# The Disconnected Mind

Unlocking secrets of healthy mental ageing

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

### Newsletter 61: Spring 2023

Welcome to the 61st edition of the Disconnected Mind Newsletter! Each issue brings news about the Lothian Birth Cohorts team, our latest research and publications, and scientific and public engagement events.

### Wave 6 data collection completed!

Testing of the LBC1936 is a core objective in each phase of The Disconnected Mind project. The Covid-19 pandemic shifted the start date of Wave 6 data collection from April 2020 to October 2021.

We are delighted to report that Wave 6 of the LBC1936 study is now complete. The team successfully completed data collection from 293 participants - now at an average age of 86 years – who attended cognitive and physical assessment at the Wellcome Trust Clinical Research Facility (WTCRF) and 196 participants who undertook a 5th brain Magnetic Resonance Imaging (MRI) scan at Edinburgh Imaging Facility (EIF), Royal Infirmary of Edinburgh. Congratulations on this impressive achievement!


LBC1936 team 2022. Left to right: Danielle Page, Simon Cox, Adele Taylor, Janie Corley, Beth Jones, Alison Pattie.

Danielle Page of the LBC1936 testing team said: *"The testing team have again been overwhelmed by the dedication of our participants to the LBC study, and their enthusiasm to returning to see us, particularly despite all of the complications posed by the COVID pandemic. We are incredibly grateful for their ongoing participation, without which the study would not exist!"*

## Staff Updates

### Thank you, Alison Pattie!

Alison Pattie has been a core member of the Lothian Birth Cohorts study since their inception in 1998. She was there when Professors Ian Deary and John Starr set the study in motion. She worked closely with the LBC1921 cohort and became an indispensable member of the cognitive testing team for Waves 1 to 5.

Alison announced her retirement in Spring 2019, but we were delighted to be able to tempt her back to the fold to help the LBC1936 testing team bring participants back after the COVID-19 delay to Wave 6. She joined the team again in October 2021 and lent her considerable experience and expertise to our efforts, helping us complete Wave 6 in good time, with the LBC1936 participants now all in their mid-80s.

Reflecting on her experience, Alison said*: "The many years I worked with the LBC studies have flown by so quickly and I consider myself very lucky to have worked with such pleasant participants and colleagues."*

She is pictured below with Mr Andrew Begg who was the 293rd and final Wave 6 participant.

Miss Alison Pattie with Mr Andrew Begg at WTCRF

LBC Director, Dr Simon Cox said: "*It's been an absolute pleasure to have Alison help with our cognitive testing once again. She is such an asset, and knows the LBCs like the back of her hand – I'm sure the participants were as delighted as we were to see her again – thanks so much Alison!"*

## Congratulations, Dr Jure Mur!

An important objective of the Lothian Birth Cohorts is the commitment to raising generations of new scientists. As a result, the study can boast with an army of successful research off-springs!

In this issue, we celebrate the achievements of Jure Mur, who joined the research team as a Wellcome Trust PhD student in Translational Neuroscience. He has recently successfully completed his degree under the supervision of several LBC members and collaborators, Drs Tom Russ, Simon Cox, Riccardo Marioni, and Graciela Muniz Terrera.

Jure's PhD thesis, entitled 'Anticholinergic use in the UK: longitudinal trends and associations with cognitive outcomes', used UK Biobank data and examined various epidemiological questions and methods, including investigation of UK prescribing trends in mediations with anticholinergic properties, and whether (and how far) differences in an individual's anticholinergic burden are significant in outcomes such as hospital admissions for falls, brain structural ageing, cognitive decline and dementia diagnosis.

His research has resulted in several high-profile publications, including an important study in *the British Journal of Clinical Pharmacology* showing that anticholinergic burden has increased by as much as 6-fold over the last 3 decades:

Mur, J. et al. (2022). 'Association between Anticholinergic Burden and Dementia in UK Biobank'. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*.

Mur, J. et al. (2022). 'Increase in Anticholinergic Burden from 1990 to 2015: Age-period-cohort Analysis in UK Biobank'. *British Journal of Clinical Pharmacology*.

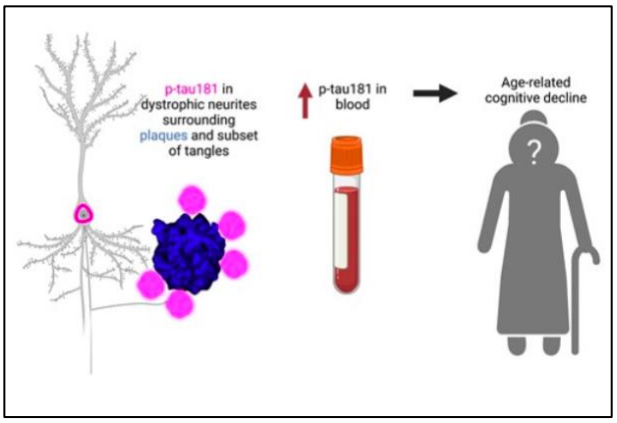
Mur, J. et al. (2021). 'Variation in VKORC1 is Associated with Vascular Dementia'. *Journal of Alzheimer's Disease*.

Mur, J. et al. (2020). 'DNA Methylation in APOE: The Relationship with Alzheimer's and with Cardiovascular Health'. *Alzheimer's and Dementia.*

Dr Mur continues working with the team as a Research Fellow.

# Scientific Highlights

## LBC1936 post-mortem brain samples used to understand mechanisms promoting cognitive resilience in older age




Neurodegenerative disorders like Alzheimer's Disease are difficult to diagnose clinically. Measures detectable in cerebrospinal fluid and positron emission tomography are available, but their use is limited because of their high costs and perceived invasiveness. Exciting recent developments show that proteins related to Alzheimer's Disease can now be measured in blood. Blood markers show great promise for distinguishing people with Alzheimer's Disease from healthy controls. It is also important to understand what role these biomarkers play in age-related cognitive decline without dementia.

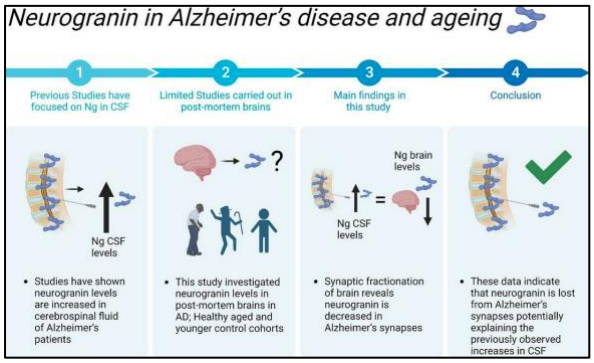
A study led by PhD student Tyler Saunders, supervised by Professor Tara Spires-Jones tested whether blood levels of several well-established biomarkers for Alzheimer's Disease – including p-tau181 – predict cognitive decline between ages 72 and 82 in 195 LBC1936 participants.

Based on LBC post-mortem brain samples, they aimed to determine if p-tau181, whose accumulation is a key pathological feature of Alzheimer's disease, could be associated with synaptic impairment in those without the disease.

The study showed that blood biomarkers like p-tau181 may be useful for age-related cognitive decline. Furthermore, the study suggests that clearance of p-tau181, mediated by special brain cells called astrocytes, may prevent synaptic degeneration and promote cognitive resilience.

Saunders, T. et al. (2023). 'Predictive Blood Biomarkers and Brain Changes Associated with Age-Related Cognitive Decline'. *Brain Communications.*

## Neurogranin in Alzheimer's synapses




Another study led by PhD student Tyler Saunders focused on the loss of neurogranin – a post-synaptic protein involved in memory formation – and its role in ageing.

The team compared neurogranin levels in post-mortem brain tissue across Alzheimer's Disease, healthy ageing (with healthy LBC agers), and mid-life cohorts.

The study found that levels of neurogranin were significantly reduced in Alzheimer's disease, suggesting that loss of brain neurogranin is associated with cognitive decline. This could also explain its increased levels in the cerebrospinal fluid (CSF).

Synaptic biomarkers such as the use of CSF neurogranin may be useful for tracking disease progression and cognitive decline in those without dementia.

Saunders, T. et al. (2023). 'Neurogranin in Alzheimer's disease and ageing: A human post-mortem study'. *Neurobiology of disease.*

## Where we grow up and live is related to our cognitive ability in older years

Neighbourhoods influence our physical and mental health. The rich longitudinal data of the LBC1936 study with its unique information about the same individuals across the life course helps us understand how environments throughout life are associated with ageing differences.

In another output from the ESRC-funded project in collaboration with the School of GeoSciences, Dr Gergo Baranyi and team focused on how neighbourhood deprivation from birth to late adulthood was associated with cognitive ageing in the LBC1936.

The key findings showed that living in disadvantaged areas of Edinburgh during mid- and late adulthood is associated with cognitive function: older adults living in deprived neighbourhoods had lower levels of general cognitive ability when they were 70 years old, and they also experienced faster cognitive decline in the following years.

Childhood neighbourhoods also contributed to late-life cognitive function: those growing up in socially advantaged neighbourhoods experienced more years spent in education, which, the authors suggest, may be one of the factors contributing to 'cognitive reserves' and delayed age-related cognitive decline.

Baranyi, G. et al. (2023). 'Neighbourhood Deprivation across Eight Decades and Late-Life Cognitive Function in the Lothian Birth Cohort 1936: A Life-Course Study'. *Age and Ageing.*

## Keeping an eye on apathy

Cerebral Small Vessel Disease is a common neurological disease in older people. It causes stroke and dementia, and it is associated with mood disturbance.

A study, led by Dr Una Clancy, examined whether neuropsychiatric and cognitive symptoms – anxiety, depression, apathy, or subjective memory complaints – could predict longitudinal changes in the white matter in the LBC1936 over six years, from age 73 to 79.

The study found that only apathy independently associates with preceding longitudinal white matter hyperintensity progression, while depression, anxiety, and subjective memory complaints do not.

The authors conclude that patients with apathy should be considered for enrolment to small vessel disease trials.

Clancy, U. et al. (2023). Are neuropsychiatric symptoms a marker of small vessel disease progression in older adults? Evidence from the Lothian Birth Cohort 1936. *International Journal of Geriatric Psychiatry.*

## Knowledge Exchange

### Dr Miles Welstead's work at the National Bureau of Economic Research Cohort Studies

The National Bureau of Economic Research (NBER), founded in 1920, is an American private non-profit research organization with commitment to undertaking and disseminating unbiased economic research among public policymakers, business professionals, and the academic community.

The NBER convenes over 120 meetings each year to bring together researchers for the opportunity to share and discuss their latest findings and launch new projects.

The annual NBER Cohort Studies meeting was held in January in Los Angeles. The workshop brought together scholars with a common interest in the analyses of life course and multigenerational events in aging; the role of cumulative exposures in aging-related outcomes; and in understanding how the economic, institutional, and demographic context has changed for different cohorts and for different racial, ethnic, gender, and socioeconomic groups within cohorts.

Dr Miles Welstead, former LBC PhD student, contributed to the meeting with a study 'Heterogeneity of Frailty Trajectories and Aassociated Factors in the Lothian Birth Cohort 1936'.

Based on his PhD thesis, the study identified several factors associated with higher frailty trajectory, including lower social class, less education, and lower childhood cognitive ability, and highlighted an urgent need for further research focusing on protective factors and interventions that could offer alternative outcomes for those from risk populations.

Miles said: *"Our findings highlight the heterogeneous nature of frailty progression and indicate that not all older adults will follow a similar path. This has clinical implications, for identifying those on steeper trajectories and implementing effective prevention strategies."*

### Professor Catharine Ward Thompson delivers a keynote address at the Spanish National Congress of Parks and Public Gardens in Madrid

In February, Professor Catharine Ward Thompson, our collaborator on the ESRC-funded Lifecourse of Place project, delivered an invited keynote address, 'Healthy Parks and Open Space: the Salutogenic Environment', at the 49th Spanish National Congress of Parks and Public Gardens (Asociación Española de Parques y Jardines Públicos) in Madrid.

Catharine presented to an audience of over 200 parks, gardens and public open space planners and managers, on the theme of 'Parks and Gardens – Natural Health Systems', reviewing her research, including work with the LBC1936 cohort, on parks and open spaces as important areas for health and wellbeing.

As a result of this presentation, Catharine was interviewed for a podcast by the World Urban Parks forum, in which she was asked about the work with LBC1936: https://edin.ac/3mTgHSk.

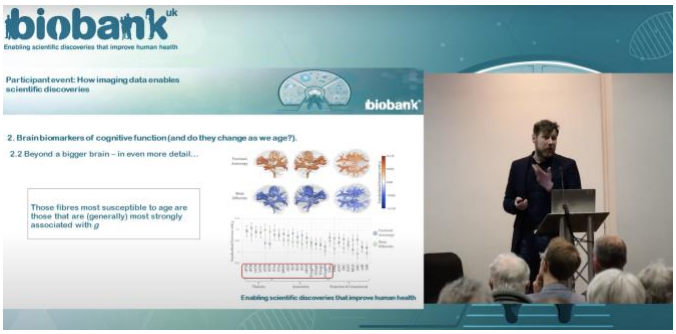
## Study director Dr Simon Cox presents to participants at UK Biobank event

UK Biobank is a large-scale biomedical database and research resource with wealth of health information from half a million UK participants. It has also developed a rich brain imaging and genetic database.

The Lothian Birth Cohorts team has, since 2013, published over 130 scientific papers that draw on the UK Biobank data. Of these, 35 publications use combined data from the LBC and UK Biobank cohorts. Many of these papers appear in top scientific journals, including Nature and Science.

The study director Dr Simon Cox was invited to join a programme of other leading scientists to share with the audience of 200 study participants how their imaging data are used to understand dementia.

Simon's talk, entitled 'Exploring brain and cognitive ageing pre-dementia' was focused on the healthy stages.




Dr Simon Cox presenting at the UK Biobank participant event

Simon said about the event: *"We have been early and productive adopters of UK Biobank data. I really enjoyed the opportunity to meet participants and tell them about just some of the discoveries we have made thanks to their brain imaging data. It also made me look forward even more to the forthcoming Lothian Birth Cohort Reunion event in May."*

You can see Simon's presentation and the rest of the programme on YouTube: https://edin.ac/3N2HDty.

## Lothian Birth Cohorts celebrate the Brain Awareness Week with a launch of a new public engagement initiative!

Dr Thomas Bak in front of 23 George Square

*BrainEd* is a new collaboration between the Lothian Birth Cohorts and Edinburgh Neuroscience, with a range of activities that aim to promote Edinburgh brain science and raise the public's brain awareness and health. The initiative was launched in March during the Brain Awareness Week with the first in a series of guided tours called Discover Neuroscience.

The tour was led by Dr Thomas Bak, Reader in Human Cognitive Neuroscience in the School of Philosophy, Psychology and Language Sciences and a licenced tour guide. In 60 minutes, Thomas, an experienced and engaging guide, surprised and entertained the participants with stories and facts inspired by the LBC research and findings, and rich local neuroscience history and heroes, and took the event participants on a walk from George Square to the National Museum of Scotland, highlighting unexpected connections between historical buildings, museum artifacts and rich Edinburgh neuroscience research.

Dr Thomas Bak with the participants in front of Bedlam Theatre

## Publication update since January 2023:

**Published:**

Baranyi, G. et al. 'Neighbourhood Deprivation across Eight Decades and Late-Life Cognitive Function in the Lothian Birth Cohort 1936: A Life-Course Study'. Age and Ageing. https://doi.org/10.1093/ageing/afad056.

Corley, J. et al. (2023). 'Predictors of Longitudinal Cognitive Ageing from Age 70 to 82 Including APOE E4 Status, Early-Life and Lifestyle Factors: The Lothian Birth Cohort 1936'. Molecular Psychiatry. https://doi.org/10.1038/s41380-022-01900-4.

Fernandez-Rozadilla, C. et al. (2023). 'Deciphering Colorectal Cancer Genetics through Multi-Omic Analysis of 100,204 Cases and 154,587 Controls of European and East Asian Ancestries'. Nature Genetics. https://doi.org/10.1038/s41588-022-01222-9.

Leighton, D. J. et al. (2023). 'Genotype-Phenotype Characterisation of Long Survivors with Motor Neuron Disease in Scotland'. Journal of Neurology 270. https://doi.org/10.1007/s00415-022-11505-0.

Saunders, T. et al. (2023). 'Neurogranin in Alzheimer's Disease and Ageing: A Human Post-Mortem Study'. Neurobiology of Disease. https://doi.org/10.1016/j.nbd.2023.105991.

Weihs, A. et al. (2023). 'Epigenome-Wide Association Study Reveals CpG Sites Associated with Thyroid Function and Regulatory Effects on KLF9'. Thyroid: Official Journal of the American Thyroid Association. https://doi.org/10.1089/thy.2022.0373.

Yang, Y. et al. (2023). 'Epigenetic and Integrative Cross-Omics Analyses of Cerebral White Matter Hyperintensities on MRI'. Brain. https://doi.org/10.1093/brain/awac290.

**Ahead of Print:**

Chundru, V. K. et al. 'Rare Genetic Variants Underlie Outlying Levels of DNA Methylation and Gene-Expression'. Human Molecular Genetics. https://doi.org/10.1093/hmg/ddad028.

Hahn, J. et al. 'DNA Methylation Analysis Is Used to Identify Novel Genetic Loci Associated with Circulating Fibrinogen Levels in Blood'. Journal of Thrombosis and Haemostasis: JTH. https://doi.org/10.1016/j.jtha.2023.01.015.

McGreevy, K. M. et al. 'DNAmFitAge: Biological Age Indicator Incorporating Physical Fitness'. Aging. https://doi.org/10.18632/aging.204538.

**Accepted /In Press:**

Saunders, T. et al. 'Predictive Blood Biomarkers and Brain Changes Associated with Age-Related Cognitive Decline'. Brain Communications.

## Contact

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NIH National Institutes of Health

The University of Edinburgh