Institution: University of Cambridge

Unit of Assessment: 4

Title of case study:
CANTAB Mobile: a tool to detect early Alzheimer's disease and mental health disorders in the clinic and in drug development

Period when the underpinning research was undertaken: Jan 2000 - present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Trevor Robbins	Director of Research	Oct 1992 - Sep 2020
Barbara Sahakian	Professor of Clinical Neuropsychology	Oct 2002 - Sep 2019

Period when the claimed impact occurred: Aug 2013 - present

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Treatment of cognitive deficits in Alzheimer's disease and other mental health disorders has long been a major unmet clinical need. The Cambridge Neuropsychological Test Automated Battery (CANTAB) underpinned by research at the University of Cambridge was invented to bridge a translational gap between basic neuroscience and classical neuropsychological assessment. The CANTAB Paired Associates Learning (PAL) test was shown to predict a subsequent diagnosis of Alzheimer's disease, enabling earlier treatment with potential pharmaceutical treatments for dementia, thereby optimizing their impact. Since August 2013 CANTAB together with the more flexible developments of CANTAB Mobile and CANTAB connect have been used in 33,803 cognitive assessments in primary and private health care, and in 261 clinical trials. Its impacts have improved patient management, contributed to pharmaceutical practice and generated substantial revenue and commercial opportunities worldwide. It is now available in almost 50 languages and has been used in over 100 countries.

2. Underpinning research

Alzheimer's disease and related dementias are not only devastating to those affected but are widely recognised to provide major caregiver and economic burden (GBP26 billion p.a. in UK; Dementia UK Report 2014, Alzheimer's Society). Early detection has been shown to optimize the impact of many potential pharmaceutical treatments for dementia. Studies with CANTAB have shown that performance on certain forms of memory test, in addition to genetic, neuroimaging and biochemical biomarkers, is sensitive to detecting Mild Cognitive Impairment as a precursor to Alzheimer's disease.

Validation work and development of CANTAB

Original findings from Cambridge University-led studies created and validated the Paired Associates Learning (PAL) test in terms of basic psychometric, neuropsychological, neuroimaging and neuropharmacological assessment. PAL was shown to predict probable Alzheimer's disease 32 months before formal diagnosis in patients with subjective memory complaints [1,2]. Further studies confirmed that the test engaged hippocampal mechanisms thought to be implicated at the early stages of Alzheimer's disease [3]. The test has also been shown by others in pharma and academia to be correlated with certain disease biomarkers, sensitive to medication with cholinergic agents, and validated in ongoing clinical trials of therapeutic agents in Alzheimer's disease and its likely prodromal state (the phase between initial appearance of symptoms and disease onset), amnestic mild cognitive disorder [4]. In 2018, an online version of PAL (later becoming CANTAB-Recruit) was developed for recruiting prodromal patients for clinical trials [5]. There has also been a growing realisation that major cognitive deficits in many other mental health disorders ranging from Parkinson's disease to depression and schizophrenia can be measured objectively by neuropsychological tests and provide possible outcome measures in clinical trials of possible therapeutic agents.

Cambridge researchers initially configured the full CANTAB test battery in 1987 and have been continually developing and applying it. The battery includes tests of other facets of cognition besides memory, including working memory, planning, cognitive flexibility, attention and inhibitory response control. In 2002 *Cambridge Cognition* was spun out with its main product being the CANTAB battery, licensed from the University of Cambridge. New developments since 2000 have included availability of the battery on other platforms including the iPad and the Web. Some of these tests are designed to parallel basic neuroscience findings in experimental animals, thus providing cross-species translational utility. Since August 2013, there have now been over 1100 publications from many different institutions internationally using the battery, including the University of Cambridge (all are listed on the Cambridge Cognition website).

Extending the use of CANTAB beyond dementia testing

Originally provided in a mobile application on a touch-sensitive iPad (CANTAB Mobile™) for use in general practitioner clinics, CANTAB has also been extended to test other cognitive and emotional domains across several platforms including online. In order to enable more secure data transfer, CANTAB-Connect was launched in 2016, developed for clinical trials. The wider utility of the CANTAB battery has been shown in studies of therapeutic agents, for example in depression [6], attention deficit hyperactivity disorder [7] and Parkinson's disease [8]. Portions of the CANTAB battery have also been used in epidemiological studies (for example the Millennium 2000/2001 Cohort) and in studies on the incidence of cognitive deficits in Parkinson's disease.

In order to extend the range of assessments in the battery to psychiatric disorders, a collaborative study with the Universities of Manchester and London (University College and King's College) devised and standardised a new computerised battery (called EMOTICOM) for assessment of emotion, motivation and social cognition [9]. The Cambridge contribution was in creating several of the tests and contributing to the development of others. Four EMOTICOM tests have been subsequently licensed to Cambridge Cognition.

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

1. *Swainson R., Hodges JR, Galton CJ, Semple J., Michael A, Dunn B.D, Iddon, J.L., **Robbins, T.W.** & Sahakian, B.J. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dementia and Geriatric Cognitive Disorders* 2001; 12: 265-280. doi: 1420-8008/01/0124-0265$17.50/0

2. *Blackwell A., **Sahakian BJ,** Vesey R, Semple J.M, **Robbins TW,** Hodges JR. Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2004; 17: 42-48. doi: 10.1159/000074081

3. *de Rover M, Pironti VA, McCabe JA, Acosta-Cabronero J, Arana FS, Morein-Zamir S, Hodges JR, **Robbins TW,** Fletcher PC, Nestor PJ, **Sahakian BJ.** Hippocampal dysfunction in patients with mild cognitive impairment: A functional neuroimaging study of a visuospatial paired associates learning task. *Neuropsychologia*. 2011; 49(7): 2060-2070. doi: 10.1016/j.neuropsychologia.2011.03.037

4. Barnett JH, Blackwell AD, **Sahakian BJ, Robbins TW**. The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research. *Curr. Top. Behav Neurosci* 2016; 28: 449-74. doi: 10.1007/7854_2015_5001.

5. *Koychev I, Lawson J, Chessell T, **Sahakian BJ.** et al Deep and frequent phenotyping study protocol: an observational study in prodromal Alzheimer's disease. *BMJ Open* 2019; 9:e024498. doi: 10.1136/bmjopen-2018-024498

6. *Kaser M, Deakin J, Michael A, Zapata C, Bansal R, Ryan D, Cormak F, Rowe J, **Sahakian BJ** Modafinil Improves episodic memory and working memory in patients with remitted depression: A double-blind, randomized, placebo-controlled study. *Biological Psychiatry: Cogn Neurosci Neuroimaging* 2017; 2:115-122. doi: 10.1016/j.bpsc.2016.11.009.

7. *Chamberlain SR, del Campo N, Dowson J, Müller U, Clark L, **Robbins TW**, **Sahakian BJ.** Atomoxetine Improved Response Inhibition in Adults with Attention Deficit/Hyperactivity Disorder. *Biological Psychiatry* 2007; 62(9): 977-984 doi: 10.1016/j.biopsych.2007.03.003

8. *Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, **Sahakian BJ, Robbins TW.** Targeting impulsivity in Parkinson's disease using atomoxetine. *Brain* 2014; 137(Pt 7): 1986-97. doi:10.1093/brain/awu117
9. *Bland AR, Roiser JP, Mehta MA, Schei T, Boland H, Campbell-Meiklejohn DK, Emsley RA, Munafo MR, Pento-Voak IS, Seara-Cardoso A, Viding E, **Sahakian BJ, Robbins TW,** Elliott R. EMOTICOM: A Neuropsychological test battery to evaluate emotion, motivation, impulsivity and social cognition. *Frontiers in Behavioral Neuroscience* 2016; 10: 25. doi.org/10.3389/fnbeh.2016.00025

Evidence of min 2* quality : *these publications have been peer reviewed; research supported by competitively won funding

Competitive funding received

1.Behavioural and Clinical Neuroscience Institute (2005-2010): MRC Centre Grant No. G1000183 and the Wellcome Trust (Strategic Award 093875/Z/ 10/Z). TWR and ET Bullmore P.I.s Total GBP 4.85 million
2. Wellcome Trust Programme grant (2005-2010) to TW Robbins, BJ Sahakian et al. (076274/Z/04/Z) GBP 1.55 million
3. Project Grant from the MRC (Lead University of Manchester 2012-2015); MR/J011894/1 (TWR and BJS, co-Is) GBP 343,290

4. Details of the impact

Facilitated by an expanding body of rigorous validation research, CANTAB's reach has been continually extending, with impacts ranging from improving health outcomes and patient management, contributions to pharmaceutical practice, to generating financial and commercial opportunities on a global scale. The rising prominence of the CANTAB battery was recognised in Prime Minister David Cameron's speech at the G8 Dementia Summit on 11 December 2013, acknowledging the "*extraordinary work of UK life sciences companies, like ..**Cambridge Cognition**,..working with others to develop new tests for Alzheimer's Disease*" [A].

Uptake of CANTAB worldwide

CANTAB tests have been approved as medical devices by various regulatory authorities. These approvals, which have been facilitated by the underpinning research described above, have enabled uptake of CANTAB tests in clinical settings and pharmaceutical practice worldwide. Both CANTAB Mobile (PAL plus) for depression screening for older adults and CANTAB-Insight (PAL, Spatial Working Memory, Matching-to-Sample cognitive assessments in adults of all ages) are CE-marked (class 1, since 2017) [B] and TGA-approved (Therapeutic Goods Administration, Australia) since 2017 [B], allowing them to be sold on the EEA and Australian markets respectively. CANTAB Mobile has additionally received FDA (Food and Drug Administration; USA) clearance since 2017 [B].

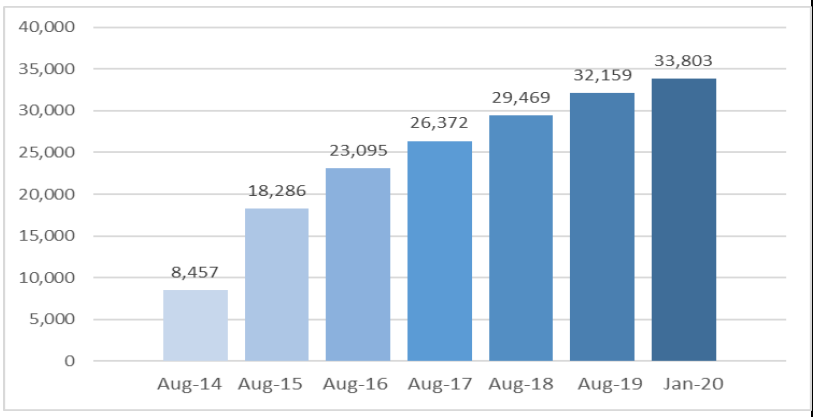

Figure 1 Cumulative CANTAB-Mobile patient assessments 2013-2020.

CANTAB-Mobile has been adopted in a large number of patient assessments, totalling 33,803 between August 2014 and January 2020 in primary and private health care [C] (Figure 1). The tool is currently available in almost 50 languages and has been used in over 100 countries (Figure 2).

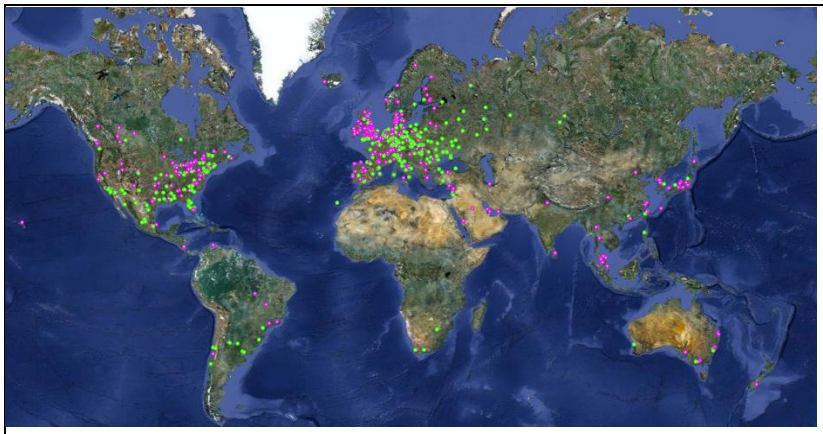

Figure 2. Map of the global locations of CANTAB pharmaceutical (green dots) and academic (pink dots) applications August 2013-present [C].

Informing patient management across the UK

CANTAB revolutionises the detection of cognitive impairment in routine clinical care by replacing traditional paper-and-pencil-based cognitive testing with a computerised "objective' mode of measurement. The introduction of CANTAB by clinical practices has translated into improved triage and diagnosis rates for patients. From a Dementia Programme manager from a Clinical Commissioning Group (CCG):"*Our dementia diagnosis rate has improved from 39% to over 46%. CANTAB Mobile has raised awareness of mild cognitive impairment in primary care and acted as a stimulus to actively encourage practices to assess patients at an early stage".* As one of a growing number of CCGs aiming to improve dementia diagnosis rates, NHS Bedfordshire CCG announced in May 2019 that it was introducing CANTAB Mobile as an early detection triage tool in a total of 50 general practices, following a successful year-long trial [D]. CANTAB Mobile "has been tested extensively throughout the NHS and was found to be 99% accurate for negative dementia diagnoses, so many patients will now avoid having to wait for a hospital appointment with a neurologist that can cause anxiety for them and their families" [D].

Working as Specialist Practitioner in Mental Health Nursing in Swansea (Wales), Clive Thomas purchased CANTAB Mobile licences for use within his Dementia Support Teams, enabling team members "*to address memory concerns with the public in a knowledgeable and professional manner [and] 'triage in' for significant memory problems whilst 'triaging out' those that needed support for other reasons*" [E]. To date, 170 people in Swansea have had a triage assessment using CANTAB Mobile. "*This success has enabled the team to offer a far greater depth of scope in terms of triage than was originally envisaged and CANTAB Mobile allows team members to signpost to the conventional memory assessment pathway with confidence and has also allowed us to explore diagnosing dementia 'closer to the patient' and in collaboration with GPs when deemed appropriate. So, from our original intention of offering early information and advice for memory changes, CANTAB Mobile has helped our team to deliver so much more, including the accurate identification and even diagnosis of non-complex dementias at Primary Care level*." [E].

Changing practice in the pharmaceutical industry

Between August 2013 and November 2020 CANTAB platforms have been used in 261 clinical trials worldwide (ClinicalTrials.gov) [F]. For example, AMGEN have adopted CANTAB in their 2017 Ebbinghaus Trial to monitor cognition function during treatment for cardiovascular disease with the human monoclonal antibody evolocumab [G]. Arising from the underpinning research on CANTAB in the MRC Deep and Frequent Phenotyping Study [5], PAL has been used in two major Phase III clinical trials using a new web-based product CANTAB Recruit, for screening of Mild Cognitive Impairment in the community [H]. Facilitating the recruitment of such early prodromal patients is now seen to be vital for testing novel preventative drug treatments. CANTAB use in clinical trials is economically significant as recruitment costs are often 33% of trial costs; under-recruitment is a major cause of trial delays costing USD8M per day [H].

Professor Sir Simon Lovestone (University of Oxford), one of the most respected clinician scientists in the field of Alzheimer's Disease, has *"found CANTAB PAL to be a sensitive test*

in the context of detecting memory problems in the elderly and in mild cognitive impairment", and considers it *"would make an excellent outcome measure in the early detection and assessment of cognitive deficits essential in trials of new agents for the treatment of early Alzheimer's disease and Mild Cognitive Impairment"* [I].

Cassava Sciences chose the CANTAB battery "because of its documented sensitivity" for their Phase 2b clinical trial of their novel therapeutic drug candidate in mild-to-moderate Alzheimer's patients. They stated that "the sensitivity afforded by CANTAB will allow smaller, faster clinical trials for this disease so urgently in need of new treatments" [J]. Greenfield BioVentures are also conducting a clinical trial using CANTAB as the primary measure of efficacy for their therapeutic candidates, due to its "superior sensitivity" [K].

During the Covid-19 pandemic, in efforts to curb COVID-19 transmission rates, the pharmaceutical industry has reduced site visits for their clinical trials and in some cases temporarily suspended patient recruitment. CANTAB Connect has enabled continuation of trials allowing patients to contribute data remotely [L].

Generating increasing revenue and developing commercial opportunities globally
CANTAB (including the PAL test) was commercialised after licensing to Cambridge Cognition Holdings plc which was listed on London Stock Exchange (AIM) in 2013. Currently employing over 70 people, Cambridge Cognition's total revenues increased by approximately 40% between 2013 and 2019, amounting to a sum of GBP39.77 million [L]. There have been over 500 CANTAB Mobile accounts set-up since January 2014 including in Germany, Greece, Sweden, the Netherlands and the USA. In 2014, Cambridge Cognition licensed four of the EMOTICOM tests of emotion and social cognition via Cambridge Enterprise for the University of Cambridge [L].

After announcing a partnership with a major pharmaceutical company to provide cognitive testing for neurological patients in India [L], Cambridge Cognition announced its expansion to the Chinese market following the development of CANTAB task variants in the key spoken (Cantonese and Mandarin) and written (Chinese simplified) languages in 2019 [L], thus furthering global reach and commercial opportunities.

5. Sources to corroborate the impact

A. G8 Dementia Summit: Prime Minister's speech. 11 December 2013, page 2
B. Regulatory approvals: (i) FDA/CE Certified Apps Directory: https://apps.healthskouts.com/. page 3 (ii) TGA approval from Australian government (iii) CANTAB Mobile awarded FDA clearance 13 January 2017
C. **Confidentia**l correspondence dated 02/10/2019 and 14/01/2020 from Cambridge Cognition
D. (i) Cambridge Cognition website Cantab Mobile product page (ii) NHS Bedfordshire CCG rolls out CANTAB Mobile to 50 practices following successful pilot study. (iii) Bedfordshire CCG adopts new technology to improve dementia diagnosis
E. Testimonial from Specialist Practitioner in Mental Health Nursing in Swansea, Wales. page 2
F. Clinical Trials.gov search results 01/08/2013 – 11/12/2021 *(Dates in US format in doc).*
G. CANTAB assessments used in EBBINGHAUS cognitive function trial for Amgen's evolocumab.
H. CANTAB Recruit software to be used in two major Phase III drug trials page 1
I. Testimonial from Janssen (subsidiary of Johnson & Johnson)
J. Testimonial from Cassava Sciences
K. Testimonial from Greenfield BioVentures
L. Cambridge Cognition: (i) Cambridge Cognition wins increasing numbers of virtual clinical trials during COVID-19 May 2020 (ii) Reports & Accounts (2013- 2019) (iii) Emoticom licensing (iv) Cambridge Cognition: First Partnership in India and New Product Launch. (v) Cambridge Cognition expands further into Chinese market.