WP 4- Project complete- End Report

Amyloid Discovery Cohort

Start date: 1 Sep 2014 **Completion date:** Mar 2019

Date of form completion: Jul 2019

Team members funded (full or part-time) by DPUK

Mrs Heidi Murray-Smith (05/2015 to 05/2019) 100% funded full time

Dr Chris Lane (05/2015 to 01/2019) 100% funded full time

Team members involved with the project but not funded by DPUK

Profs Jonathan Schott, Nick Fox, Marcus Richards; Drs Sarah Keuss, Sarah Buchanan, Ashvini Keshavan, Matt Harris, Tom Parker, Sarah James, Dave Cash, Ian Malone, Andy Wong; Mrs Kirsty Lu, Hannah Carr, Ivanna Pavisic, Molly Cooper; Mr Will Coath

Objectives

To establish a cohort of 500 men and women from the MRC National Survey of Health and Development (the UK1946 birth cohort) characterised for amyloid status using amyloid PET imaging with concurrently acquired structural MRI and blood and urine. WP4 supports the third DPUK strategic objective of re-purposing cohorts for discovery studies.

1. Establish a biomarker resource of blood and urine samples with paired T1-volume scans and known brain amyloid status for biomarker discovery and validation, which will feed into WP6 (Biomarkers) and experimental medicine WPs.
2. Provide paired amyloid PET and MRI imaging for imputation and correlative analyses with other platform cohorts collecting volumetric MRI and blood samples.
3. Determine the relationships between PET Aβ load and blood measures of Aβ-42/tau, and brain atrophy in a cohort of identical age, of direct relevance to WP14 (risk stratification and biostatistics), allowing other cohorts (e.g. Prevent) to cross-validate results.
4. Provide a well-characterised cohort in which novel imaging markers (e.g. of tau or microglial activation/inflammation) can be tested in the future.
5. Data uploaded to DPUK portal.

Dependencies to and from other work packages, networks and themes

- WP4, WP5, and WP6 protocols to be integrated.
- Relationship between objective 2 and imaging informatics.
- Relationship between objective 3 and WP14.

Lessons Learnt

- The processes for scheduling of the participant visits and organising staff resources worked well. Similar processes will be implemented for future phases of data collection.
- The delays in the project schedule were primarily the result of issues with the tracer production / arrival, resulting in the need to reschedule numerous scans. This could possibly have been mitigated by using a tracer produced closer to London (to limit traffic delays) or a tracer with more flexibility in its production time and QC processes.
- The imaging pipelines to analyse and transfer data from the PET/MRI scanner to UCL and from UCL to the DPUK platform took some time to set up. Lessons learned from those technical endeavours will make similar activities more efficient to set up in the future.
- No issues noted for the collection and storage of blood and urine as a biomarker resource.

Were all Milestones completed: Yes

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective 1				
D1.1 Complete cross-sectional data collected	M1.1.1 Protocols finalised	M1.1.1 Complete	M1.1.1 WP4, WP5 (FAD cohort) and WP6 (Biomarkers) protocols to be integrated	JS
	M1.1.2 Agreements established for tracer delivery	M1.1.2 Complete		
	M1.1.3 Ethics approval obtained	M1.1.3 Complete		
	M1.1.4 Begin data collection	M1.1.4 Complete		
	M1.1.5 250 participants recruited (50%)	M1.1.5 Complete		
	M1.1.6 Data collection complete	M1.1.6 Complete		
D1.2 Determine the relationships between PET AB-42/tau, and brain atrophy	M1.2.1 Conduct preliminary image analysis in first 250 participants	M1.2.1 Complete	M1.1.4	JS
	M1.2.2 Conduct analyses in all participants	M1.2.2 Ongoing	M1.1.5	
Objective 2:				
D2.1 Amyloid optimised image processing pipeline using the DPUK imaging informatics platform	M2.1.1 Connect to the DPUK image processing platform	M2.1.1 Complete	M1.1.1 and imaging informatics	CM, SO, JS
	M2.1.2 Develop image processing protocols	M2.1.2 Complete		
	M2.1.3 Conduct preliminary analysis on first 250 participants	M2.1.3 Complete	M1.1.4	
	M2.1.4 Conduct analyses on all participants	M2.1.4 Complete	M1.1.5	
Objective 3:				
D3.1 Complete cross-sectional data collected	M3.1.1 Prepare statistical models	M3.1.1 Complete	M1.1.4 and WP14	JS
	M3.1.2 Conduct preliminary image analysis on first 250 participants	M3.1.2 Complete		
	M3.1.3 Conduct analysis on all 500 participants	M3.1.3 Complete	M1.1.5	
Objective 4:				
D4.1 Recruit 500 individuals to the study	M1.1.1 Identified potential suitable participants from NSHD who attended a previous clinic visit and have minimum life course data set	M1.1.1 Complete	None	JS
Objective 5:				
D5.1 Data uploaded to DPUK data portal	M5.1.1 Data collection completed	M5.1.1 Complete	M1.1.5	JS, RL
	M5.1.2 Data processing completed	M5.1.2 Complete		
	M5.1.3 Data transfer completed	M5.1.3 Complete		
Outcomes ***Published***	**PUBLICATIONS**			

1) Lane, C., T.D. Parker, D.M. Cash, K. Macpherson, E. Donnachie, et al. 2017. Study protocol: Insight 46 – a neuroscience sub-study of the MRC National Survey of Health and Development. BMC Neurology. 17(1):75**. DOI:** 10.1186/s12883-017-0846-x.
2) James SN, Lane CA, Parter TD, Lu K, Collins JD, Murray-Smith H, Byford M, Wong A, Keshavan A, Buchanan S, Keuss SE, Kuh D, Fox NC, Schott JM, Richards M. 2018. Using a birth cohort to study brain health and preclinical dementia: Recruitment and participation rates in Insight 46. *BMC Research Reports.* *doi.org/10.1186/s13104-018-3995-0*
3) Keuss SE, Parker TD, Lane CA, Hoskote C, Shah S, Cash DM, Keshavan A, Buchanan SM, Murray-Smith H, Beasley DJ, Malone IA, Thomas DL, Barnes A, Wong A, Barker S, Richards M, Fox NC, Schott JM. 2019. Incidental findings on blood tests and brain imaging: results from the first phase of Insight 46, a longitudinal prospective sub-study of the 1946 British birth cohort. *BMJ Open*. doi: 10.1136/bmjopen-2019-029502
4) Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James S-N, Keshavan A, Murray-Smith H, Wong A, Buchanan SM, Keuss SE, Gordon E, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Hardy R, Richards M, Fox N, Schott HM. 2019. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurology*. doi: https://doi.org/10.1016/S1474-4422(19)30228-5
5) Parker TD, Cash DM, Lane CA, Macpherson K, Malone I, Nicholas JM, James SN, Keshavan A, Murray-Smith H, Wong A, Buchanan S, Keuss, S, Sudre C, Barnes J, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Richards M, Fox NC, Schott JM. Hippocampal subfield volumes and pre-clinical Alzheimer's disease in 408 cognitively normal adults born in 1946. doi: https://doi.org/10.1371/journal.pone.0224030

Revisions accepted, awaiting publication

- Lu K, Nicholas JM, Collins JD, James SN, Parker TD, Lane, CAS, Keshavan A, Keuss SE, Buchanan SM, Murray-Smith H, Cash DM, Sudre CH, Malone IB, Coath W, Modat M, Barker S, Wong A, Kuh D, Henley SMD, Crutch SJ, Fox NC, Richards M, Schott JM. Cognition at age 70: life course predictors and associations with Alzheimer's disease pathology. [awaiting publication in Neurology]
- Parker T et al. Pure tone audiometry and cerebral pathology in healthy older adults. [awaiting publication in the Journal of Neurology, Neurosurgery, and Psychiatry]

In preparation

- Buchanan et al. Olfactory testing does not predict ß-amyloid, MRI measures of neurodegeneration or vascular pathology in the British 1946 birth cohort.
- Parker T et al. The influence of white matter hyperintensity volume on cortical thickness in healthy 70-year olds
- Lane et al. Early adulthood vascular risk most strongly predicts brain volumes and white matter disease, but not amyloid status, at age 69-71 years – evidence from a British Birth cohort.
- Keshavan A, et al. Plasma amyloid, tau and serum neurofilament light chain in Insight 46 – associations with cognition and brain imaging.
- Keshavan A, et al. Relationships between cerebral amyloid pathology using two independent methods for plasma amyloid beta measurement in the 1946 birth cohort.
- James S, et al. Associations between midlife blood pressure and later-life white matter disease are not mediated by arterial stiffness and cardiac dysfunction: findings from the British birth cohort.
- James SN, et al. Associations between life course affective symptoms and late-life cerebral pathology in a population-based birth cohort.
- James SN, et al. Associations between prior head injury and later-life cognition is partly mediated by lower brain volume, but not □-amyloid or white matter damage at age 70: findings from Insight 46.
- James SN, et al. Divergent associations between life course cognitive trajectories and brain pathologies: findings from the 1946 British birth cohort.

ABSTRACTS, POSTERS, and PRESENTATIONS

AAIC – 2017, 2018

- Cash DM, et al. A comparison of techniques for quantifying amyloid burden on a combined PET/MR scanner. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):12.
- James SN, et al. Midlife affective symptoms are associated with lower brain volumes in later life: evidence from a prospective UK birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):212.
- Lane CA, et al. Vascular and early life influences on cerebrovascular disease in Insight 46: a sub-study of the MRC National Survey of Health and Development (NSHD) British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):851.
- Parker T, et al. Brain volume, cerebral β-amyloid deposition, and ageing: a study of over 200 individuals born in the same week in 1946. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):1464.
- Schott JM, et al. Exploring the population prevalence of β-amyloid burden: an analysis of 250 individuals born in mainland britain in the same week in 1946. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):1088.
- James SN et al. Head injury with loss of consciousness and subsequent cognitive decline: follow-up in the 1946 British birth cohort study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2018;14(7):278.
- Lane CA, et al. Influences of blood pressure and blood pressure trajectories on cerebral pathology at age 70: results from a British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2018;14(7): 626.

AAIC –July 2019

- Schott JM, et al. The 1946 birth cohort - relationships between cerebral amyloid pathology using two independent methods for plasma amyloid beta measurement. *AAIC* 2019; **featured research session**
- James SN, et al. Divergent associations between life course cognitive trajectories and brain pathologies: findings from the 1946 British birth cohort. *AAIC* 2019; **abstract submitted, oral presentation**.
- Lane CA, et al. Early adulthood vascular risk strongly predicts brain volumes and white matter disease, but not amyloid status, at age 69-71 years – evidence from a British Birth cohort. *AAIC* 2019; **abstract submitted, oral presentation**
- Parker TD, et al. Age, β-amyloid and cognition selectively influence hippocampal subfield volume: a study of 408 healthy adults born in 1946. *AAIC* 2019; **abstract submitted, oral presentation**
- Cash DM, et al. Longitudinal rates of amyloid accumulation in a 70-year old British birth cohort. *AAIC* 2019; **abstract submitted, poster**
- Coath W, et al. Centiloid scale transformation of Florbetapir data acquired on a PET/MT scanner. *AAIC* 2019; **abstract submitted, poster**
- Kehsavan A, et al. Plasma amyloid, tau and serum neurofilament light chain in Insight 46, the neuroscience sub-study of the 1946 British birth cohort – associations with cognition, brain imaging and cerebral amyloid. *AAIC* 2019; **abstract submitted, poster**

Other

- Schott J. 2015. Determining the causes and consequences of brain amyloidosis, atrophy and cerebrovascular disease: a longitudinal amyloid-PET/MRI study of the MRC British 1946 birth cohort. DPUK Collaboration Seminar; **presentation**
- Lane C, Parker T, Murray-Smith H. 2015. A longitudinal amyloid-PET/MRI study of the MRC NSHD British 1946 birth cohort. 2015 DPUK Symposium; **poster**
- Lane C. 2015. Determining the causes and consequences of brain amyloidosis, atrophy and cerebrovascular disease: a longitudinal amyloid-PET/MRI study of the MRC British 1946 birth cohort. UCL Dementia Research Centre Lunchtime Meeting; **presentation**
- Murray-Smith H. 2015. A longitudinal amyloid-PET/MRI study of the MRC NSHD British 1946 birth cohort. 2015 Leonard Wolfson Experimental Neurology Centre International Clinical Trials Day; **poster**

- Murray-Smith H. 2015. The MRC National Survey of Health and Development (NSHD) Neuroimaging Sub-study: INSIGHT 46. Leonard Wolfson Experimental Neurology Centre Training Day; **presentation**
- Lane C. 2016. Work Package 4: Amyloid Discovery Cohort. 2016 DPUK Symposium; **poster**
- Richards M. 2017. Preliminary Insight 46 data. 2017 DPUK Annual Meeting; **presentation**
- Lu (Macpherson) K. 2017. Visuomotor integration in Insight 46, a neuroscience sub-study of the MRC National Survey of Health and Development. 2017 Queen Square Symposium; **presentation**
- James S. 2018. Life-course incidence of head Injury and subsequent later-life cognition. 2018 DPUK Conference; **poster (first prize award for best poster)**
- Keshavan A. 2018. Exploring the role of blood-based biomarkers for Alzheimer's disease in a pre-clinical cohort: Insight 46 – The Neuroimaging Sub-study of the MRC National Survey of Health and Development. 2018 UCL Queen Square Symposium; **poster**
- James S. 2018. Traumatic brain injury with loss of consciousness and subsequent cognitive trajectories. UK Frontiers in Traumatic Brain Injury Conference; **invited presentation**
- 2018. Brain damage from cardiovascular disease starts earlier than you think. ALZFORUM; **news article mentioning Insight 46**
- James S, Lu K, Carr H, Popham M. 2018. Insight 46: Scanning people in the longest-running British Birth Cohort. ARUK / UCL network public engagement meeting, *Meet the Scientists*; **stall with information about National Survey of Health and Development and Insight 46**
- James S. 2018. Investigating risk factors for dementia: Over 65 years of follow-up in the 1946 Birth Cohort. British Heart Foundation; **presentation**
- James S. 2018. What have we learnt about longitudinal studies? UK Sports Concussion Research Symposium; **invited presentation**
- Buchanan S. 2019. The cognitive profile associated with mild parkinsonian signs in a British Birth Cohort. 2019 Movement Disorders Society Congress; **abstract submitted**
- Keshavan A. 2019. Blood biomarkers of amyloid, tau and neurofilament light chain in the 1946 British birth cohort – relationships with cerebral amyloid and brain imaging. ARUK Student Day; **presentation**
- Buchanan S. 2019. Relationships between walking speed, cognition & brain pathologies – an imaging study of the 1946 birth cohort. Association of British Neurologists Annual Meeting 2019; **abstract submitted, oral presentation**

PhDs

Awarded

- Lane C. 2018. The influence of life course vascular risk on brain pathologies and cognition in later life — a neuroimaging study of the British 1946 birth cohort.
- Parker T. 2019. The consequences of, and relationship between, amyloid, grey matter microstructural change and atrophy in the MRC NSHD 1946 birth cohort.

Upgrades complete

- Keshavan A. Blood and cerebrospinal fluid-based biomarkers for neurodegenerative disease: from clinical to pre-clinical cohort. Submission in 2019
- Lu K. Insight 46: Characterising early cognitive changes and possible associations between cognitive and other AD biomarkers. Submission in 2019
- Buchanan S. Movement and neurodegeneration in the MRC National Survey of Health and
- Development (NSHD; 1946 birth cohort). Submission in 2020

Executive Summary of Project

"Insight 46" is a neuroscience sub-study of the MRC National Survey of Health and Development. This is the oldest British birth cohort studies and has followed 5,362 individuals since their birth in England, Scotland and Wales during one week in March 1946. These individuals have been tracked in 24 waves of data collection incorporating a wide range of health and functional measures, including repeat measures of cognitive function. Now aged 73 years, a small fraction have overt dementia,

but estimates suggest that ~1/3 of individuals in this age group may be in the preclinical stages of Alzheimer's Disease. The aim of Insight 46 is to recruit 500 study members selected at random from those who attended a clinical visit at 60-64 years and on whom relevant lifecourse data are available. The sub-study involves a prospective two time-point (0, 24 month) data collection covering clinical, neuropsychological, β-amyloid positron emission tomography and magnetic resonance imaging, biomarker and genetic information. Data collection started in 2015 (age 69). Cross-sectional data collection was completed in January 2018, and data analyses models and optimised statistical methodologies have been/are being applied to the full cross-sectional data set. Imaging pipelines for amyloid PET and multi-modal MR imaging have been optimised. Longitudinal data collection is underway and will be completed in early 2020.

As a result of additional funding from the Weston foundation, SIMOA-based assays of β-amyloid, tau, p-tau and NFL on the cross-sectional Insight 46 samples have been completed.

The study team are analysing the cross-sectional data, and early findings have been (2017, 2018, 2019) presented at the Alzheimer's Association International Conference, the world's largest dementia research gathering, which generated much interest, including an article on the Alzforum website. A number of papers utilising cross-sectional data have been accepted for submission, are under review or in preparation (see above).

WP 4 End Report.pdf