Final Project Report – Cognitive Assessment

Introduction

The principal aim of work package 10 (WP10) was to repurpose the UK Biobank cohort for cognitive ageing and dementia-relevant research. Its members including senior academics working in the fields of cognitive ageing, dementia epidemiology, and psychometrics, were in a strong position to lead on this initiative. A key objective was to develop and oversee the implementation of an enhanced UK Biobank cognitive assessment (described in *Section I*) that can sensitively measure changes in cognitive function in this population over time. This enhancement was implemented in Q4 2016 and, to date, approximately 25,000 UK Biobank participants have completed the enhanced cognitive assessment. The intention of UK Biobank was to conduct repeat cognitive testing using this enhanced battery to a subsample of those participating in repeat imaging assessments, and *Section II* describes how WP10 has supported UK Biobank in this endeavour.

An important consideration of longitudinal research into dementia is the need to track cognitive performance over time, for as long as possible, particularly of participants experiencing rapid cognitive decline who are more likely to withdraw their participation. Therefore, WP10 made recommendations to UK Biobank regarding the recruitment of informants such as carers and family members (detailed in *Section III*), and alternative recontact strategies for assessing high risk individuals for cognitive decline (see *Section IV*), to alleviate attrition bias from the study.

For researchers using cognitive data released by UK Biobank, WP10 produced reports on the psychometric properties of the individual tests. To achieve this, work package members CF-R and IJD, based in Edinburgh, conducted a validation study by recruiting and testing 160 adults on the UK Biobank tests alongside well-standardised psychometric tests of equivalent cognitive domains. This study was completed at the end of 2018 and is now submitted for publication – details of the study including the main results are reported in *Section V*.

WP10 was also commissioned to do work in identifying dementia syndromes from cognitive test scores across all of DPUK's population cohort studies. This work began with an analysis of UK Biobank baseline cognitive data in association with incident dementia recorded in hospital and mortality records, which has recently been accepted for publication in *Alzheimer's and Dementia* (see Section VI). Plans to extend these analyses to other population cohorts were prohibited by the lack of electronic health records available through the DPUK data portal during this project's timeline. However, groundwork to assess the availability of cognitive data across these studies was used in the compilation of a comprehensive Cognitive Testing directory of all DPUK's cohorts, for researchers to access for free.

Following a request from the MRC Oversight Board in 2019, WP10 delivered content for a cognitive testing resource for the DPUK website. This is a brief resource that points researchers less familiar with cognitive testing to more-detailed, already-available resources on cognitive testing. It includes the cognitive testing directory, and a report on the test characteristics of the UK Biobank cognitive assessment will also be made available through this resource. See:
https://www.dementiasplatform.uk/for-researchers/get-ahead-with-cognitive-test-data-1

Section I: Enhancement of UK Biobank Cognitive Test Battery

Rationale

A major focus of the work package in supporting UK Biobank to become a dedicated dementia research resource, was to develop an enhanced UK Biobank cognitive assessment battery. At the UK Biobank baseline assessment participants completed a bespoke and brief five-minute battery of cognitive function, including tests of verbal-numerical ('fluid') reasoning, prospective memory, visual

episodic memory, working memory, and processing speed. Whereas these tests were designed to assess those cognitive domains affected by healthy and pathological ageing, they were not comprehensive enough (i.e. no tests of executive function), they were very brief, and some were considered to have modest stability (Lyall et al, 2016; doi: 10.1371/journal.pone.0154222).

Content of the battery

The enhanced battery developed by members of WP10 focused on assessing a wider range of cognitive abilities that are known to change with age and other neurodegenerative conditions, such as processing speed, verbal declarative memory, non-verbal reasoning, and executive functioning. The additional inclusion of a measure of crystallised intelligence (vocabulary) was for estimating prior/pre-morbid cognitive level, something which is important when trying to identify cognitive decline. The final list of tests included:

1. **Trails A and B** – *executive function*

Description: In the first part of this test, the participant must click on all the numbers on the screen in sequential order. In the second part, the participant must switch between the numbers and letters on the screen (e.g., 1, A, 2, B). The participant is to work as quickly and as accurately as possible. This test was originally developed for the UK Biobank web-based assessment.

2. Digit-symbol substitution test – *processing speed*

Digit-symbol pairs are presented to the participant on the screen. During the task, the participant is presented with a symbol with empty boxes below. The task is to select which number corresponds with the symbol. The participant must work as quickly and as accurately as possible. This test was originally developed for the UK Biobank web-based assessment.

3. NIH Toolbox picture vocabulary test – *premorbid cognitive level*

A word and four pictures are presented on the screen. The participant must select the picture that is closest in meaning to the target word. The words presented range in difficulty easy to difficult. This test was introduced as part of the cognitive enhancement and was implemented for the first time at the UK Biobank imaging study.

4. Matrices – COGNITO – *non-verbal fluid reasoning*

This computerised test presented participants with a logically-constructed design that is missing a piece. The participant must choose, from different alternatives, the piece that completes the design. The items start easy and become more difficult. This test was introduced as part of the cognitive enhancement and was implemented for the first time at the UK Biobank imaging study.

5. Paired associate learning – *verbal declarative memory*

Twelve pairs of words are presented on a screen. The participant is instructed to try to remember these word pairs. The words remain on screen for 30 seconds. After a ~5-minute delay, the participant is given one of the words from the word-pair. They must decide, from a list of alternatives, which word was paired with the presented word. This test was introduced as part of the cognitive enhancement and was implemented for the first time at the UK Biobank imaging study.

6. One-touch Tower of London test – *executive function*

In this computerised task the participant is to indicate how many moves it would take to move pegs on a board from the first state displayed, to the second state displayed following a set of rules. The participant is to click on the number of moves they think it would take, without actually moving any of the pegs. This test was introduced as part of the cognitive enhancement and was implemented for the first time at the UK Biobank imaging study.

Implementation

This cognitive enhancement was implemented into the UK Biobank imaging study in Q4 2016. It is anticipated that approximately 90,000 UK Biobank participants will complete the enhanced cognitive tests, and to date data are available to researchers on approximately 25,000.

Section II: Supporting the provision of repeat cognitive assessment at imaging

UK Biobank originally planned to conduct repeat imaging on 10,000 of the UK Biobank participants at 24 months follow-up. WP10 advised UK Biobank that the enhanced cognitive test battery should be administered at the repeat imaging assessment and that the repeat sample should be individuals who had already completed the enhanced cognitive assessment at their first imaging visit. WP10 members attended the imaging centre in Southport to observe participants undergoing the touchscreen cognitive assessment and make recommendations for any required changes in advance of repeat testing. UK Biobank had concerns about the length of the enhanced cognitive assessment (approx. 30 mins). Using data from the first participants to complete the enhanced cognitive test battery, WP10 prepared a report on the psychometric properties of the enhanced cognitive assessment (sent to UK Biobank on 09 2017). This report was used to advise UK Biobank which cognitive tests should be retained, and which tests WP10 thought should be removed. Following this advice, UK Biobank planned to remove two of the cognitive tests from the enhancement. WP10 plan to make available to researchers the report on the psychometrics of the enhanced UK Biobank cognitive assessment. To date UK Biobank have not instigated repeat imaging assessments; however, they plan to do so in the future.

Section III: Recruitment of informants

Informants (carers, family members), can be highly valuable sources of information in situations where participants are suffering significant cognitive decline and may be lost to cognitive follow-up. Therefore, WP10 and others requested that UK Biobank recruit informants as part of their follow-up study protocol. WP10 prepared standard operating procedures for the informant measure of cognitive functioning (IQCODE) and sent this to UK Biobank (09 2016) with recommendations for its administration to participants' informants. UK Biobank agreed in principle to this, although it is understood that this is not a priority for the UK Biobank cohort at present.

Section IV: Contact and re-contact strategies

This final objective of WP10 was to develop cost-effective contact and re-contact strategies. WP10's original plan was to identify UK Biobank participants who may be at risk of more severe cognitive decline and contact these individuals for more detailed cognitive assessments via telephone. Early on, this was discussed with UK Biobank and declared not possible because UK Biobank have a policy in which participants cannot be identified and selected based on their test scores. In addition, telephone testing was declared too costly. WP10 have, however, provided UK Biobank with more general advice and support regarding cognitive testing, and will continue to do so until the end of this work package.

Section V: Calibration and psychometrics of cognitive assessment

The programme aimed to describe and explore some important psychometric properties of the available cognitive data in UK Biobank, in two ways:

The first component involved evaluating the comparability of scores between testing modes (web vs. phone), testing environments (home vs. imaging assessment), and between informant and participant sources. Telephone cognitive testing was quickly judged non-feasible by UK Biobank, because of the cost. Furthermore, due to the lack of informant recruitment by UK Biobank, the work package was unable to make a comparison between data collected from informant and participant sources. Therefore, WP10 have been unable to carry out these calibration analyses owing to UK Biobank's decisions.

The second component of the calibration studies involved validation of the enhanced cognitive test battery (this includes all baseline UK Biobank tests) against well-known and well-validated cognitive tests. The rest of this section provides details of that validation study. There were lengthy delays, at the UK Biobank end, in getting a stand-alone version of the UK Biobank cognitive test battery. WP10 were eventually given a working version of the UK Biobank cognitive assessment in March 2018 and data collection for the validation study began the same month. Participant recruitment ended on Friday 2nd November 2018 and a total of 160 participants were recruited. A sub-sample of 52 participants returned for a second visit to measure the test-retest reliability of the UK Biobank cognitive tests. WP10 analysed these data and the results have now been submitted for peer-review publication, and are available as a preprint on *Medrxiv.org:* https://doi.org/10.1101/19002204
Mostly, the reliability and validity of the UK Biobank tests were modest to good. A summary of the main findings are as follows:
Most tests showed modest to good concurrent validity when compared to well-validated tests thought to measure the same cognitive domains. Concurrent validity of the UK Biobank Picture Vocabulary and Trail Making tests were especially good.
A reasonably good measure of general cognitive ability can be created using all of the UK Biobank cognitive tests, as well as using only the five baseline UK Biobank cognitive tests. These measures of general cognitive ability created using UK Biobank tests correlate highly with a measure of general cognitive ability created using more standard cognitive tests (r = 0.79 for g created with UKB baseline tests; r = 0.83 for g created with all UKB tests).
Most UK Biobank tests showed adequate-to-good short-term (4 week) test-retest reliability. Test-retest reliability was especially good for UKB Picture Vocabulary and Trail Making part B.

Section VI: Identification of dementia syndromes

WP10 aimed to investigate the feasibility of cognitive testing strategies for distinguishing between cognitive syndromes such as AD, frontotemporal lobar degeneration and dementia with Lewy bodies in population studies. The first part of this work involved an analysis of UK Biobank baseline cognitive data in association with incident dementia during 8-years of follow-up, which has been accepted for publication in the journal *Alzheimer's and Dementia* (see publications list). The second part involved a comprehensive inventory of all cognitive tests across DPUK's cohort studies, which has been compiled into a Cognitive Test Directory, available via DPUK's website. However, within the timeline of this project diagnostic healthcare data were not available via the DPUK data portal to conduct further analyses of other population cohort studies.

UK Biobank study

WP10 analysed baseline cognitive test performance in UK Biobank in association with incident dementia syndromes (AD and vascular dementia, or VaD) identified through electronic health records (i.e. hospital episode statistics and death records). Differential effects of particular cognitive-domain related tasks were observed in association with specific incident dementia syndromes in this study that involved three to eight years of follow up. For example, a reaction time task was more highly predictive of VaD than AD, and in contrast, a prospective memory task was more highly predictive of AD versus VaD. The study also considered the role of constitutional and modifiable risk factors for dementia in relation to these specific syndromes. Whereas the investigation could extend to considering other dementia syndromes (i.e. frontotemporal lobar degeneration; dementia with Lewy bodies), their prevalence is currently too low in UK Biobank.

Cognitive testing in DPUK's cohort studies

To make progress in considering cognitive testing strategies for distinguishing between dementia syndromes in other population studies, WP10 prepared a preliminary internal report documenting: (1) all cognitive tests administered in 18 other DPUK population cohorts, along with the timing of their administration, and, the cognitive domain(s) they each relate to; (2) dementia variables or means to identify incident dementia syndromes in each cohort. This work was presented as a poster

at the DPUK annual conference in March 2018. In 2019 when the request from MRC was made to create a cognitive testing resource on the DPUK website, a full directory of cognitive tests on all DPUK's cohorts was published in pdf as a free resource for researchers.

Conclusions

The Cognitive Assessment work package achieved its main objective of enhancing the cognitive testing battery of UK Biobank. It also completed a validation study of 160 adults on the cognitive tests, and this work will support scientists using these data in their studies. The already successful implementation of the UK Biobank enhanced cognitive battery means that researchers will be able to study cognitive ageing trajectories in this cohort, hopefully for years to come. The extended work of WP10 in characterising all existing DPUK cohorts in terms of their cognitive test measures, which is part of a free online resource, will be of great value to researchers needing to navigate large numbers of population cohorts in search of the relevant cognitive measures. The work package members produced a number of substantial peer-reviewed reports relevant to its aims, which are already either published, accepted, or submitted for publication.

Recommendations

During the timeline of this project not all plans to repurpose UK Biobank as a dementia-focused research resource have been fulfilled. Some have been prohibited by UK Biobank owing to costs (telephone interviews) or its policies (reselection according to cognitive performance). Others are achievable but have not yet been prioritised by UK Biobank. Our recommendation for this cohort would be to instigate alternative non-web based cognitive assessments to ameliorate the risk of non-participation in cognitive measurement. It is well-known that participants with relatively lower cognitive function, steeper cognitive decline, and/or dementia diagnoses are more likely to withdraw or abstain from studies. For UK Biobank to be a leading epidemiological study in the dementia research field we continue to recommend that the cohort considers recruitment of informants and/or administration of subjective memory questions, to retain a full range of cognitive performers for ongoing analyses that will profit research for years to come. We also continue to suggest the inclusion of a second imaging follow-up with repeat cognitive testing. The work package has already published a study demonstrating the value of the UK Biobank baseline cognitive tests in predicting incident dementia up to eight years later. If we can continue to capture a wide distribution of cognitive abilities over longitudinal follow-up we will be in a better position to characterise dementia and its associated risk factors in the lifetime of this population study.

To researchers using cognitive data in UK Biobank we recommend use of the reports we have produced on the psychometric properties of UK Biobank cognitive tests, in order to understand the capabilities of these data. We also recommend researchers access the Cognitive Testing area of the DPUK website where we have deposited advice on cognitive testing, as well as a directory for researchers who wish to identify cognitive data within currently subscribed DPUK cohorts.