Institution: University of St Andrews

Unit of Assessment: A4 – Psychology, Psychiatry and Neuroscience

Title of case study: The rodent attentional set-shifting task and the pharmaceutical industry

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

The 'rodent attentional set-shifting task' provides a novel method for assessing cognitive impairments in rodents that are directly equivalent to those seen in several psychiatric and neurological disorders. The research has had significant and broad **impact on commerce**, as evidenced by: i) **commercial adoption of a new process across the pharmaceutical industry** through use of the task in pre-clinical testing of putative therapeutic compounds and inclusion of the task in NIMH-sponsored guidelines for schizophrenia clinical trials; and ii) **demonstrable collaborations with industry**, including a Royal Society Industry fellowship, CASE studentships and academic research contracts.

2. Underpinning research (indicative maximum 500 words)

The research described here was conducted in the laboratory of Prof. Verity Brown, who has been employed in the School since 1993. The key paper that presented the 'rodent attentional set-shifting task' was published in 2000 (Birrell and Brown, 2000) and has been cited over 490 times.

Cognitive flexibility, including the ability to shift attention between components of complex stimuli, is an important executive function. In humans, areas of prefrontal cortex are important for executive functions, which are impaired in disorders such as schizophrenia and Parkinson's disease, causing considerable difficulties in everyday life. The research in Brown's lab has shown that rats have some similar cognitive processes and underlying neural architecture to humans (Brown and Bowman, 2002). Cross-species similarities provide an opportunity for 'translational research', whereby an animal can be used to develop new pharmaceutical therapies for humans.

Working with colleagues from the pharmaceutical industry from 1993 onwards, Brown saw that researchers in both academic and industry settings needed a rodent behavioural task that could measure attentional set-shifting in a manner that was directly comparable to human tasks. In humans, tasks of attentional set-shifting involve focusing attention on one aspect ('dimension') of a visual stimulus (e.g., its shape or colour) and then shifting attention to the other. Given that rats rely more on their senses of smell and touch than on vision, Brown devised a task that avoided using visual stimuli, thereby providing a major breakthrough in measuring attentional processes in rodents. This task offered a new process in the form of a 'translational tool' that was amenable to pharmacological manipulation (Tait *et al*., 2007) and that could be used in the development of drugs for cognitive impairments.

Rats are foraging animals so Birrell and Brown (2000) buried food in digging bowls, distinguishable by the digging media (e.g., sand versus grit) and odour (e.g., ginger versus cinnamon). Rats were trained to find food on the basis of one of these dimensions (e.g., the digging media), while the other dimension (e.g., the odour) was irrelevant. The stimuli were then replaced with novel exemplars in several acquisition stages, but, crucially, at one stage — the extra-dimensional (ED) shift — the relevant characteristic was changed. Rats, like humans, required a larger number of trials to make an ED shift than an intra-dimensional (ID) shift.

Importantly, Brown and her group showed that experimental lesions of areas of prefrontal cortex were associated with precisely the same pattern of set-shifting impairments as in humans with

neurocognitive disorders (McAlonan and Brown, 2003), confirming the translational value of the task. Working with Merck scientists, the researchers also showed that rats could be tested multiple times on the task with good test-retest reliability (Tait *et al*., 2009), enabling within-subjects designs, so improving statistical power and significantly reducing the number of animals used.

The pharmaceutical industry has been involved in supporting the development of the task from the beginning: for example, a BBSRC CASE PhD studentship sponsored by GlaxoSmithKline (1999-2002) resulted in the first publication from an industry laboratory using the task (Hatcher *et al*., 2005). Brown's links with the pharmaceutical industry were enhanced by a Royal Society Industry Fellowship, sponsored by Organon (2007-2009) and extended by Merck (2009-2012), and by extensive collaborative research ventures. In total, 10 different pharmaceutical companies have supported 6 CASE PhD studentships and provided research funding or materials to Brown's lab since 1994. Brown was awarded Fellowship of the Royal Society of Edinburgh in 2012.

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

Researchers at the University of St Andrews are in **bold**; industry collaborators are in *italics*. IF = currrent impact factor; citations are from Scopus.

Birrell, J. M. and **Brown, V. J.** (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *Journal of Neuroscience,* 20: 4320-4324. **IF = 7.9; citations = 491**, http://www.jneurosci.org/content/20/11/4320.full#abstract-1.

Brown, V. J. and **Bowman, E. M.** (2002). Rodent models of prefrontal cortical function. *Trends in Neurosciences,* 25: 340-343. **IF = 14.5; citations = 140**, doi:10.1016/S0166-2236(02)02164-1.

Hatcher, P. D., **Brown, V. J.**, **Tait, D. S.**, Bate, S., Overend, P., Hagan, J. J. and Jones, D. N. C. (2005). 5-HT6 receptor antagonists improve performance in an attentional set shifting task in rats. *Psychopharmacology*, 181: 253-259. **IF = 4.3; citations = 71**, doi: 10.1007/s00213-005-2261-z.

McAlonan, K. and **Brown V. J.** (2003). Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. *Behavioural Brain Res.,* 146: 7-103. **IF = 3.7; citations = 239**, doi: 10.1016/j.bbr.2003.09.019.

Tait, D. S., **Brown, V. J.**, **Farovik, A.**, Theobald, D. E., Dalley, J. W. and Robbins, T. W. (2007). Lesions of the dorsal noradrenergic bundle impair attentional set-shifting in the rat. *European Journal of Neuroscience,* 25: 3719-3724 **IF = 3.6; citations = 53**, doi: 10.1111/j.1460-9568.2007.05612.x.

Tait, D. S., *Marston, H. M*., *Shahid, M.* and **Brown, V. J.** (2009). Asenapine restores cognitive flexibility in rats with lesions of the medial prefrontal cortex. *Psychopharmacology*, 202: 295-306. **IF = 4.3; citations = 27**, doi: 10.1007/s00213-008-1364-8.

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

The research has had significant and broad **impact on commerce**, as evidenced by: i) **commercial adoption of a new process** - the set-shifting task has been used by pharmaceutical companies in preclinical drug development and has been included in the revised NIMH-sponsored guidelines for schizophrenia clinical trials; and ii) **demonstrable collaborations with industry**, including research contracts to academic intermediaries in both the UK and USA.

i) Commercial adoption of a new process and change of practice within the pharmaceutical industry The rodent attentional set-shifting task is now used globally in the pharmaceutical industry to test drugs with putative cognitive enhancement properties. *Evidence of significance and breadth of impact* is provided by: a) **direct confirmation from the pharmaceutical companies** that the task is used in-house for drug development and **published data** showing broad use of the task across the industry, and b) **inclusion of the task in clinical guidelines** for schizophrenia.

a) Use of task by pharmaceutical companies We have direct confirmation that the Birrell and Brown (2000) set-shifting task has been used in-house by several pharmaceutical companies

during the REF period. For example, a Head of Department in **Lundbeck** confirms that the Birrell and Brown task has been used as part of their preclinical drug development since 2009:

'*our company has employed the Birrell and Brown (2000) attentional set-shifting taskas part of our ongoing research aiming at developing new drugs for treatment of CNS diseases. The Birrell and Brown task is* ***one of our central assays*** *when the executive domain of cognition is among the target domains in question, and I can confirm that positive data from this task have* ***supported decisions to progress several of our drug discovery projects***' (**S1**).

The Head of Department also states that the Birrell and Brown (2000) task:

'*has made a* ***significant contribution to drug discovery in our company****. The back-translatability of your set-shifting task has provided us with a* ***crucial new methodology*** *for addressing cognition in a drug research setting.*' (**S1**)

Organon (which was taken over by Merck in 2007) also made extensive use of the Birrell and Brown (2000) set-shifting task, and data from the task were included in the **preclinical development of *asenapine***, a second generation anti-psychotic that has been marketed by Merck since 2009 as a treatment for mania in schizophrenia and bipolar disorder. As evidence, data from the attention set-shifting task are referred to in the **European Medicines Agency** (EMA) submission for approval of asenapine (**S6**); asenapine has also been approved by the **US Food and Drug Administration** (**S6**). In addition, a previous employee of Organon has confirmed that the Birrell and Brown (2000) task was:

'*a* ***key behavioural assay*** *used by Organon during the development of asenapine. The task was specifically used during preclinical testing of this compound'* (**S2**).

A contact within the pharmaceutical industry, currently employed at TPP Global Development and with access to industry databases, confirmed that data from the Birrell and Brown (2000) task have also been used in the preclinical drug development stages for other compounds that have reached phase I and phase II clinical trials, and stated that the Birrell and Brown (2000) task:

'is by far the ***most practical, validated, and translatable rodent task*** *currently available for exploring executive function within a drug discovery setting and therefore forms a* ***critical part of behavioural test batteries across the whole pharmaceutical industry****'* (**S2**).

A literature search of published articles provides further evidence for extensive use of the task within industry. During the REF period, **employees of 12 major pharmaceutical companies** are listed as co-authors on articles that include data from the Birrell and Brown (2000) task; including GlaxoSmith-Klein, Johnson & Johnson, Lundbeck, Lilly, Pfizer and Schering-Plough (**S7**).

b) Inclusion of the task in CNTRICS guidelines The *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) initiative, funded by the **US National Institute of Mental Health** (NIMH) in 2008, resulted in a set of criteria by which the cognitive deficits of schizophrenia could be objectively evaluated for the first time. On the back of MATRICS, a group of pharmaceutical industry scientists and academics engaged in the **NIMH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia** (CNTRICS) initiative, which devised guidelines for assessing these cognitive deficits in preclinical trials. The attentional set-shifting task was one of the core tasks adopted in new CNTRICS guidelines for clinical trials in schizophrenia. Brown was an invited speaker at the 2011 CNTRICS workshop on '*Selecting translational animal model paradigms*' (**S8**) and inclusion of appropriate animal models of schizophrenia was key to the development of the guidelines. A CNTRICS steering group member has confirmed that selection for inclusion is evidence that the task:

'*has* ***set the standard for translational research practice*** *in psychiatry*' and that inclusion of the task in the guidelines '*will* ***assure new higher standards for the measurement of executive function*** *in both preclinical research and clinical trials*' (**S3**).

ii) Demonstrable collaborations with industry The impact has resulted from sustained and significant collaboration with industry, including a *Royal Society Industry Fellowship* to Brown, research funding to Brown's research laboratory, and research contracts to other academic intermediaries in the UK and USA. *Evidence of significance and breadth of impact:*

a) *Royal Society funding and support for collaborations with industry* Brown was awarded a ***Royal Society Industry Fellowship***, sponsored by Organon in 2006, which was extended until 2012 via Merck sponsorship. The outcome of the fellowship included training scientists within Merck both specifically on the set-shifting task, as well as more generally in interactions in a knowledge transfer partnership. Brown organised a 2011 **Royal Society International Scientific Seminar** meeting on '*Novel approaches to drug development in the 21st Century*' at the Kavli Centre to which researchers from both academic and industrial settings contributed. This meeting resulted in a short article in **Nature**, written by the attendees (Insel, T., Sahakian, B., Voon, V., Nye, J., Brown, V. J., et al. 2012. Drug research: a plan for mental illness. *Nature* 483: 269).

b) Provision of research contracts and funding to Brown During the REF period, Brown's laboratory has received research contracts totalling **£707k from 5 pharmaceutical companies** (Lundbeck, Merck, Organon, Schering Plough and TPP) and from the ***Scottish Universities Life Sciences Alliance*** (SULSA) (**S9**). These funds have supported postdoctoral researcher salary, CASE PhD studentships and research costs. In addition, Lilly has sent investigational compounds (e.g., mGLUR5s) to Brown, in order for the efficacy to be assessed on the set-shifting task.

c) Provision of research contracts to contract research organisations and other academics The Birrell and Brown (2000) task is offered by international contract research organisations (e.g, WuXi Apptec, China; **S10**), and academic researchers in the UK and abroad have been awarded research contracts to conduct the set-shifting task on behalf of pharmaceutical companies. For example, industry contracts have been awarded to academic colleagues at the University of Manchester, U.K. (**S4**) and the University of Texas, San Antonio, U.S.A. (**S5**) to run the Birrell and Brown (2000) rodent attentional set-shifting task.

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

S1 Letter from Head of Department, Synaptic Transmission I, Lundbeck, confirming use of the task during drug development at this company.

S2 Letter from Head of Pharmacology, TPP Global Development, confirming use of the task in the development of asenapine and more generally across the pharmaceutical industry.

S3 Letter from CNTRICS Executive Committee member, Columbia University, confirming inclusion of the task in CNTRICS and implications for standards in preclinical and clinical trials.

S4 Email confirmation of research contract awards from colleague at the University of Manchester.

S5 Email confirmation of research contract awards from colleague at the University of Texas, USA.

S6 Organon's asenapine submission to the EU pharmaceutical administrative body cites results derived from set-shifting during drug development (EMA public assessment report; page 13; http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001177/human_med_001379.jsp&mid=WC0b01ac058001d124); and asenapine has been approved by US FDA (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173876.pdf).

S7 Scopus literature search output held on record by University of St Andrews demonstrates that set-shifting is widely employed in the pharmaceutical industry.

S8 http://cntrics.ucdavis.edu/c2meeting4talks.shtml confirms Brown spoke at CNTRICS Meeting 4.

S9 University records confirm details of funding for research contracts and CASE studentships.

S10 WuXi website content and methods sheet http://www.wuxiapptec.com/bio_cns.html confirms commercial research use of the set-shifting task (page 3).