WP 10 – Complete – End Report

Cognitive Assessment
Start date: 1 July 2014. **Completion date: 30 June 2019**
Date of form completion: 31 July 2019

Team members <u>funded</u> (full or part-time) by DPUK
Ms Chloe Fawns-Ritchie, University of Edinburgh, Dr Catherine Calvin, University of Oxford
Team members involved with the project but <u>not</u> funded by DPUK
Professor Ian J Deary, University of Edinburgh, Professor John Gallacher, University of Oxford, Professor Marcus Richards, University College London, Professor John Starr, University of Edinburgh
ECR's (2 funded team members as named above)

Overall work package objectives:
To build on UK Biobank cognitive testing infrastructure and deliver additional cognitive phenotyping in 100,000 participants with concurrent 3T MRI.

1) Enhance the UKB cognitive battery: by the addition of tests for crystallised intelligence and executive function. The addition of cognitive testing to this cohort will enable it to become a dedicated dementia research cohort (months 1-12).
2) Provide repeat cognitive assessment at repeat imaging: recruited for repeat brain imaging at 24 months follow-up (months 24-60).
3) 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 (months 12-60).
4) Calibration and psychometrics of cognitive assessment: The programme aims to fully describe and explore the psychometric properties of the available cognitive data. One important component is the comparability of scores between testing modes (web vs. phone), testing environments (home vs. imaging assessment), and between informant and participants sources. An additional component of the calibration studies should be to validate the enhanced cognitive test battery against well-known and well-validated cognitive tests (months 20-48).
5) Identification of dementia syndromes: We will 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 (months 20-40).
6) Contact and re-contact strategies: We will develop cost-effective contact and re-contact strategies (months 37-48).

Dependencies to and from other work packages, networks and themes

Dependent on UK Biobank to translate the enhanced battery to computer adaptive testing and initialise the computer tests while trouble-shoot any issues.

Dependent on UK Biobank to carry forward SOPs and initiate recruitment.

Lessons Learnt (what went well, what did you have to change)

What went well

Work package 10 was largely successful in its initiative to repurpose the UK Biobank cohort for cognitive ageing and dementia-relevant research. It did this by designing an enhanced cognitive assessment battery for UK Biobank (objective 1), so that key aspects of cognitive functioning affected by healthy and pathological ageing, as well as an indicator of premorbid cognitive ability, would be measured in participants returning for follow-up. However, it is important to emphasise that this was still done under the restrictions of the tests being self-administered, the whole battery taking only a short time, and retaining the original UK Biobank cognitive tests. The UK Biobank enhanced cognitive test battery was translated to a touchscreen computer programme and has now been implemented as part of returning participants'

imaging assessments, with cognitive data available on ~25,000 participants to date. Work package members CF-R and IJD visited the research site in Southport to observe participants completing these tests, and to make further recommendations to UK Biobank as to which tests performed reliably and which cognitive tests should be maintained. We expect this enhanced assessment to be carried forward to repeat imaging assessments (objective 2). Finally, work package members CF-R and IJD, based at the University of Edinburgh, successfully designed and completed a validation study of the enhanced cognitive assessment, to assess its performance in relation to a well-validated neuropsychological battery (objective 4). This went to plan, with the timely recruitment of 160 adults who completed both sets of tests administered by a single researcher (Chloe Fawns-Ritchie). A subset of 52 members of the sample also returned four weeks later to repeat the UK Biobank cognitive tests for the analysis of short-term test-retest reliability. The reliability and validity of the enhanced cognitive battery devised by the work package have been written up and submitted for peer-review publication (listed in *Top five scientific publications* below), which will be a valuable resource for researchers using these data; it was also posted on medRxiv. The aim to identify dementia syndromes in UK Biobank and their prediction by cognitive variables (objective 5) was also achieved, and this study was recently accepted for publication in *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*

What objectives were unfulfilled

There were elements of WP10's original initiative to repurpose UK Biobank as a dementia research resource that were not possible to complete in the timeline of this project. These were entirely dependent on approval and implementation from UK Biobank, which understandably has its own set of priorities and timescales. The work package delivered timely reports to UK Biobank (see below section on *Internal reports sent to UK Biobank*), and members have continued to talk with UK Biobank for the duration of this project on these important objectives, including repeat cognitive testing 24 months after imaging (objective 2) and the recruitment of informants (objective 3). UK Biobank scientists agreed to the importance of these in principle but have so far not implemented them. Consequently, original plans to analyse differences in cognitive performance scores between testing modes, testing environments, and informant vs. participant sources (part of objective 4), could not be fulfilled. One original aim of WP10 was to determine the feasibility of telephone cognitive testing in UK Biobank. Early in the work package this was ruled out by UK Biobank due to the costs involved. The final objective by the work package of initiating re-contact strategies for participants on the basis of their cognitive performance (objective 6) was ruled out early on in the project due to restrictions in UK Biobank's ethical policies; that is, they do not allow call-back based on results. The contacting of informants remains of interest to UK Biobank but they have not started the processes of doing that yet.

What did we change

As a result of the above unfulfilled objectives, WP10 instead turned a focus towards the following:

1. An investigation of psychometric properties of the UK Biobank baseline and enhanced cognitive assessments. UK Biobank is increasingly being used in dementia-focused investigations, but for researchers to have confidence in using the cognitive data it is important that the psychometric properties of these tests are known. The work package has created a report (listed in *Web-based outputs* below) that will be made available to all researchers interested in this resource and using any one of the UK Biobank cognitive tests in their own studies.
2. The development of cognitive testing resources for researchers visiting the Dementias Platform UK website (requested by MRC in 2019), and particularly for those interested in exploiting cognitive data from cross-cohort studies through the Dementias Platform UK data portal. These are available at: *https://www.dementiasplatform.uk/for-researchers/get-ahead-with-cognitive-test-data-1* and include the downloadable *Cognitive Test Directory* of DPUK's cohort studies.
3. The undertaking of epidemiological studies utilising the cognitive data in DPUK's cohorts. These have largely involved UK Biobank data (see *scientific publications* below) and are submitted for publication. With the DPUK data portal fully operational since 2018, WP10 member C. Calvin is completing work on two cross-cohort studies looking at midlife risk factors in association with changes in cognitive task performance (DPUK studies #0170 and #A004) and is collaborating on some others (#0144 and #0160).

Were all Milestones completed: No

Milestones 3.1.2, 3.1.3 and 3.1.4 were not completed due to UK Biobank not implementing recruitment of informants as advised by the work package (see explanation above). Milestone 6.1.2 was not completed due to UK Biobank ethical policies not allowing call back on the basis of cognitive results.				
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 The enhanced web-battery will be administered to all 100,000 UKB participants who will be 3T brain imaged between 2016 and 2018.	M1.1.1 Completion of enhanced cognitive test battery	M1.1.1 Complete	dependent on WP3, WP9, WP12	Chloe Fawns-Ritchie
	M1.1.2 Assess the enhanced battery – alpha and beta testing	M1.1.2 Complete	dependent on WP3	
	M1.1.3 Assess in-clinic timing	M1.1.3 Complete	dependent on WP3	
	M1.1.4 Implement enhanced cognitive test battery at imaging session	M1.1.4 Complete	dependent on WP3	
Objective 2:				
D2.1 Conduct repeat cognitive testing using the enhanced cognitive battery in 10,000 UKB participants	M2.1.1 Decide if any changes to current cognitive battery are required.	M2.1.1 Complete	dependent on WP3, WP9, WP12	Chloe Fawns-Ritchie
	M2.1.2 Prepare proposal for repeat cognitive testing at imaging testing	M2.1.2 Complete	dependent on WP9	
Objective 3:				
D3.1 Develop methods for informant recruitment and informant based cognitive and functional assessment	M3.1.1 Prepare standard operating procedures for informant questionnaire.	M3.1.1 Dec 2018	Dependent on agreement from UKB.	Chloe Fawns-Ritchie
	M3.1.2 Assist UK Biobank writing ethics for contacting informants.	M3.1.2 Mar 2019		
	M3.1.3 Collection of informant information initiated	M3.1.3 Jun 2019		
	M3.1.4 Informant assessment – completed	M3.1.4 Jan 2023		
Objective 4:				
D4.1 Conduct a series of calibration studies.	M4.1.1 Proposal for calibration study	M4.1.1 Complete		Chloe Fawns-Ritchie
	M4.1.2 Conduct calibration studies	M4.1.2 Complete		
	M4.1.2 a Write report on preliminary test characteristics	M4.1.2a Complete		
	M4.1.2b Source test materials for validation study	M4.2.2b Complete		
Objective 5:				
D5.1 Adding tests that are sensitive to specific dementia sub-types to the web-battery	M5.1.1 Develop a collaborative strategy with WP9 for identifying dementia syndromes in UK Biobank and their prediction by cognitive variables.	M5.1.1 Complete		Catherine Calvin
	M5.1.2 Systematic literature review	M5.1.2 Complete		
	M5.1.3 Test development and application.	M5.1.3 Complete		All
	M5.1.4 Develop a collaborative strategy within WP10 (and perhaps with WP9) for identifying dementia syndromes across other DPUK cohorts,	M5.1.4 Complete		Catherine Calvin

	and look at opportunities for cross-cohort studies by harmonisation of cognitive data.			
Objective 6:				
D6.1 Identify methods to maximise response using email, mail and phone prompts	M6.1.1a Propose re-contact strategies – original	M6.1.1a Complete	M6.1.1 dependent on WP12	Chloe Fawns-Ritchie
	M6.1.1b Propose re-contact strategies – revised. General advice on re-contact to maximise cognitive testing responses.	M6.1.1b Complete		
	M6.1.2 Implement re-contact strategies	M6.1.2 Closed		

Outcomes

Top five scientific publications

- **Calvin CM, et al. (2017) Childhood intelligence in relation to major causes of death in 68 year follow-up: prospective population study. BMJ; 357:j2708**

Evidence from this whole population birth cohort study linking childhood intelligence test scores to causes of death, in a follow-up period spanning ages 11 to 79 years, demonstrated how this childhood trait is associated with lifetime risk of dementia-related mortality, with a stronger effect in women relative to men. This highlights the importance of considering a lifespan approach to studying dementia risk and to developing intervention strategies.

- **Calvin CM, et al. Predicting incident dementia 3-8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. *Alzheimer's and Dementia*; *The Journal of the Alzheimer's Association*: accepted on 20 June 2019.**

This observational study demonstrated an association between preclinical cognitive capability in adulthood and risk of incident dementia ascertained through data linkage to routine electronic health records, thereby avoiding the issue of attrition common to previous studies. It accounted for a range of constitutional, genetic and modifiable risk factors for dementia, and found evidence that brief cognitive testing could be a valuable addition to population screening for dementia risk.

- **Cox SR, et al (2019). Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal* [Epub ahead of print] https://doi.org/10.1093/eurheartj/ehz100.**

Using data from 9722 Biobank participants, aged 44-79 years, the authors studied the association between multiple vascular risk factors (VRF) and brain micro/macrostructure. The effect sizes were small, but higher levels of VRFs were associated with poorer grey and white macrostructure and microstructure and the effects were additive. The brain areas most strongly affected were those previously linked with 'typical' Alzheimer's Disease, and with more complex cognitive functions. These results suggest that even in otherwise healthy participants, and even in middle age, the brain is vulnerable to VRFs, and that cognitive decline could be partly ameliorated by addressing malleable VRFs.

- **Cox SR, et al. (2019). Structural brain imaging correlates of general intelligence in UK Biobank. Intelligence, 76, 101376. doi: https://doi.org/10.1016/j.intell.2019.101376**

Using data from the UK Biobank imaging study, this paper examined the brain imaging correlates of general intelligence (overall n = 29,004; n for participants providing MRI and scores on all four cognitive tests of interest = 7,318). A general factor of intelligence was created using four of the UK Biobank cognitive tests. In this study, larger total brain volume was associated with higher intelligence. This is one of the largest studies of the association between brain size and intelligence.

- **Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. [Submitted for peer-review. Preprint at *Medrxiv.org:* https://doi.org/10.1101/19002204]**

This study investigated the concurrent validity and short-term test-retest reliability of the full UK Biobank cognitive test battery. A sample of 160 participants (mean age=62.59, SD=10.24) completed the UK Biobank cognitive assessment and a range of well-validated cognitive tests, and 52 participants returned 4 weeks later to repeat the UK Biobank tests. The UK Biobank cognitive tests showed a range of correlations with corresponding well-validated tests, i.e. those tests that were thought to assess the same underlying cognitive ability (mean Pearson r=0.53, range=0.22 to 0.83, p≤.005). Four-week test-retest reliabilities of the UK Biobank tests were moderate-to-high (mean Pearson r=0.55, range=0.40 to 0.89, p≤.003). Despite the brief, non-standard nature of the UK Biobank cognitive tests, some showed substantial concurrent validity and test-retest reliability.

Other scientific publications

- **Calvin CM, et al. (2019) Sex-specific moderation by lifestyle and psychosocial factors on the genetic contributions to adiposity in 112,151 individuals from UK Biobank. *Scientific Reports*; 9:363.**
- **Calvin CM, et al. (2017). Moderating lifestyle and psychosocial factors on genetic susceptibility to dementia comorbidities: An MRC Dementias Platform UK (DPUK)-supported study. *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*; 13(7): P1179.**
- **Fawns-Ritchie C, et al. (2017). Do demographic and vascular risk factors predict cognitive change in 11,070 UK Biobank participants? *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*; 13(7): P1556. [Published conference abstract]**
- **Hagenaars, SP, et al. (2018). Genetic risk for neurodegenerative disorders, and its overlap with cognitive ability and physical function. *PLOS ONE*; *13*(6); p.e0198187.**

Neurodegenerative disorders such as Alzheimer's disease and frontotemporal dementia are characterised by cognitive impairment. This study investigated whether genetic risk for neurodegenerative disorders was associated with lower cognitive function in a sample of healthy middle-aged and older adults. Higher polygenic risk for Alzheimer's disease, Amyotrophic Lateral Sclerosis and frontotemporal dementia was associated with lower cognitive ability. This study highlights that, in healthy individuals, there is some overlap between polygenic risk of neurodegenerative diseases and cognitive function.

Web-based publications

- **Calvin C, et al. Dementias Platform UK: Cognitive Test Directory. Oxford, UK: DPUK; 2019. Downloadable from: https://www.dementiasplatform.uk/for-researchers/get-ahead-with-cognitive-test-data-1/cognitive-test-directory**

The Dementias Platform UK (DPUK) Cognitive testing directory has been specifically produced as a resource for researchers exploiting the cognitive data available from cohort studies in the DPUK Data Portal. The pdf document can be downloaded from the 'Using cognitive test data' section of the DPUK website (for more details, see *other outputs* below), and gives details of cognitive testing for 39 cohort studies that appear in a recent article about the DPUK Data Portal (doi: https://doi.org/10.1101/582155) . The directory is particularly beneficial to researchers undertaking cross-cohort studies and therefore identify comparable cognitive data across studies. Whereas a wide array of cognitive tests was used across the different studies, the directory identifies the specific cognitive domain targeted by each test to enable cross-cohort comparisons to be made.

- **Fawns-Ritchie C, Deary IJ, on behalf of Dementias Platform UK work package 10. Test characteristics of the enhanced UK Biobank Cognitive Assessment. 21 September 2017. Available soon on https://dementiasplatform.uk/**

This report provides the details of all the cognitive tests that have so far been used in UK Biobank assessment centres, including the original touchscreen computer tests administered at baseline, the web-based adapted tests for online follow-up assessment, and, the subsequent enhanced battery of touchscreen computer tests administered at imaging visits. The main focus of the report is however the enhanced cognitive battery; the rationale for selecting each of its tests, the cognitive domains

that each test relates to, and, the psychometric properties of the tests according to analyses of the first ~5000 participants who completed them at the imaging study. The report is therefore very informative to researchers using these cognitive data in their investigations of UK Biobank.

- **Jindra, C, Kim C-H, Calvin C. Harmonised cohorts for DemVasc: Technical Report and Codebook.** To be made available shortly.

This technical report and codebook illustrates how data from three population cohort studies – including the English Longitudinal Study of Ageing (UK), Whitehall II (UK), and the Health and Retirement Study (US) - have been harmonised and coded to allow for a coordinated analysis of these studies. The study ('DemVasc') is interested in understanding the change in trends of dementia prevalence according to smoking behaviour and other vascular-related risk factors, and is funded by a DPUK Discovery Award (PI: C-H Jindra). Coding of Whitehall II and standardisation of the cognitive variables was led by C Calvin.

Other web-based outputs

DPUK web-based resource: Using cognitive test data. Available at: https://www.dementiasplatform.uk/for-researchers/get-ahead-with-cognitive-test-data-1

Work package 10 have provided the content for a series of webpages on the DPUK website providing helpful resources for researchers looking to assess cognitive function in their research. These will enable researchers to either select the appropriate cognitive tests for use in their planned studies or identify existing cohort data with the relevant cognitive variables for their analyses. In summary the web resource provides:

3) Key resources outlining which cognitive functions and which cognitive tests are frequently used in research with older adults

4) A downloadable directory of the cognitive tests assessed in each of DPUK's cohorts

5) Detailed reports on the psychometric work carried by WP10 on the UK Biobank cognitive assessment.

Scientific talks and posters

- Calvin C. (2017). *Do cognitive test data in UK Biobank add to prediction of incident dementia?* Oral presentation at Dementias Platform UK Annual Conference, Royal College of Obstetricians and Gynaecologists, London on 4 May 2017.
- Calvin C. (2018). *Data portal workshop [included work of the cognitive assessment team in developing meta-data for the online researcher discovery tools]*. Oral presentation at Dementias Platform UK Annual Conference, British Medical Association, London on 23 April 2018.
- Calvin C, et al. (2018). *Cognitive measures in DPUK cohorts: A resource for researchers*. Poster presentation at Dementias Platform UK Annual Conference, British Medical Association, London on 23 April 2018.
- Calvin C, et al. (2018). *Predicting incident dementia from cognitive test performance in UK Biobank*. Poster presentation at Alzheimer's Research UK, QEII, London on 20–21 March 2018.
- Fawns-Ritchie C. (2018). *Impact across the platform: Perspective of an ECR.* Oral presentation at Dementias Platform UK Annual Conference, British Medical Association, London on 23 April 2018.
- Fawns-Ritchie C, et al. (2017) *MRC Dementias Platform UK WP10: Examination of the psychometric properties of UK Biobank cognitive tests.* Poster at Dementias Platform UK Annual Conference, Royal College of Obstetricians and Gynaecologists, London on 4 May 2017.
- Fawns-Ritchie C, et al. (2018). *Psychometric evaluation the cognitive assessment in UK Biobank: Dementias Platform UK Cognitive Assessment*. Poster presentation at Alzheimer's Research UK, QEII, London on 20–21 March 2018.
- Fawns-Ritchie C, Starr JM, Deary IJ. *Preliminary psychometric results from the enhanced UK Biobank cognitive test battery: Dementias Platform UK Cognitive Assessment*. Poster presentation at Dementias Platform UK Annual Conference, British Medical Association, London on 23 April 2018.

Internal reports sent to UK Biobank (in date order):

21 Nov 2014: *Proposed cognitive tests for an enhanced UK Biobank cognitive battery*. Authors: Fawns-Ritchie C & Deary IJ, on behalf of Dementias Platform UK WP10 PIs: Deary IJ, Starr JM, Gallacher J, Richards M.

1 Sept 2016: *SOPs for IQCODE: Participant consent and administration*. Authors: Dementias Platform UK cognitive assessment WP10

28 Nov 2016: *Proposal: Subjective memory questions in UK Biobank.* Authors: Fawns-Ritchie C, Deary IJ, Starr J.

8 Mar 2017: *Observation of the enhanced UK Biobank cognitive assessment*. Authors: Fawns-Ritchie C & Deary IJ, on behalf of Dementias Platform UK WP 10.

21 Sep 2017: *Recommendations on the retention of cognitive tests in the UK Biobank cognitive test battery*. Authors: Dementias Platform UK cognitive assessment WP10.

Executive Summary of Project

Background

The UK Biobank cohort of ~500,000 men and women (aged 40 to 73 years at baseline) has the potential of becoming a rich dementia-focused resource for researchers. To achieve this DPUK's Cognitive Assessment Work Package (WP10) was set up to develop and oversee the implementation of an enhanced cognitive assessment battery for longitudinal follow-up of this cohort, by adding tests to the brief computer-based battery administered at baseline. WP10 also advised and supported UK Biobank in the ongoing assessment of cognitive function in this cohort and provided psychometric analyses of the tests' performances.

Methods

Members of WP10 consulted and agreed upon a selection of tests for the enhanced cognitive battery, which measure performance in the cognitive domains most sensitive to changes in healthy and pathological ageing. These include processing speed, executive function, and episodic memory. A test of crystallised intelligence was also incorporated as an estimate of premorbid cognitive functioning. The final battery approved by UK Biobank involved seven additional tests to the baseline battery. WP10 members further advised UK Biobank on: recruitment of informants, reporting on subjective memory complaints, and, their site-visit observations on the reliability of the enhanced cognitive battery. To formally assess the test-retest reliability and concurrent validity of the UK Biobank enhanced battery, members of WP10 located in Edinburgh conducted a study of 160 adults who completed the 12 UK Biobank tests alongside 18 well-validated and standardised psychometric tests of equivalent cognitive domains. The cognitive assessment took approximately 2.5 hours to complete. A subset of 52 participants returned to repeat the UK Biobank tests after about 4 weeks, to test short-term reliability.

Results

UK Biobank implemented the enhanced cognitive battery at the imaging assessment (target: n=90,000), and there are currently data on ~25,000 participants. Site visits by WP10's CF-R and IJD have further improved the protocol for ongoing assessment. UK Biobank have not yet instigated recruitment of informants, 24-month repeat imaging visits, nor administration of subjective memory questionnaires. UK Biobank have ruled out telephone assessments for cost reasons. In the validation study of the enhanced battery 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 Picture Vocabulary and Trail Making tests were especially good ($r = 0.83$ and 0.66 respectively, when compared to the original versions of these tests). Four-week test-retest reliability was moderate-to-high (mean Pearson $r=0.55$, range=0.40 to 0.89, $p \leq .003$). Psychometric properties of all UK Biobank's cognitive tests have been written up by WP10 in a report for researchers. Other resources for researchers produced by WP10 cover advice on cognitive testing measures, and a cognitive testing directory of all DPUK's existing cohort studies (n = 39). The project also produced several publications on epidemiological studies using the cognitive data in UK Biobank.

Conclusion

Work package 10 was successful in its initiative to repurpose the UK Biobank cohort as a dementia research resource, by its development of an enhanced cognitive test battery for follow-up assessment. This will enable researchers to trace cognitive ageing trajectories in UK Biobank participants who remain in the study. The WP10 reports on psychometric properties of the cognitive tests form part of a set of valuable resources for researchers using these data in the years to come.

Full Project End Report

WP10 End Report.pdf