| **Institution:** |
| University of Cambridge |

| **Unit of Assessment:** |
| UoA4 |

| **Title of case study:** |
| CANTAB-PAL: a novel mobile application for detecting Alzheimer's disease and assessing therapeutic interventions |

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

CANTAB-Paired Associates Learning (PAL) was developed to detect early memory problems in Alzheimer's disease; and was recently (in 2012) launched by Cambridge Cognition (floated on the London Stock Exchange in April 2013) as a mobile (iPad) application (CANTABmobile™) suitable for use in GP clinics. This and other cognitive tests from the CANTAB battery have also been employed in 77 clinical trials since 2008, involving hundreds of sites world-wide, by most of the major pharmaceutical companies and by biotech, device and nutraceutical companies. CANTABmobile™ currently has 166 licensed user-practitioners including six clinical commissioning groups implementing the national initiative for early diagnosis.

2. Underpinning research (indicative maximum 500 words)

Prior to 1993, CANTAB (Cambridge Neuropsychological Test Automated Battery) had been originally devised in 1987 by Trevor Robbins (then Lecturer; Professor since 1997), and colleagues in the Department of Experimental Psychology, with Barbara Sahakian (then at the Institute of Psychiatry, University of London) for diagnosing cognitive impairments in patients with Alzheimer's or Parkinson's disease. This computerised cognitive neuropsychological test battery assessed memory (including paired-associates learning; PAL), and executive capacities. Innovative features were the use of (i) touch-screen technology to assess cognition in humans and (ii) common tests for assessing cognition in experimental animals, enabling cross-species, back-translational, studies and thus the evaluation of novel medications. Beginning in 1993, Robbins, Sahakian (University Lecturer in the Department of Psychiatry, Cambridge; Professor, from 2002) and colleagues undertook a large scale standardisation of CANTAB, in collaboration with Professor Patrick Rabbitt (Manchester University), including PAL in 780+ normal volunteers aged 50-80+ to quantify the normal (i.e. non-diseased) range of responses, and to provide data stratified by age.[1] This information was crucial for later development of the clinical instrument for detecting abnormalities in memory functioning. Further validation of the battery for dementia confirmed predicted sensitivity to cognitive deficits using CANTAB-PAL and executive function in studies on brain damaged humans with lesions of the frontal and temporal cortex.[2]

Cross-species translation of the battery to monkeys and rodents, important for drug discovery and development by pharmaceutical companies, was demonstrated during the period from 1993-2007 by Robbins and Angela Roberts (then Royal Society Fellow, Department of Experimental Psychology; Professor of Behavioural Neuroscience, Department of Physiology, Development and Neuroscience from 2010). They implemented a 'monkey-CANTAB' battery including the PAL test in collaboration with Scripps Institute, La Jolla, California.[3]

In an MRC-funded LINK project in partnership with GlaxoSmithKline (1998-2001), CANTAB-PAL was shown to be sensitive to detection of Alzheimer's disease, both in patients presenting at the Addenbrooke's Hospital NHS Memory Clinic with 'questionable dementia' and in a community sample (collaboration with the OPTIMA project, University of Oxford).[4] An algorithm was developed accurately predicting the development of a diagnosis of Alzheimer's disease within 3 years in the patients with questionable dementia, and significant subsequent intellectual deterioration over 5 years in healthy elderly volunteers.[4] In conjunction with other tests it was almost 100% sensitive for these samples. This algorithm was developed by Dr Andrew Blackwell, a post-doctoral fellow (Wellcome Trust funded, working with Robbins and Sahakian) who later joined Cambridge Cognition as its Chief Scientific Officer to lead subsequent commercial distribution and refinement of the CANTAB battery, in particular the PAL test. As consultants to Cambridge Cognition, Robbins and Sahakian continued to contribute to these refinements.[5] These findings in patients with 'questionable dementia' or Mild Cognitive Impairment (MCI) have been corroborated in several studies. The PAL test was also able to discriminate cognitive impairment due to depression from that due to dementia, an historically difficult diagnosis.[5]

The PAL test has subsequently been combined with neuroimaging methodology in order to provide accurate biomarkers for drug development and also enhance its capacity for early detection of

Alzheimer's disease. In 2011, Sahakian, Robbins and others published a functional neuroimaging study of an analogue of the PAL test in patients with MCI and healthy volunteers, finding as predicted, involvement of the hippocampus, a brain structure implicated in the earliest stages of Alzheimer's disease.6

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

1. Robbins, T.W., James, M., Owen, A., Sahakian, B.J., McInnes, L. and Rabbitt, P.M. (1994) Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. Dementia, 5, 266-281
http://dx.doi.org/10.1159/0006735

2. Owen, A.M., Sahakian, B.J., Semple, J., Polkey, C.E., Robbins, T.W. (1995) Visuospatial short term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdala-hippocampectomy in man. Neuropsychologia, 33, 1-24 http:/dx.doi.org/10.1016/0028-3932(94)00098-A

3. Weed, M.R., Taffe, M.A., Polis, I., Roberts, A.C., Robbins, T.W., Koob, G.F., Bloom, F.E. & Gold, L.H. (1999) Performance norms for a rhesus monkey neuropsychological testing battery: acquisition and long-term performance. Cognitive Brain Research, 8, 185-201.
http://dx.doi.org/10.1016/S0926-6410(99)00020-8

4. Swainson R, Hodges JR, Galton CJ, Semple J, Michael A., Dunn BD, Iddon J.L. Robbins TW & Sahakian BJ (2001) Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dementia and Geriatric Cognitive Disorders. 12, 265-280 http://dx.doi.org/10.1159/000051269

5. Blackwell, A.D., Sahakian, B.J., Vesey, R., Semple, J.M., Robbins, T.W. & Hodges, J.R. (2004) Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 17, 42-48. http://dx.doi.org/10.1159/000074081

6. de Rover, M., Pironti, V.A., McCabe, J.A., Acosta-Cabronero, J., Arana, F.S., Morein-Zamir, S., Hodges, J.R., Robbins, T.W., Fletcher, P.C., Nestor, P.J. & Sahakian, B.J. (2011) Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. Neuropsychologia, 49, 2060-2070.
http://dx.doi.org/10.1016/j.neuropsychologia.2011.03.037

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

Cambridge Cognition[7] was spun out in 2002 with its main product being the CANTAB battery, licensed from the University of Cambridge. Part of the economic impact has been sales to research institutions: it is currently used in more than 1000 departments in over 700 universities and clinical research institutions internationally and has an extensive bibliography.[7] The software was revised by *Cambridge Cognition* in 2003 to comply with pharmaceutical regulations for data encoding. Real-time data streaming from numerous international clinical trial sites was introduced in 2011. In 2012 *Cambridge Cognition* released CANTABmobile™, a portable version of PAL, to provide a diagnostic to detect Alzheimer's disease more accurately and at an earlier, and therefore more 'treatable', stage.[8]

Clinical and Pharmaceutical Company Impact: The main clinical application of the CANTAB battery, including PAL, has been to diagnose cognitive impairment and assess novel

pharmaceutical treatments. Following the underpinning research, a series of industry-led trials using CANTAB-PAL e.g.[9] determined a 'cognitive signature' identifying people at risk for dementia and their likely rate of intellectual deterioration. Normative data collated from >8000 individuals (augmenting reference 1 above) provided a baseline stratified by age, gender and educational attainment. The test has 100% sensitivity and 92% specificity in detecting Alzheimer's disease and is superior to the standard ADAS-COG. More than 120 studies involving clinical trials have used the software (77 since 2008;[10] 57 currently listed on the U.S. National Institutes of Health clinical trials website[11]), with the largest proportion being trials in mild-to-moderate Alzheimer's disease sponsored by 10 of the 12 major pharmaceutical companies and by biotech, device and nutraceutical companies.[10]

Commercial impact: The CANTAB battery is the main product of *Cambridge Cognition*[7] which employs around 50 staff in its Head Office near Cambridge, U.K., and has two US-based business development staff. A large proportion of the science and software teams are ex-PhDs from the University of Cambridge (several from the Robbins and Sahakian laboratories). As standalone reportable segments, the sale of the battery to clinical research academic groups and pharmaceutical companies for use in drug trials has been profitable since 2009 and *Cambridge Cognition* is listed on AIM[7] (previously funded by venture capital). A new product, CANTABmobile™, was launched in May 2012 as a *Conformité Européenne* (CE) approved Class II medical device.[8] In September 2012, the company was listed number 92 in the Sunday Times list of the 100 fastest growing private technology companies in the UK, on the back of annual sales growth of 40%, (achieving revenues of £5.8M in 2012).[12]

Additionally, in November 2012, *Cambridge Cognition*, the medical imaging company IXICO and other partners received a grant of £3.3 million from the Government-funded Biomedical Catalyst Programme to build and test a prototype national dementia early diagnosis service using CANTAB. The service involves GP referral of patients needing further assessment for possible dementia to a Brain Health Centre, following an initial CANTABmobile™ test. Once referred, patients receive an MRI brain scan and more detailed cognitive assessment comprising CANTAB tests on an iPad. Computer algorithms based on machine learning analyse the brain scans to assess signs of atrophy, combined with an assessment of blood vessel damage in the brain and the results of cognitive assessment. The initial aim of the project is to demonstrate increasing rates of diagnosis and reducing time to diagnosis of Alzheimer's disease from 18 months to three.

Clinical services including NHS impact: Research suggests that earlier diagnosis is cost effective due to more effective interventions and prolonged independence.[13] The UK Primary Care Trust Commissioning Board has started trialling CANTABmobile™ with a small number of GPs. CANTABmobile™ currently has 166 licensed users including six clinical commissioning groups implementing the national initiative for early diagnosis, and private healthcare groups, a pharmacy chain and a customer in Germany, the first sale for the Company outside the UK.[14]

The Brain Health Centres project (2012), including CANTAB-PAL, is endorsed by national clinical director for dementia, Professor Alistair Burns: "I am very impressed by the Brain Health Centre project which has the real potential to contribute to making the UK a world leader in dementia care by raising diagnosis rates - a key ambition of the Prime Minister's dementia challenge. Combining innovative technologies in this way should help us to spot early signs of dementia, giving us time to offer patients better support and care"; (press release on *Cambridge Cognition* website[7]).

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

7. Use of CANTAB internationally, bibliography and press releases http://www.camcog.com/
8. Video of CANTAB mobile in use http://www.cantabmobile.com/video.asp?id=3
9. Fowler K.S. Saling M. M. Conway E. L. Semple J. Louis W. J. (2002) Paired associate performance in the early detection of DAT Journal of the International Neuropsychological Society, 8, 58-71 DOI: http://dx.doi.org/10.1017/S1355617701020069
10. Use of CANTAB in pharmaceutical trials. http://www.camcog.com/pharma-trials.asp
11. Use of CANTAB in pharmaceutical trials. http://clinicaltrials.gov/ct2/results?term=CANTAB&Search=Search

12.SundayTimesTechTrack100:
http://www.fasttrack.co.uk/fasttrack/leagues/tech100leaguetable.asp?siteID=3&searchName=&yr=2012&sort=num&area1=99

13.Getsios D., Blume S., Ishak KJ., Maclaine G. & Hernández L (2012) An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimer's Disease and Dementia, 8(1):22-30. DOI: http://dx.doi.org/10.1016/j.jalz.2010.07.001

14 News item on CANTABmobile (26 June 2013)
 http://www.cantabmobile.com/news-item.asp?id=8

Testaments to the current utility of CANTAB for clinical assessment of cognitive deficits and utility for pharmaceutical companies can be obtained from:

15. Global Therapeutic Area Head, Janssen, J&J Pharmaceuticals Research and Development, 1125 Trenton-Harburton Road, Titusville NJ 08506, USA. Letter of endorsement provided

16. Lead Technologist for Medical and Healthcare at Technology Strategy Board, Swindon, U.K.