# Centre for Cognitive Ageing and Cognitive Epidemiology

Cognitive decline is the single most feared aspect of growing old. It is also the most costly, in terms of the financial, the personal and societal burden. Many organisations—governmental, academic, research-funding, professional and charitable—have announced that is has to be addressed, that too little progress has been made in the field, and that more integrated research is needed to understand the mechanisms of cognitive ageing . The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology will answer this call directly by working on identifying the risk factors for, and mechanisms of, individual differences in age-related cognitive decline–**cognitive ageing**–and its relationship to morbidity and mortality in later life–**cognitive epidemiology**.

## The Centre's objectives

The Centre will initially run from 2008 to 2013. It will enhance the University of Edinburgh's research on lifelong health and wellbeing, especially with regard to cognition. It will have a doctoral training programme and clinical research fellowship. The Centre's objectives are:

- **To explore lifecourse influences on cognitive ageing** and pathways whereby cognitive ability in early life affects later health—**cognitive epidemiology**. As a contribution to this it will maintain, develop and exploit the unique long-term human cohort studies assembled in Scotland as new national resources.
- **To advance knowledge** by research into biological, neurological, genetic, social, economic, and psychological aspects of cognitive ageing in humans and lifecourse mammalian model systems.
- **To develop and evaluate methods** in psychological, genetic, other biological, and brain imaging science to assess, monitor, and prevent or ameliorate decline in mental functions with a view to providing a rational basis for translating this into potential interventions.
- **To train an essential and novel kind of researcher** capable of accessing the best technologies to maximise opportunities for working in multidisciplinary teams in cognitive aging and cognitive epidemiology across clinical and basic science.

## The leading Centre scientists are

### Director

Prof Ian Deary (Psychology)

### Co-directors

Prof Jonathan Seckl (Centre for Cardiovascular Sciences)
Prof John Starr (The Geriatric Medicine Unit)

### Research group leaders

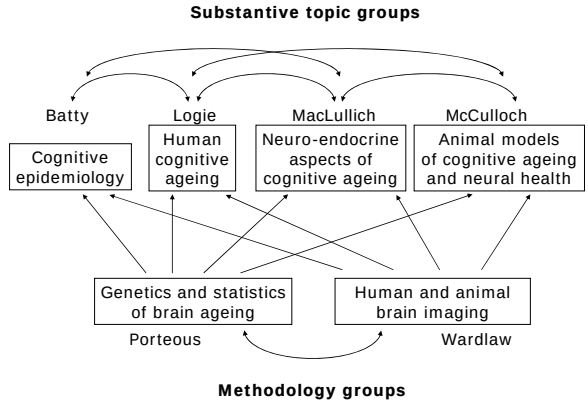
Dr David Batty (MRC Social & Public Health Sciences Unit)
Prof Robert Logie (Psychology)
Prof Jim McCulloch (Centre for Cognitive & Neural Systems)
Prof David Porteous (Molecular Medicine Centre)
Prof Alasdair MacLullich (The Geriatric Medicine Unit)
Prof Joanna Wardlaw (Division of Clinical Neurosciences)

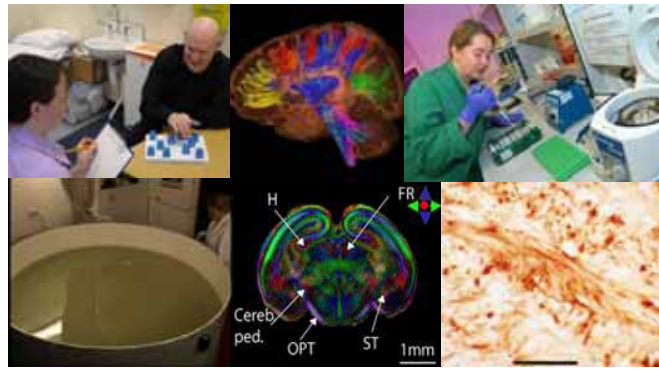
## Core staff employed in the Centre include

Researcher/Scientific Administrator (Psychology)
Database IT Manager and Web Designer (Psychology)
Geneticist (Molecular Medicine Centre)
Statistician (Psychology)
Genetic Statistician/Bioinformatician (Molecular Medicine Centre)
Knowledge Transfer Officer (Psychology)
Human Testing Technician (Psychology)
Animal Dev$^{t}$ Technician (Centre for Cardiovascular Sciences)
Brain Imaging Dev$^{t}$ Technician (Clinical Neurosciences)
Administrative Secretary (Psychology)

## The Centre's Collaborating Network

The Centre consists of **six research groups**, each focusing on a different area of cognitive ageing and cognitive epidemiology. They are linked through collaborations in grants, publications, and postgraduate student supervision.




## The Centre's contributing scientists are

Dr Sharon Abrahams, Dr Mark Bastin, Prof Tim Bates, Prof Harry Campbell, Dr Kathy Evans, Prof Sergio Della Sala, Mr Geoff Der, Dr Jennifer Foley, Prof Brian Frier, Dr Catharine Gale, Dr Alan Gow, Dr Roanna Hall, Dr Gillian Hamilton, Dr Sarah Harris, Dr Lorna Houlihan, Prof Megan Holmes, Dr Karen Horsburgh, Dr Wendy Johnson, Dr Michelle Luciano, Prof William MacNee, Dr Sarah MacPherson, Prof Ian Marshall, Dr Alexa Morcom, Dr Susan Munoz Maniega, Prof Richard Morris, Dr Lars Penke, Dr Jackie Price, Dr Beverly Roberts, Prof Neil Roberts, Dr Tom Russ, Dr Susie Shenkin, Dr Cathie Sudlow, Dr Pippa Thomson, Dr Maria Valdes-Hernandez, Prof Peter Visscher, Dr Thomas Wolbers, Dr Emma Wood, Prof Alan Wright, Dr Joyce Yau.

**www.ccace.ed.ac.uk**

# THE LOTHIAN BIRTH COHORT 1936 STUDY

## Determinants of normal cognitive ageing in surviving participants of the Scottish Mental Survey 1947

Ian Deary, John Starr, Lawrence Whalley, Valerie Wilson, David Porteous, Harry Campbell & Peter Visscher
Alan Gow, Michelle Taylor, Janie Corley, Caroline Brett, Caroline Cameron, Sarah Harris, Wendy Johnson, Michelle Luciano, Shirley Jia & Geraldine McNeill

### • Aims

1. To recruit and examine 1000 surviving participants of the Scottish Mental Survey 1947
2. To collect detailed cognitive phenotypes, including assessment of the specific domains of cognitive function and speed of information processing
3. To collect demographic, medical and physical information to relate to cognitive ageing
4. To collect and store DNA and to examine candidate genes for variation in cognitive ageing
5. To examine the role of information processing speed as a possible explanatory variable in cognitive ageing
6. To establish baseline measures to follow-up the participants as they grow older

### • Background

Decline in memory and other thinking skills is among the most feared aspects of growing old. Cognitive impairment is associated with lower quality of life, loss of independence and is the biggest cause of older people becoming institutionalised. Worldwide, there is currently great research effort aimed at finding out why some people's mental abilities age better than others. The Lothian Birth Cohort 1936 Study will test for determinants of differences in cognitive ageing at age about 70. Because this research involves measuring how people's mental skills have changed, it is ideal to have a measure of mental efficiency from youth but few studies have this. Scotland is special; it collected mental test data on almost everyone born in 1936 at age 11 in the Scottish Mental Survey of 1947 (SMS1947). The Lothian Birth Cohort 1936 Study is using this information and has retested 1091 of these individuals to find out why some people do worse or better than expected from their ability at age 11 in 1947. Among the causes sought are genetic influences, speed of processing, occupation, education, and medical factors.

### • The Lothian Birth Cohort 1936

Individuals who were included in the SMS1947 were identified and recruited from Edinburgh and the surrounding areas (the Lothians). The 1091 participants recruited are known as the Lothian Birth Cohort 1936 (LBC1936). Between July 2004 and May 2007, each participant attended the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital in Edinburgh to undergo cognitive and physical tests, and to answer questions about their medical history. Full details of the recruitment and testing procedures can be found in Deary et al. (2007).

**The 1000th participant in the Lothian Birth Cohort 1936 Study**

The 1000th LBC1936 participant completes his Moray House Test for the second time (left). He first took the test at school in June 1947, when aged about 11. The clinical assessment also included a detailed physical examination (right).

### • Measures

***Cognitive Tests:*** Re-administer the Moray House Test to assess cognitive change between age 11 and about age 70; Mini-Mental State Examination (MMSE) to screen for dementia; Matrix Reasoning and Block Design from the Wechsler Intelligence Scale (WAIS-III) and Verbal Fluency to assess current fluid ability; Logical Memory, Verbal Paired Associates, and Spatial Span from the Wechsler Memory Scale (WMS-III) to assess memory; Letter Number Sequencing and Digit Span Backwards from the WAIS-III to assess working memory; Reaction Time (simple and choice), Inspection Time and WAIS-III Digit-Symbol Coding to assess information processing speed.

***Demographic and Medical Information:*** Social and demographic history, medical history, medication history, and a physical examination including: height, weight, demispan, blood pressure, lung function tests, visual acuity, and grip strength. Self-reported mood was assessed using the Hospital Anxiety and Depression Scale. Blood samples were taken for haematological and biochemical analyses.

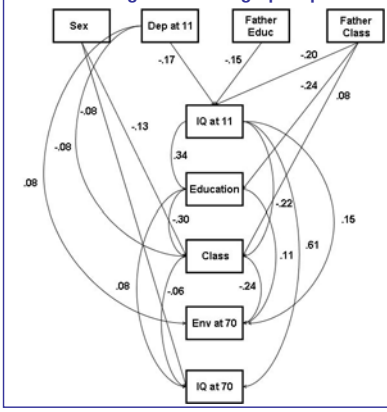
***Genetic Analyses:*** Blood was drawn for DNA extraction, storage and genotyping. This will be a uniquely valuable resource (of stored phenotypes and DNA) for future studies to identify genes for cognitive ageing

***Psychosocial and Nutritional Factors:*** Influences on cognitive ageing include lifestyle and other personal factors. Following the clinic appointment participants were asked to complete a series of questionnaires at home and return them by post. The questionnaire booklet included assessments of personality traits (Five Factor Model), quality of life (WHO Quality of Life Questionnaire), social support and intellectual engagement, and nutrition (Food Frequency Questionnaire).

### • Results: some initial examples

***Demographics:*** The effect of a range of demographic factors on cognitive function at age 70 have been examined. Firstly, men had better cognitive function than women at age 70. Childhood mental ability (age 11), the number of years in full-time education, and individual social class also contributed. When these variables were controlled, age 11 home environmental quality (a composite measure combining the number of rooms in the home, the number of people living in there, whether toilet facilities were indoor or outdoor, and the number of people sharing these), father's social class, father's education, and age 70 home environmental quality (from The Scottish Index of Multiple Deprivation, 2006) made no contribution. The details of this model are shown in Figure 1.

**Figure 1: Demographic predictors of mental ability at age 70**




Path diagram for the model of sex, age 11 home environmental quality (Dep at 11), father's education and social class, age 11 IQ, own educational attainment in years, own social class, home environmental quality at age 70, and age 70 IQ. Path coefficients are standardised. Only statistically significant paths are shown.

Age 11 and 70 IQ are derived from the Moray House Test, controlled for age in days at the time of testing and converted to an IQ type scale.

***Diet:*** The food frequency questionnaire completed by the LBC1936 collected detailed information on the dietary intake of B vitamins, antioxidant nutrients, flavonoids and fatty acids. Both riboflavin and vitamin B12 from food were associated with better performance on tests of immediate memory. Total riboflavin intake (from food and supplements) was positively associated with reasoning ability. There were also clear food patterns; meat consumption (including all types of meat) was inversely associated with crystallised ability.

***Genetic factors:*** The genetic determinants of cognitive ability and cognitive ageing are being sought in the LBC1936. Gene variants previously associated with Alzheimer's disease, autism or cognition have been genotyped in the LBC1936, including NCSTN, DISC1, ADRB2, WRN, BDNF, SORL1, KL, PPP1R1B, PRNP, COMT and SHANK3. None of the tested variants were found to be associated with cognitive ability/ageing in the LBC1936 (all *p*-values > 0.01). However, *APOE*, a gene linked to Alzheimer's disease, was associated with measures of processing speed when childhood IQ was factored into analysis (there was no association between *APOE* and measures of memory). Individuals who possessed the e4 allele variant of the *APOE* gene showed a weaker correlation between childhood IQ and adult processing speed than those without the e4 genetic variant. The LBC1936 are to be included in a large genome-wide association study of non-pathological cognitive ageing.

### • Future Plans

The results from this wave of data collection will provide an invaluable first look into old age, and funding has been secured to follow-up the LBC1936 participants in subsequent waves from age 70 onwards. This is part of *The Disconnected Mind* project being funded by Help the Aged. The research has the potential to a add a great deal to what is known about the influences on the ageing process so that the quality of life of many people can be improved.

*Funding - The LBC1936 Study is supported by a Research into Ageing programme grant.*

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**Secretary for the LBC1936 Study**
Paula Davies (Tel. 0131 651 1681)

**Educational Collaborators**
Scottish Council for Research in Education

**Clinical Collaborators**
Wellcome Trust Clinical Research Facility

**Primary Care Collaborators**
Lothian Health Board

# THE DISCONNECTED MIND

**The Disconnected Mind aims to understand how changes in the brain's white matter – its connectivity – contribute to age-related cognitive decline in humans.**

Decline in mental capability is the major cause of institutionalisation among older people, a great loss in life's quality to the sufferers and their families, and a huge financial cost to the nation. The aim of The Disconnected Mind is to make a novel contribution to understanding why people's cognitive functions decline as they grow older. The project's principal focus is on the brain's white matter – the connections between the nerve cells in the brain. Without intact and healthy connections, thinking is slower and mental functions are impaired. The core hypothesis of the project is: age-related cognitive decline, especially the fundamental efficiency of information processing, is importantly affected by declining white matter integrity. The Disconnected Mind is an integrated programme including human studies and translates, to humans, knowledge of the genetic, molecular and cellular mechanisms underlying brain white matter changes and altered cognitive ability in experimental models.

**We aim to understand:**

- **why brain white matter deteriorates in old people;**
- **why some people's white matter deteriorates more than others;**
- **and why this causes deterioration in various cognitive functions.**

**The Lothian Birth Cohort 1936**

The first human cohort in The Disconnected Mind comprises a unique group of older people whose mental functions have been studied in childhood and in old age; they are the 1000+ members of the Lothian Birth Cohort 1936 (LBC1936). All were assessed at 70 years old and are currently participating in a second wave of cognitive and physical testing at the Wellcome Trust Clinical Research Facility, Edinburgh. In addition, the LBC1936 are undergoing detailed MR brain imaging and carotid Doppler assessments at the SFC Brain Imaging Research Centre (SBIRC).

LBC1936 progress is reported in a series of accompanying posters across the areas of: phenotypes and lifestyle, genetics, and imaging. In terms of lifestyle, the LBC1936 have provided details of their dietary patterns, and Corley et al. report the associations between caffeine intake and cognitive function. In addition to changes in mental abilities, quality of life is an important outcome for older people; to this end, Brett et al. examine the psychosocial and lifestyle predictors of this.

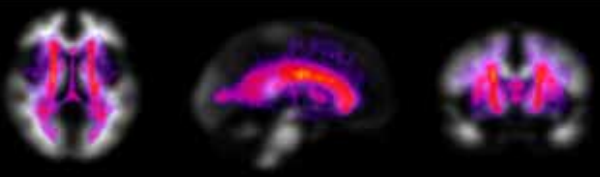

**Comprehensive testing in The Disconnected Mind**

This compilation captures just some of the testing that goes on with the Lothian Birth Cohort 1936. It includes factors in the following domains: social, lifestyle, mood, wellbeing, cognition, physical, sensory, medical, genetic, brain imaging, blood markers, and many more. The cohort is examined for the diverse determinants of cognitive ageing; and other outcomes related to quality of life.

The Disconnected Mind has developed new, sensitive magnetic resonance brain imaging (MRI)-based techniques to assess the integrity of white matter. These give detailed information about the internal fine structure of the brain's connections in a non-invasive examination (with further details on the image processing on the accompanying posters: Valdés Hernández et al. and Muñoz Maniega et al.).

Examples of some of the derived brain images can be seen in the panel below. These techniques are producing quantitative imaging biomarkers which are then correlated with the cognitive data to investigate the biological basis of cognitive ageing (more details about the relationship between iron deposits in the brain and cognitive function can be seen on the poster of Penke et al.).

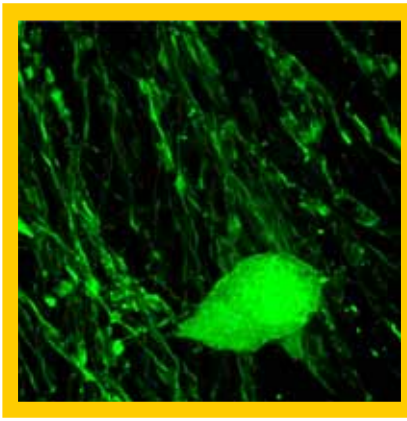
**Brain images from The Disconnected Mind**



These images map the distribution of white lesions across a group of LBC1936 participants.

**Animal and experimental models**

Experimental studies in rodents parallel the human studies in The Disconnected Mind. These models are used to evaluate the impact of factors upon white matter lesion progression. The aim is to define early structural changes in white matter, underlying mechanisms and the impact of these on cognitive ability. It is hypothesised that vascular disturbances, such as hypotensive episodes and/or hypoperfusion, are an important cause of subcortical ischaemia, chronic white matter dysfunction and accelerated cognitive decline. These hypotheses are being tested in reproducible experimental models in which vascular disturbances can be controlled and neuropathological changes in white matter clearly defined.



**Cellular imaging in The Disconnected Mind**

Oligodendrocytes are the cells that produce the insulation of the axons (the myelin sheath). This image shows a single oligodendrocyte in one of the major white matter tracts of the brain, the corpus callosum, from a transgenic mouse. The whole oligodendrocyte cell, including its myelin sheath, is labelled with "green fluorescent protein" that is exclusively expressed in all cells of the oligodendroglia lineage. These transgenic mice will allow the detection of subtle changes in the myelin sheaths due to chronic cerebral hypoperfusion.

The use of a model of chronic hypoperfusion is key to this work, and has been further examined in terms of the white matter damage it induces (for example, the accompanying poster of Gliddon et al. reports on the time course of these changes). The effect of these subtle structural changes on behaviour, particularly memory, have been studied (with more details on the poster of Tsenkina et al.). The experimental models are examined by a number of imaging techniques in order to learn more about the cellular and molecular mechanisms by which white matter damage is produced (see the panel above). This includes brain imaging using parallel protocols to those in the human studies (described here by the posters of Bastin et al. and Holland et al.), and structural pathology to assess the brain using detailed structural analysis of white matter (including the use of confocal laser scanning microscopy, described by Reimer et al.).

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**Researchers: Caroline Brett, Robin Coltman, Janie Corley, Stephanie Daumas, Gail Davies, Ruth Deighton, Tommy Dingwall, Jill Fowler, Catherine Gliddon, Alan Gow, Sarah Harris, Ross Henderson, Philip Holland, Lorna Houlihan, Karim Khallout, Severine Launay, Michelle Luciano, Kevin McGhee, Susana Muñoz Maniega, Catherine Murray, Alison Pattie, Lars Penke, Michell Reimer, Natalie Royle, Fiona Scott, Jessica Smith, Aisling Spain, Yanina Tsenkina, Maria Valdés Hernández**

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