CHIEF SCIENTIST OFFICE

Clinical translation of an automated brain MRI health index to predict dementia

AIMS

Dementia is a global public health issue with huge socio-economic burden (see here for UK-specific data: https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers), which is only growing as the global population ages. It is challenging to predict who is most at risk of cognitive decline, but we know that most dementia exhibits mixed pathology, some of which is accessible through magnetic resonance imaging (MRI).The Brain Health Index (BHI) is an automated way to combined different types of structural MRI scan, enabling different information to be gained from each. When establishing such numerical measures, it is important to establish baselines in healthy populations, and then understand how neurodegenerative change affects these baseline values.

The project had three key aims:
1. Determine normative ranges for BHI.
2. Validate BHI in a research cohort which is rich in information about each participants' health and life.
3. Assess the ability of BHI to predict dementia using routine clinical brain MRI.

KEY FINDINGS

1a) Normative values were determined for male and female individuals aged 48 – 77 years old.

1b) BHI scores were significantly higher in female than male participants.

1c) Several known risk factors for brain health result in significantly lower BHI scores.

2a) BHI predicts cognition cross-sectionally when considering three cognitive tests – the Mini Mental State Examination (MMSE), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Four Mountains Test (4MT) – in a cohort of 1,496 participants.

2b) BHI scores do not change significantly in a cohort of 197 participants over a 2-year time period.

3a) Scans for 978 individuals from the clinical routine were made available through the NHS SafeHaven.

3b) We identified issues around naming conventions, mislabelling and scan quality. However, we have worked with others to find solutions and anticipate finishing the case-control experiment and will feedback our experiences to help future researchers accessing SafeHaven imaging resource.

WHAT DID THE STUDY INVOLVE?

The BHI is an approach to quantifying brain integrity through using different types of MRI scan in combination, thereby providing additional information than when using a single brain MRI to measure brain health. The BHI study comprised three work packages. The first built upon prior work which developed the original computation of the BHI, by establishing normative reference values in older age using the UK Biobank cohort. The second used the European Prevention of Alzheimer's Dementia (EPAD) cohort to further validate the utility of the BHI and understand its relationship to a selection of cognitive tests. The final work package assessed the possible utility of the BHI when using clinically-acquired MRI scans.

Our project was informed by feedback from various stakeholders. Focus groups with stroke survivors and others at risk of cognitive problems, identified prediction of decline as a research priority.

Through SINAPSE (Scottish Imaging Network: A Platform for Scientific Excellence) – a group of seven Scottish universities and NHS and industry partners, which focuses on different types of medical imaging and developing the new generation of researchers who use them - and other groups, clinicians told us that biomarkers should be feasible with imaging facilities available in the NHS.

The disruption of the viral pandemic precluded our plans for in-person meetings in the early stages of the project. Through presenting the work at meetings with people living with dementia, we have received useful feedback. Groups of people with lived experience have previously fed back to us that they prefer to talk about multiple projects at one meeting, rather than have to meet very regularly, hence why our PPI has been carried out at such events.

For clinicians and the research community, we had a final meeting themed around the practical application of imaging biomarkers, in February 2024 (part funded by ARUK). This meeting proved very successful, bringing together various people involved in dementia research. The conversation had there is informing a big study led by Professor William Whiteley in Edinburgh. The Global Alzheimer's Platform is also considering including BHI in their Bio-Hermes 2 study, which would again further the utility of, and access to, BHI.

Study findings have been presented at conferences attended by clinicians, researchers, and people living with dementia, and their feedback received.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

In our work within the UK Biobank cohort, we established normative values of the BHI for a cohort aged 48 – 77 years old. BHI scores range from 0 to 1 (or 0-100% of 'healthy' tissue [as defined by the BHI], if you prefer to think of it like that). For males aged 48, the average score was 0.728, and for females of the same age was 0.72. At age 77, males had an average score of 0.622, and females of 0.646. This provides a useful reference point for future clinical research. The curves are shown in the figure to the left below. From an MRI perspective, the normative values create a map across the brain which varies in intensity throughout (this same 0-100 idea). We average the values across this map to determine the BHI scores above. The maps can also show regions in the brain with less coverage, which may reflect structural differences between people, whether just due to normal human variation, or dementia. These maps are shown in the figure to the right, below (these are maps from people who are considered to be in the 'healthy' group).

Relationships between several known brain health risk factors (these are all related to the cardiovascular system, and include conditions like diabetes, but also metrics of health like weight and BMI) and BHI scores were established, showing the impact of these risk factors on the brain in older age. Cross-sectionally, the BHI has shown significant positive relationships with the MMSE, RBANS, and 4MT cognitive tests – which assess different aspects of cognition - further validating this approach in the assessment of brain health. However, longitudinal scan availability significantly reduced the cohort from 1,496 subjects to just 197. As such, elucidation of the longitudinal behaviour of the BHI and its relationship to these cognitive tests over time required additional subjects for robust modelling.

NHS SafeHaven work remains ongoing due to issues with naming conventions, mislabelling, and scan qualities. However, we have worked with others to resolve these and will share our findings once complete. The work on the BHI has added to the field by providing a resource that will be freely accessible by other researchers, who can then apply this to other conditions which affect the brain and its health. With a dementia focus, it is also being taken forward by others to investigate different possible risk factors that were not looked at in the current work, due to the limitations of the cohorts we used.

Below: Normative BHI score curves for male and female subjects.
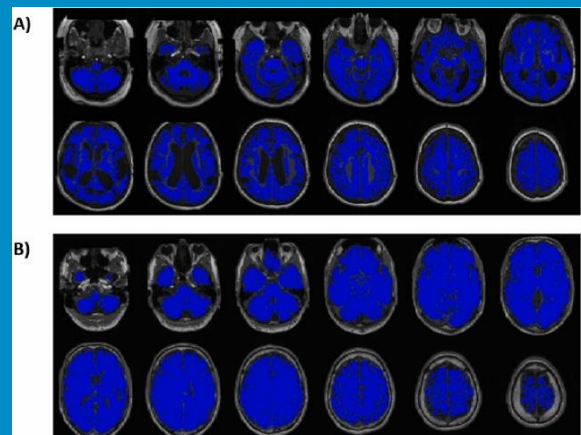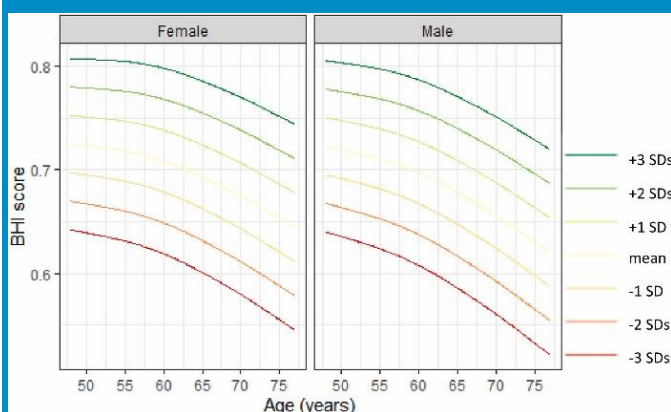
Above: Example BHI maps of A) a 74-year-old male (score = 0.524) and B) a 50-year-old male (score = 0.74).

WHAT IMPACT COULD THE FINDINGS HAVE?

Publication of normative ranges in an open-access journal means that they can be used by anyone. We have been approached by other researchers looking at different neurological conditions and aspects of brain health who would like to use the BHI and interpret using these norms. The work carried out in EPAD was necessary to further validate the BHI, which had not previously been validated in a 'standard' memory clinic population, nor compared with our chosen test batteries. Investigating the utility of BHI within clinically-acquired scans has also fuelled discussion around NHS scan quality for research repurposing. The February 2024 meeting has also directly fed into other studies which are currently ongoing or in the pipeline.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Thus far, two studies have been published – '*Normative values of the Brain Health Index in UK Biobank',* and *'Validation of the brain health index in the European Prevention of Alzheimer's Dementia cohort'*. The work carried out using the NHS SafeHaven cohort will provide a basis for ongoing dialogue around the utility of clinically-acquired scans for retrospective research use. The research findings have been presented at several national conferences – DPUK Translation 2023, UK Dementia Research Institute Vascular ECR meeting, the Scottish Dementia Research Consortium (2022 and 2023), and the Alzheimer Research UK Scotland meeting. The work carried out as part of this project has informed an array of subsequent studies, including the work of Dr Watt's Masters in Public Health student, and the BHI will soon be available to anyone who would like to use it.

CONCLUSION

BHI is a valid approach to quantifying brain integrity, and through the work we have presented it is now available for other researchers to utilise it as a tool for their own interpretation. The application of BHI to historical NHS scans was not successful at scale but this does not preclude its use prospectively. Whilst this is disappointing, it is still important that we can show that it is not yet useful for use in the NHS.

Beyond the study itself, this project has also developed Dr Jodi Watt as a researcher, helping to develop their skills as a dementia researcher who came from an imaging space. Jodi is now working on another study which aims to find a drug for repurposing, which may be useful for people living with dementia.

RESEARCH TEAM & CONTACT

Professor Terry Quinn and Dr Jodi Watt

Academic Geriatric Medicine, New Lister Building, Glasgow Royal Infirmary, Glasgow, G4 0SF.

terry.quinn@glasgow.ac.uk
jodi.watt@glasgow.ac.uk

Prof. Quinn: 0141 956 0519

Additional Information
The commencement of the project was delayed due to issues around the coronavirus pandemic, and problems with staffing.