to assess cognition in patients (e.g., CANTAB). This has had impact as follows: (1) sales: over 400 units; (2) preclinical research: because of its potential for translation of the tasks, the apparatus is influencing how pharmaceutical companies conduct CNS research; (3) spinoff industry: contract research organisations now include touchscreen-based cognitive assays in their services.

2. Underpinning research (indicative maximum 500 words)

Bussey (Lecturer 2000; Senior Lecturer 2003; Reader 2010; Professor, 2013) and Saksida (Lecturer 2001; Senior Lecturer 2007; Reader, 2012) in the Department of Psychology specialise in the assessment of cognition in animals. In 2000, Bussey and Saksida started their laboratory in Cambridge, and a consequence of their research programme into fundamental aspects of cognition has been the development of a touchscreen-based cognitive testing system for preclinical rodent models of CNS disease. The major advantage of using a touchscreen interface is that it is identical to the human equivalent, enabling very similar (and in some cases identical) paradigms and methodologies to be used when studying preclinical and patient populations.[1,2] The system was originally highly promising but difficult to implement. To bring this product to market and into the laboratories of academia and *Big Pharma*, a large amount of experimentation was required, as follows:

(1) Production of a physical prototype that was designed to make the touchscreen system commercially viable and user-friendly, on the basis of research done in Bussey and Saksida's laboratory. For example, the chamber has a unique trapezoidal wall shape to focus the animal's attention; specialized infrared touchscreens that are sensitive to rodent nosepokes whilst not disturbing the animal; and a unique configurable design in which the food delivery system can be moved to allow for a wider variety of cognitive tests. These innovations needed to be tested with experimental models using both rats and mice, to ensure robustness and reliability. Bussey and Saksida have published papers describing over 30 such experiments since 2000. Although the general features of the apparatus have proven robust, many experiments are ongoing which are enabling more subtle modifications such as optimization of the nature of the shapes presented on the screen, the design of the 'mask' that directs the animals' response to the screen and the best food reward to maximize performance.[3]

(2) Saksida wrote the software that was used to carry out many experiments to test that the tasks can be learned by animals in a reasonable amount of time, and to run experiments needed to validate the tasks. Then the control software was expanded to make it possible for non-specialist users to run the system, change parameters and collect data. Again, a large number of experiments were run to ensure that the software is bug-free and user-friendly. Then, the software had to be re-coded by Campden Instruments to a professional standard; again, experiments in our laboratory were required to ensure that the programs run properly. This process continues as new tasks are developed.

(3) Bussey and Saksida developed and validated a suite of tasks to parallel those used in human test batteries such as CANTAB, developed for human use. There is now a battery of about 15 tasks tapping into various aspects of cognitive function such as attention, memory and visual discrimination. All of these tasks had to be validated both in terms of behaviour (ensuring that the animals behave as they should when parameters are altered) and the brain (i.e., that the task relies on the right brain circuits) involving considerable additional experimentation, all of which has so far been carried out in the Bussey/Saksida laboratory or via direct collaboration.[4,5]

Since commercialization in 2009, independent papers validating touchscreen tasks have also been published.

(4) As the bulk of the work leading up to this project had involved rats, Saksida and Bussey developed a version of the touchscreen apparatus suitable for mice. Mice present particular problems for an endeavour such as this. First, for anatomical and physiological reasons, apparatus for the mouse has to have different features from that used in the rat and, as described above, this had to be tested in actual mice. Secondly, unlike rats, strains of mice vary wildly in their behavioural response to tasks like these. Bussey and Saksida had to test a number of mouse strains to ensure that they could be used with the apparatus. Finally, mouse models of disease, e.g., Huntington's or Alzheimer's mice, present with particular challenges such as motor and motivational changes and so these models had to be tested for compatibility with the apparatus and tasks.[6]. On-going research by Bussey and Saksida continues to develop the apparatus further.

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

1. Bussey, T.J., Holmes A., Lyon, L., Mar, A.C., McAllister, K.A.L., Nithianantharajah, J., Oomen, C.A. & Saksida, L.M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. *Neuropharmacology*, Special Issue on Schizophrenia, 62(3):1191-1203.
2. Nithianantharajah, J, Komiyama N.H., McKechanie, A., Johnstone, M., Blackwood D.H., St Clair, D., Emes R.D., van de Lagemaat L.N., Saksida L.M., Bussey T.J. * & Grant, S.G.N. * (2013) Synaptic scaffold evolution generated components of vertebrate cognitive complexity, *Nature Neuroscience*, 16 (1):16-24.
3. Bussey, T.J., Padain, T.L., Skillings, E.A., Winters, B.D., Morton, A.J., & Saksida, L.M. (2008). The touchscreen cognitive testing method for rodents: How to get the best out of your rat. *Learning & Memory,* 15, 516-523.
4. Romberg C., Bussey T.J., Saksida L.M. (2011). Attentional impairments in the triple transgenic mouse model of Alzheimer's disease: Rescue with donepezil (Aricept). *Journal of Neuroscience*, 31, 3500-3507.
5. Talpos, J., Winters, B.D., Dias, R., Saksida, L.M. & Bussey, T.J. (2009). A touchscreen-automated paired-associate learning (PAL) task sensitive to pharmacological manipulation of the hippocampus: a translational model of cognitive impairments in neurodegenerative disease. *Psychopharmacology,* 205(1):157-68.
6. Morton, A.J., Skillings, E., Bussey, T.J. & Saksida, L.M. (2006). Measuring cognitive deficits in disabled mice using an automated interactive touchscreen system. *Nature Methods,* 3, 767. Awarded the "highly commended" prize in the NC3Rs 3Rs competition, 2008.

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

(1) Commercialization

The Bussey-Saksida Rodent Touchscreen Chamber was licensed to Campden Instruments (CI; parent company Lafayette Instruments) on 1 February 2008; and the company launched two commercial products, distinct chambers for rat and mouse, in early 2009. Additional series of tests developed by Drs Bussey and Saksida were the subject of further licenses on 24 December 2009 and 1 July 2010. Further task development continues by Bussey and Saksida, and as new tasks are validated and published they are licensed to Campden Instruments. Drs Bussey and Saksida continue working with this company to market the touchscreen chambers and to advise purchasers on their setup and utilisation.

The impact on Campden Instruments has been highly beneficial.[1,2,3.] The touchscreen chambers represent a significant increase in sales for the company (they have added about £400-500K p.a. to Campden's turnover over the last 2-3 years); broadening its portfolio in the behavioural marketplace; and enabling this to become an export-led company. As a result, Campden Instruments has added three operatives to its factory workforce. There is a clear link between this commercial success and the work done by Bussey and Saksida at Cambridge, specifically:

(1) the development of the prototype equipment in the Bussey-Saksida laboratory, combined with Campden Instruments' engineering expertise leading to cost reduction and the development of the high sensitivity touchscreens; and (2) the on-going development and validation of the tasks.

(2) Preclinical Research: through the opportunity for translation of the tasks, the apparatus has influenced how pharmaceutical companies conduct CNS research.

The system is attractive to pharmaceutical companies because of the high level of reproducibility and comparability of results between different chambers and in different geographic locations. Other beneficial features are the translational potential including the fact that better preclinical data should lead to fewer drug failures during clinical trials. In addition, the high throughput and automated nature of the system are beneficial in a commercial setting, as is the fact that the system is user friendly and relatively failsafe for non-experts in rodent behaviour. By March 2013, 138 rat chambers and 302 mouse chambers had been sold worldwide to both academic institutions and pharmaceutical companies.

Two very large research consortia have featured this system as a core component of their programmes. The NEWMEDS consortium, one of the largest ever academic-industry collaborations, was funded in September 2009 for 5 years by the Innovative Medicines Initiative to find new methods for the development of drugs for schizophrenia and depression. Ten major biopharmaceutical companies are involved, including AstraZeneca, Eli Lilly[8], Janssen Pharmaceutica, Lundbeck A/S, Novartis, Orion, Pfizer, Roche, Servier and Abbott. The project focuses on developing new animal models to identify innovative and effective drugs for schizophrenia. The behavioural test battery designed to characterize animal models of schizophrenia extensively involves Bussey-Saksida touchscreen tasks. PharmaCog, a sister IMI-funded initiative to NEWMEDS targeting Alzheimer's Disease, also has a significant rodent touchscreen component. Academic and commercial members of the consortium have purchased Bussey-Saksida chambers for use in underpinning project work.

(3) Spinoff industry: Contract Research Organisations have included touchscreen-based cognitive assays in their services.

Examples include Synome[4] who indicate on their website that: 'The cognitive characterisation of mouse models of human brain disorders is important for their use in screening potential therapeutic agents.' Synome offers a battery of touchscreen cognitive tasks, designed in consultation with both Bussey and Saksida, who act as external advisors to the company.[5]

The company Transpharmation provides translational pre-clinical pharmacology services to the pharmaceutical and biotechnology industry, with the aim of better understanding potential new medicines as they transition into the clinic. They also offer a battery of Bussey-Saksida cognitive tests[6], and Bussey provided consultancy to this company when they were initiating their services[7].

(**4) Specialist advisory role in maximising the translation of effective therapies from animal models to clinical practice.**

For example, the touchscreen system featured and was demonstrated by Bussey and Saksida at the following:

July, 2012, Washington DC: National Institutes of Health Opportunity Network workshop, *Improving Animal Models of Human Behavioral and Social Processes*. The purpose of the workshop was to discuss strategies for improving the design and construction of animal models for understanding human behavioral and social processes

March, 2012, Washington DC: Institute of Medicine Forum on Neuroscience and Nervous System Disorders workshop: "*Improving Translation of Animal Models for Nervous System Disorders*".

In addition, since development of the mouse version, commercial interest in the system has been

very high. It has been featured as a key cognitive testing method in 'What's Wrong With My Mouse: Behavioral phenotyping of transgenic and knockout mice' (Crawley, 2007), the standard guide to behavioural testing for mouse researchers including those in Industry. It has also been featured in a number of popular articles in high-impact journals reaching a broad and non-academic readership, including *Nature*.

5) Impact on the 3Rs

The 3Rs are a widely accepted ethical framework for conducting scientific experiments using animals humanely: 1. replacement - use of non-animal methods; 2. reduction - methods which reduce the number of animals used; and 3. refinement - methods which improve animal welfare. Our paper in *Nature Methods* (Ref 6, section 3) was awarded the 'highly commended' prize in the NC3Rs 3Rs competition, 2008.

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

1. Letter from Director, Campden Instruments

2. Product page: www.campden-inst.com/product_detail.asp?ItemID=1970

3. CamTouch technical standard: http://www.limef.com/downloads/camtouch.pdf

4. Letter from Chairman, Synome

5. http://www.synome.eu/technology/touchscreen-cognitive-testing/31-touchscreen-cognitive-testing

6.http://www.transpharmation.co.uk/services/cognition-models

7. Referee; Managing Director, Transpharmation

8. Referee; Senior Research Scientist, Eli Lilly