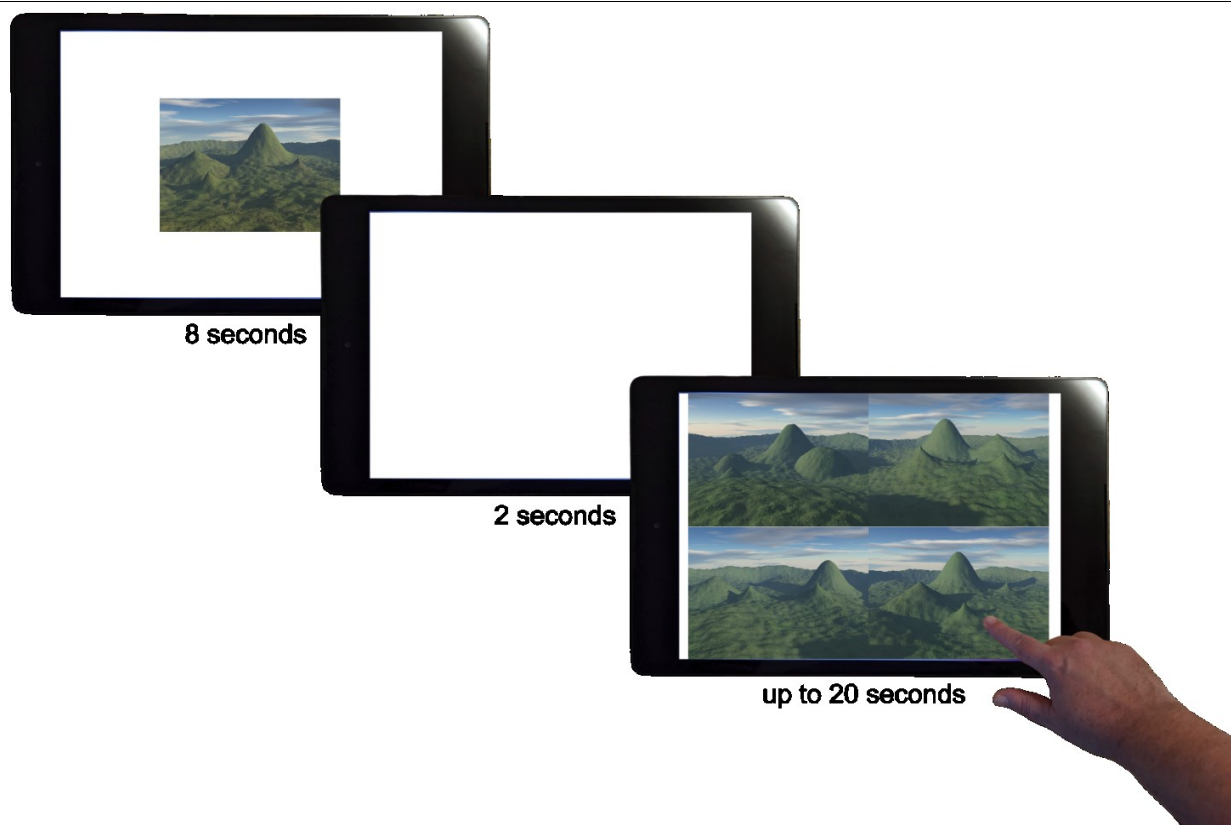


<b>Institution:</b> University of York		
<b>Unit of Assessment:</b> 4 - Psychology, Psychiatry and Neuroscience		
<b>Title of case study:</b> The Four Mountains Test: Assessing Hippocampal Function in Health and Disease with Applications to Drug Evaluation and Space Medicine		
<b>Period when the underpinning research was undertaken:</b> 2007 – 2016		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Tom Hartley	Senior Lecturer in Psychology	2005 – present
<b>Period when the claimed impact occurred:</b> 2016 – 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<b>1. Summary of the impact</b> (indicative maximum 100 words) <p>The Four Mountains Test is a neuropsychological assessment that can detect the earliest stages of Alzheimer's Disease (AD) by measuring a form of spatial memory. It identifies individuals who are most likely to go on to develop AD before a clear-cut medical diagnosis is possible. Unlike many other memory tests, it does not depend on knowledge of a particular language or culture, and can thus be deployed internationally. The beneficiaries are clinical trial operators and sponsors, including global pharmaceutical companies, clinical research organisations and charities. The test's sensitivity to preclinical changes, its quick and easy administration format and its cross-cultural suitability are key features contributing to improved trial efficiency and effectiveness.</p> <p>The Four Mountains Test is also useful in determining whether cognitive performance is affected by environmental factors and training in safety-critical settings. It has been adopted in a series of space agency sponsored studies to quantify the effects of long-term spaceflight on astronauts' cognition, ultimately being selected for use aboard the International Space Station. Here the beneficiaries are the international space agencies and astronauts.</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words) <p>Extensive research on the neuroscience of spatial cognition and memory has identified the hippocampus as playing a crucial role in representing the spatial structure of the environment (3.1). The hippocampus is one of the first brain regions to be affected in AD, and changes in its function may therefore serve as an early indicator of the disease. Hartley, in collaboration with colleagues at University College London (5.1), devised the Four Mountains Test in order to assess a specific form of spatial memory that is dependent on hippocampal functioning. The test requires participants to recognise places using carefully constructed computer-generated landscapes to ensure that successful performance depends on memory for the layout of the environment (which relies on the hippocampus), and not merely visual memory for isolated features, such as objects and landmarks (which can be supported by other parts of the brain). In the test, the participant views a landscape for 8 seconds and, after a 2 second pause, has to choose which of four options represents the previously viewed landscape as seen from a different perspective (see Figure 1).</p>		



*Figure 1. Schematic showing an example item in tablet-based version of the Four Mountains Test. The task is to identify the same place, when seen from a different viewpoint. This type of “allocentric” spatial memory depends on the hippocampal formation, a brain region which is damaged in the earliest stages of Alzheimer’s Disease.*

An initial study demonstrated that patients with damage to the hippocampus had a specific impairment in performance on the Four Mountains Test (3.2). Patients with hippocampal damage performed significantly worse than participants in both the young (average age 28) and old (average age 65) control groups. In contrast, the patients did not differ from the control groups in their performance on a task of non-spatial memory that was not dependent on hippocampal functioning. These findings highlight how the Four Mountains Test is able to identify hippocampal damage using a behavioural procedure that is quick and easy to administer.

Our more recent research has applied the Four Mountains Test to patients with early-stage AD, Mild-Cognitive Impairment (which often leads to AD), and other forms of dementia (fronto-temporal dementia/semantic dementia) that do not typically involve the hippocampus in their earliest stages. This research showed that Four Mountains Test scores were specifically impaired in the diseases that involve early hippocampal pathology (AD and Mild-Cognitive Impairment), distinguishing patients with these conditions from both healthy controls and those with other forms of dementia (3.3). Scores on the Four Mountains Test can also identify individuals with AD pathology at the preclinical stage, typically several years before an unambiguous diagnosis can be made. Scores were impaired in Mild-Cognitive Impairment patients with biomarkers indicative of AD pathology (who later progressed to AD) relative to those who did not have AD pathology biomarkers (3.4). Together, these references show the utility of using the Four Mountains Test as a baseline/screening measure to identify at an early stage individuals at an increased risk of developing AD.

In our research involving healthy participants, we have combined administration of the Four Mountains Test with MRI brain scanning (3.5). This study revealed a positive association between performance on the Four Mountains Test and the volume of the hippocampus; performance on the test improved as hippocampal volume increased. These results indicate that

performance on the Four Mountains Test can be used to index changes over time in brain structure and functioning that may occur in healthy individuals who are working in challenging environments (e.g., physically confined spaces, conditions of weightlessness, exposure to elevated CO<sub>2</sub> concentrations).

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

All of the references below are published in peer-reviewed journals.

**3.1. Hartley, T.,** Lever, C., Burgess, N., & O'Keefe, J. (2014). Space in the brain: how the hippocampal formation supports spatial cognition. *Phil Trans Roy Soc B*. 369 (1635). DOI: [10.1098/rstb.2012.0510](https://doi.org/10.1098/rstb.2012.0510).

**3.2. Hartley, T.,** Bird, C. M., Chan, D., Cipolotti, L., Husain, M., Vargha-Khadem, F., & Burgess, N. (2007). The hippocampus is required for short-term topographical memory in humans. *Hippocampus*, 17, 34-48. DOI: [10.1002/hipo.20240](https://doi.org/10.1002/hipo.20240)

**3.3. Bird, C. M., Chan, D., Hartley, T.,** Pijnenburg, Y. A., Rossor, M. N., & Burgess, N. (2010). Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus*, 20, 1154-1169. DOI: [10.1002/hipo.20715](https://doi.org/10.1002/hipo.20715).

**3.4. Chan, D., Gallaher, L. M., Moodley, K., Minati, L., Burgess, N., & Hartley, T.** (2016). The 4 Mountains Test: A Short Test of Spatial Memory with High Sensitivity for the Diagnosis of Pre-dementia Alzheimer's Disease. *J. Vis. Exp.* (116), e54454. DOI: [10.3791/54454](https://doi.org/10.3791/54454).

**3.5. Hartley, T., & Harlow, R.** (2012). An association between human hippocampal volume and topographical memory in healthy young adults. *Frontiers in Human Neuroscience*, 6:338. DOI: [10.3389/fnhum.2012.00338](https://doi.org/10.3389/fnhum.2012.00338)

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

The Four Mountains Test is a quick-to-administer behavioural task that can be used to assess aspects of brain functioning associated with preclinical signs of AD or adverse environmental conditions. Its use circumvents the need for expensive and invasive procedures (e.g., brain imaging, sampling cerebrospinal fluid), meaning that the Four Mountains Test is not only extremely cost-effective, but vastly increases the potential reach of hippocampal assessment. Extensive translational work at York has been key to ensuring the utility of the Four Mountains Tests in a wide range of settings. Hartley has developed tablet-based versions of the Four Mountains Test (see [fourmountains.org.uk](http://fourmountains.org.uk)), meaning that it can be administered in any location where a tablet can be used. Hartley has also worked collaboratively with end-users of this research to create bespoke versions of the Four Mountains Test that are tailored to their specific requirements.

#### Applications to Alzheimer's Disease

The Four Mountains Test has been adopted as a cognitive outcome measure for large scale clinical trials assessing the viability of new treatments for AD, providing a vital tool in the development and evaluation of effective therapeutic approaches. The primary beneficiaries are drug companies, clinical research organisations and charities who organise, administer and sponsor such trials. They opt for the Four Mountains Test due to its sensitivity and because it can efficiently identify eligible participants—those whose performance matches the profile of problematic functioning in those brain regions affected in the early stages of AD.

The Innovative Medicines Initiative (IMI) European Prevention of Alzheimer's Dementia (EPAD) consortium is a unique pan-European partnership involving government, pharmaceutical companies (including Janssen, Eli Lilly, Merck Sharp & Dohme, Novartis and Pfizer), Clinical Research Organisations (such as IQVia), charities and non-profit making medical research organisations (e.g., university medical schools). Because the AD disease process takes decades to produce symptoms, the EPAD project has adopted a new and unique "platform trial" structure whereby a large cohort of participants is recruited before they meet formal diagnostic criteria for AD, with samples then selected for parallel drug trials. Recruitment to the cohort stage ran between May 2016 and June 2020. The Four Mountains Test was selected for inclusion in the EPAD protocol and it has been administered to all 2,094 participants. Testing took place at 26 clinics across Europe, including sites in the UK, France, Spain, the Netherlands, Sweden, Switzerland and Italy. To accommodate the use of the test, Hartley worked closely with

the EPAD consortium, their contractors, collaborators and legal team to develop and license a trial-compliant version of the test which has been translated into multiple European languages. “We selected the Four Mountains Test because ... review of the literature highlighted the test’s sensitivity to cognitive changes that co-occur with the first biomarker changes seen in pre-clinical Alzheimer’s Disease. Measures of this sort are extremely important for trial efficiency as they help identify a homogenous preclinical AD population for investigation thereby reducing screen failures as well as identifying individuals that may benefit from pharmacological intervention. The cross-cultural suitability of the test is also a key advantage for international trials, that is, many other relevant cognitive tests often depend on knowledge of a specific language or culture, and these can be difficult to deploy internationally. Across countries and study sites our experience is that the Four Mountains Test is quick and easy to administer at scale.” Pharmaceutical executive and Co-Chair IMI-EPAD Scientific Advisory Group for Clinical and Cognitive Outcomes (5.2).

In addition to being employed as a screening tool, the Four Mountains Test has been used to assess cognitive outcomes of clinical trials focusing on AD, following a recommendation from the EPAD consortium (5.3, p. 190 and 192). The Four Mountains Test has also been adopted in a trial sponsored by the Australian Alzheimer’s Research Foundation to investigate the effect of testosterone therapy on the treatment of prodromal AD in 200 patients. Again, Hartley worked with the trial organisers to provide a specialised tablet-based implementation of the test.

“We chose the Four Mountains Test for inclusion in our protocol for three main reasons: first, because it measures topographical memory - a different domain of cognitive competence to the more typical verbal memory tests, but one that is believed to be strongly dependent on the hippocampus, the primary site for memory and the primary target of neuropathological changes associated with Alzheimer’s disease. Second, because of research showing that it is sensitive and selective to the neuropathological changes in the early stages of Alzheimer’s disease and finally, because it is easy to deliver in a clinical setting, taking less than 15 minutes.” Director of Research, Australian Alzheimer’s Research Foundation (5.4).

The Four Mountains Test was also adopted for use in the PREVENT study, sponsored by the Alzheimer’s Association and Alzheimer’s Society. This is a longitudinal prospective cohort study which recruits volunteers (currently 700) in early middle age (40-60) with varying degrees of genetic and familial risk for AD, but no current diagnosis. Early results from this ongoing study show that the Four Mountains Test is the best predictor of genetic/familial risk out of the wide range of cognitive tests administered.

“The 4MT [Four Mountains Test] was also found to be a better predictor of risk than tests of episodic memory, verbal fluency, or executive functioning. The results suggest that allocentric rather than egocentric processing may be a potential indicator of risk for late-onset AD, consistent with the hypothesis that the earliest cognitive changes in AD are driven by tau-related degeneration in the medial temporal lobe [where the hippocampus is located] rather than amyloid-only deposition in the medial parietal lobe.” (5.5, abstract).

Overall, as a baseline and outcome measure for clinical trials, the Four Mountains Test has been selected to identify participants who may benefit from pharmacological intervention and to provide an indication of the efficacy of treatments in improving or slowing the decline of key cognitive capacities. The impact of the test is in improving trial efficiency and contributing to the evaluation of these treatments.

### **Application to Space Medicine**

In long duration spaceflight, such as missions aboard the international space station (ISS), astronauts are required to operate in an extremely confined environment, with low gravity and sometimes elevated CO<sub>2</sub> levels, all of which can have undesirable effects on cognition. The hippocampus is particularly vulnerable to these effects. Space agencies such as the European Space Agency (ESA), National Aeronautics and Space Agency (NASA) and the German Aerospace Center (DLR) thus carry out medical research with astronauts to optimise their health

and psychological function during extended missions. To meet the need for psychological testing of hippocampal function in this context, the Four Mountains Test has been used in a sequence of eight space agency sponsored projects. This culminated in the Four Mountains Test being selected for the ISS-based HypoCampus and Spatial Cognition Integrated One-Year Mission projects, with Hartley developing a new version of the test that met ESA and NASA technical requirements and included longitudinal test sets to allow for repeat testing over time. Prior to launch, astronauts take the test along with other measures of brain and cognitive function, and they are followed up at regular intervals during the flight and on their return to earth.

“The space agencies are collectively interested in the marked cognitive and neural changes that occur during extended spaceflight, because they have important implications for the health and mental capacity of astronauts involved in both current ISS missions and the long-duration flights that will be required for future missions involving human exploration beyond earth orbit. ... We selected the Four Mountains Test because it directly targets hippocampal function, measures topographical memory (a cognitive function that plays an important role in human space exploration), because it is backed by solid peer-reviewed research in healthy people and patients, and because it is particularly straightforward and quick to administer during the mission itself.” Project Lead, HypoCampus project (5.6).

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

- 5.1. Joint Invention Agreement (University of York, UCL).
- 5.2. Testimonial from Co-Chair Scientific Advisory Group, Clinical and Cognitive Outcomes, IMI-EPAD.
- 5.3. Ritchie, K., Ropacki, M., Albala, B., Harrison, J., Kaye, J., Kramer, J., Randolph, C. & Ritchie, C. W. (2017). Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project. *Alzheimer's & Dementia*, 13(2), 186-195.
- 5.4. Testimonial from Director of Research, Australian Alzheimer's Research Foundation and Director of the Centre for Healthy Ageing.
- 5.5. Ritchie, K., Carrière, I., Howett, D., Su, L., Hornberger, M., O'Brien, J. T., Ritchie, C.W. & Chan, D. (2018). Allocentric and egocentric spatial processing in middle-aged adults at high risk of late-onset Alzheimer's disease: the PREVENT dementia study. *Journal of Alzheimer's Disease*, 65(3), 885-896.
- 5.6. Testimonial from HypoCampus Project Lead on Space Medicine projects with space agencies ESA, NASA and DLR.