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 65: Spring 2024

Welcome to the Spring edition of the Disconnected Mind Newsletter! Catch up on the latest news from the Lothian Birth Cohorts team, our latest research and publications, and scientific and public engagement events.

Wave 7 of the LBC1936 begins!

The first Wave 7 participant with Sabela Mendez at the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital

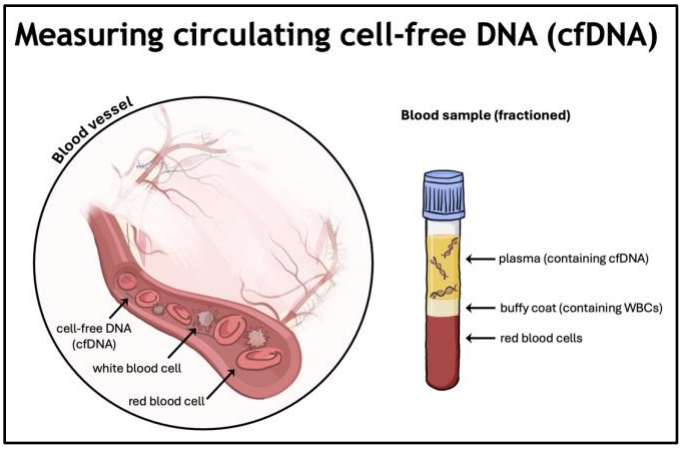
The LBC1936 team has been working hard preparing for Wave 7 of data collection and we are delighted to report that the team have now started testing the first participants! We hope to welcome back approximately 200 participants for cognitive testing and 125 participants for an MRI scan. The participants, now at an average age of 88, will contribute invaluable information on many aspects of their cognitive ability, life and health. Our dedicated testing team currently comprises Dr Janie Corley, Sabela Mendez, and Adele Taylor. Janie, who has been with the LBC cognitive testing team since the beginning of the LBC1936 study and has, as the longest serving member of the team, a wealth of experience welcomed the first participant on Thursday 21 March at the WTCRF, together with the newest member of the team, Sabela Mendez. Janie said: "*It's wonderful to see our amazing participants again. Their ongoing commitment to the study continues to enrich our understanding of ageing."*

Sabela, who joined the group in September and is meeting the participants for the first time, added: *"I'm truly excited to finally meet our participants in person and learn from their unique experiences and perspectives, and I'm also thrilled to be a part of this next milestone for the LBC cohort."*

The estimated time to complete this wave is one year.

Scientific Highlights

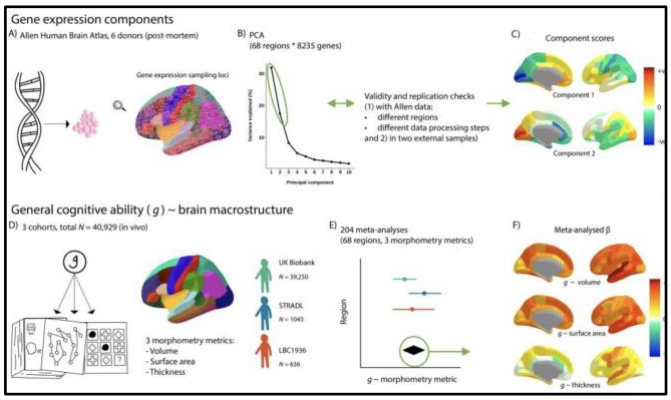
Cell-free DNA testing with LBC1936 blood samples



Measuring circulating cell-free DNA (Credit: Dr Eleanor Conole)

The LBC1936 blood samples are to be used for a laboratory method that involves analysing free (i.e., non-cellular) DNA circulating in the blood stream. Cell-free DNA are short fragments of degraded DNA that are released to body fluids such as blood plasma, urine, or cerebrospinal fluid. The ability to extract circulating DNA from the human plasma has been used for the detection and characterization of some cancers and to monitor cancer therapy; it has also been used as a biomarker for other conditions, including stroke and diabetes. The LBC team has recently completed a £1.1M collaborative agreement with CFDX – a biotech company developing a precision neuroscience platform – to measure the methylation of cell-free DNA from brain cells. The work will be based on longitudinal LBC1936 blood samples to build models for diagnosis and trajectory of cognitive ageing and Alzheimer's Disease.

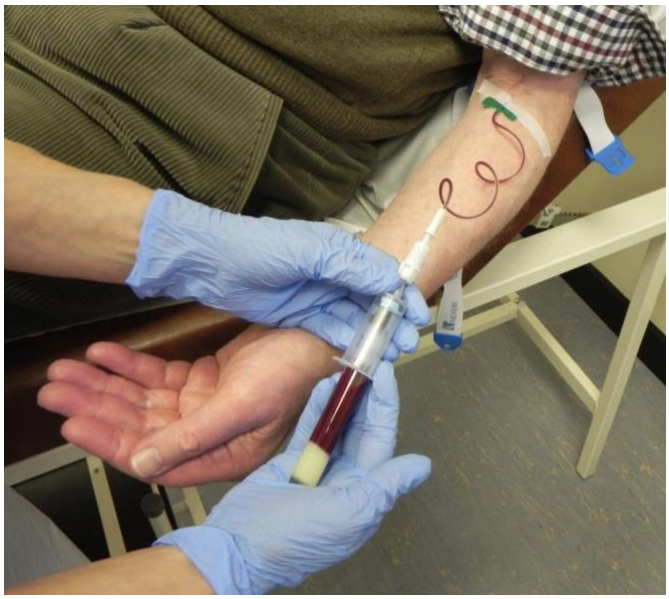
Understanding gene expression patterns in areas of the brain linked to complex cognitive functioning



A paper led by Dr Jo Moodie used a novel method to understand the relationship between gene expression in the brain and general cognitive functioning. The aim was to examine which specific genes are more highly expressed in brain regions that are most strongly related to general cognitive functioning. To address this question the team combined micro- and macro-level information about the brain, using MRI and cognitive data from three cohort studies (including the LBC1936) together with post-mortem data from 6 donors in the Allen Human Brain Atlas. First, the team identified two general patterns that largely govern brain regional differences in the protein expression of over 8,000 genes. They validated these general patterns in post-mortem samples. Next, they identified the brain regions most associated with differences in general cognitive functioning by meta-analysing MRI and cognitive data across 40,000 individuals. Finally, the team found that (1) the two patterns of gene expression were significantly correlated with areas associated with general cognitive function, and (2) there were a further 29 genes associated with cognitive brain regions *beyond* the two patterns of gene expression. Some of those genes have been previously associated with neurodegenerative and psychiatric disorders, and some are potentially novel candidate genes for cognitive traits. Following up these new targets may further our understanding of the underlying molecular neurobiology of complex cognitive functioning.

Moodie, J.E. *et al.* (2024). General and specific patterns of cortical gene expression as spatial correlates of complex cognitive functioning. *Human Brian Mapping.*

LBC1936 blood samples used in a genome-wide association study to better understand blood clotting

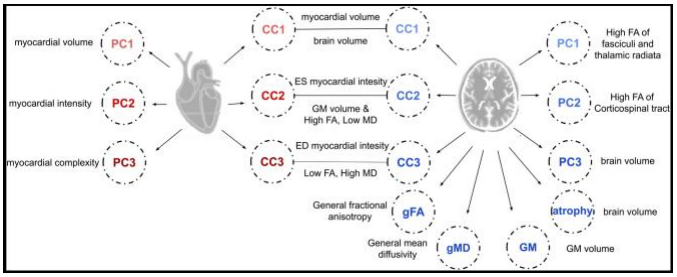


LBC1936 participant's blood sample donation

The LBC participants provide a wealth of invaluable data that help scientists make new important discoveries on many aspects of health. Most recently, their blood samples contributed to a new international genome-wide association study that aimed to better understand the underlying genetic basis of coagulation. Coagulation or blood clotting is a response to bleeding from a damaged blood vessel. It requires that blood cell components (platelets) and coagulation factors form a blood clot at the site of the injury. One of the coagulation proteins that is essential for blood clotting is known as *Factor VIII* (FVIII). When inactive, FVIII circulates in the bloodstream bound to a protein carrier known as *von Willebrand factor* (VWF). When injury to the blood vessel occurs, FVIII activates and separates from VWF, which sets off a cascade of additional chemical reactions that form a blood clot. Levels of FVIII and VWF associated with venous thromboembolism, coronary artery disease, ischemic stroke, and peripheral artery disease are highly heritable. The study identified new genetic regions associated with their levels, and clarified mechanisms underlying their function and release. These findings can help us more accurately assess genetic risk scores associated with bleeding or thrombosis and improve our understanding of new potential therapeutic targets for these conditions.

de Vries, P. S. *et al.* (2024). A genetic association study of circulating coagulation Factor VIII and von Willebrand Factor levels. *Blood.*

"What's good for the heart is good for the brain": Detailed modelling of the heart-brain axis



Schematic illustration for heart-brain axis with extracted latent variables for vascular risk, cognitive function, heart structure and brain structure

Factors that increase the risk of vascular disease – including diabetes, high body mass index and hypertension – are associated with poorer cognitive function. Though both vascular and neural systems must play a role in this environment-cognitive relationship, the facets of brain and heart that figure most prominently in this relationship are not well understood. Fullbright scholar Akshay Jaggi approached LBC director Simon Cox and Dr Eleanor Conole to collaborate in a large cross-centre study, now published in *Imaging Neuroscience*, examining data from thousands of UK Biobank participants.

The study aimed to better understand how the heart-brain axis mediates the relationship between cardiovascular risk factors and cognitive functioning, by combining vascular risk factors, cognitive functioning, cardiac magnetic resonance imaging, and brain MRIs. A selection of brain and heart measures that were most strongly correlated with each other showed the strongest mediation effects. The authors identified a key link for how *low myocardial intensity* – when the supply of blood to the heart is suddenly blocked – could associate with a reduced amount of blood flow in the brain impacting particular subcortical structures, like the *thalamus*. The overall results of the study are consistent with the hypothesis that vascular risk drives changes in cardiovascular structure that lead to alterations in brain structure and subsequent cognitive decline.

Jaggi, A. *et al.* (2024). A structural heart-brain axis mediates the association between cardiovascular risk and cognitive function. *Imaging Neuroscience.*

LBC1921 and LBC1936 data give insights into the genetic basis of thyroid function and disease

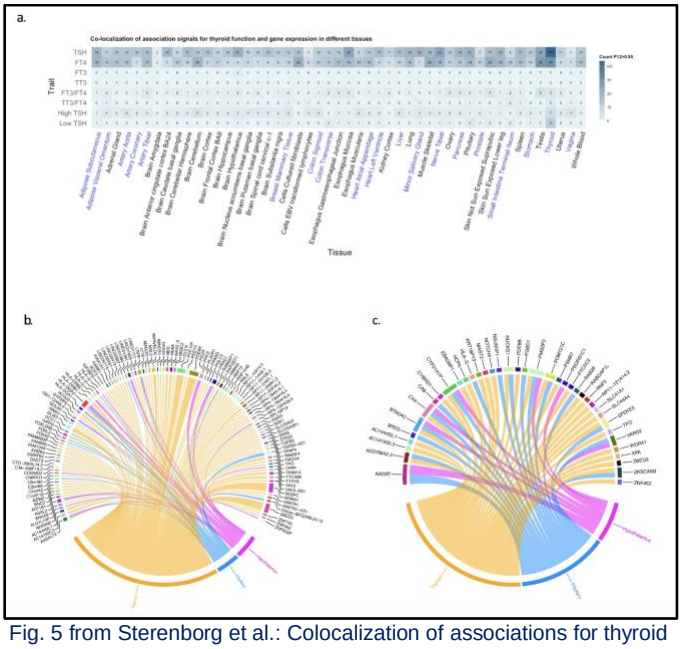


Fig. 5 from Sterenborg et al.: Colocalization of associations for thyroid function parameters and gene expression.

The thyroid is a major endocrine gland. Its primary function is the production of two thyroid hormones -- *triiodothyronine* (T3) and *thyroxine* (T4). The thyroid hormones have a wide range of effects on the body, including the basal metabolic rate, the rate and strength of heartbeat, breathing, intake and consumption of oxygen, influencing blood flow and the body's temperature. Thyroid dysfunction is associated with increased risks of coronary heart disease, atrial fibrillation, stroke, type 2 diabetes, dementia, depression, and mortality. Genetic factors that influence thyroid function play a significant role in thyroid function and are responsible for 58-71% of variation in levels of thyroid hormones across individuals. However, only a fraction of the genetic footprint of thyroid function has been clarified. The LBC1936 and LBC1921 data contributed to a new large genome-wide association meta-analysis of thyroid function, based on 46 studies with 271,040 individuals of European ancestry, yielding novel insights into the genetic basis underlying thyroid function and diseases, including thyroid cancer and highlighted the pleiotropic effects of thyroid function on various diseases.

Sterenborg, R. B. T. M. *et al.* (2024). Multi-trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications. *Nature Communications.*

Knowledge Exchange

Lothian Birth Cohorts and love of languages: Dr Thomas Bak delivers Christmas Lecture at the Centre for Open Learning

Dr Thomas Bak is a Reader in Human Cognitive Neuroscience at the University of Edinburgh and an LBC collaborator. His research interests include dementia and cognitive, emotional and social aspects of multilingualism and language learning. Learning languages is also one of his passions and he is equally committed to sharing his interest in multilingualism with the wider public. It is therefore no surprise that Thomas was invited to deliver the special *Christmas Lecture* for the Centre for Open Learning at the University of Edinburgh. Thomas took the audience of over 50 attendees on a tour through languages of the world and surprising facts and personal stories, documenting the benefits of language learning for our wellbeing. Presenting in the newly refurbished Godfrey Thomson Hall on Moray House Campus, Thomas did not fail to acknowledge Sir Godfrey Thomson and his nationwide IQ tests administered to Scottish 11-year-olds in 1932 and 1947, that form the foundation of LBC research on cognitive ageing across the life course. The audience learned about Thomas' collaboration with LBC researchers in his investigation into bilingualism as a potentially protective factor against age-related cognitive decline. After the talk, attendees followed up with questions about LBC research and participants with Dr Barbora Skarabela, who was manning a demonstration table where audience members could examine 3D-printed brains based on LBC data, test themselves on practice questions from the original Scottish Mental Survey and hear about marginal gains for healthy cognitive ageing.

Dr Janie Corley and Professor Catharine Ward Thompson offer evidence for an inquiry on urban green spaces in the House of Commons

Green spaces, including parks, woodlands and allotments, are recognised as an important asset for supporting health and wellbeing. Public Health England estimate that £2.1 billion could be saved in health costs each year if everyone in England had good access to green spaces where they could exercise, providing evidence that living in a greener environment can promote and protect good health. A recent inquiry into Urban Green Spaces by the Environment, Food and Rural Affairs Committee of the UK Parliament has now focused on the ecological, environmental and human benefits of green spaces, with the aim to explore the most effective solutions to make cities greener and nature rich. Lothian Birth Cohort studies have provided important insights into green spaces across the life course, and the key findings were summarised and submitted as written evidence by Dr Janie Corley. Janie's evidence, now published on the Committee's website, concludes: *"The findings from the LBC studies make an especially valuable contribution to understanding how aspects of physical environment can act as protective factors against cognitive decline. Moreover, these findings are amongst the first to shed light on the lifelong impact of early-life environmental circumstances, particularly the accessibility of local parks. These effects are particularly noteworthy for women and those in lower socioeconomic groups during adulthood. This research underscores the necessity of ensuring consistent and equitable access to urban green spaces throughout one's life to safeguard our future health."*

Professor Catharine Ward Thompson, Professor of Landscape Architecture at the University of Edinburgh also contributed to the inquiry and was invited to provide oral evidence at the House of Commons in December.

As one of the co-investigators on a recently completed ESRC-funded project *'Lifecourse of place: How environments throughout life can support healthy ageing'* based on LBC data, she too drew on some of the findings from Lothian Birth Cohorts, particularly related to inequality and later cognitive and mental health, and the importance of accessible quality green spaces in childhood. Catharine said: *"We have some really interesting longitudinal research looking at the life course effects. Astonishingly, in a longitudinal study of a cohort of people [from Scotland], we can see that the group of people who had had access to green space in childhood showed a slower cognitive decline when they were over 70."* The Committee continued their inquiry in January with oral evidence focusing on how successfully the Government and local authorities are protecting and increasing urban green spaces.

Publication update

Published:

Ball, E. L. *et al.* (2024). Childhood intelligence and risk of depression in later-life: A longitudinal data-linkage study. *SSM – Population Health*. https://doi.org/10.1016/j.ssmph.2023.101560

de Vries, P. S. *et al.* (2024). A genetic association study of circulating coagulation Factor VIII and von Willebrand Factor levels. *Blood.* https://doi.org/10.1182/blood.2023021452

Higbee, D. H. *et al.* (2024). Genome-wide association study of preserved ratio impaired spirometry (PRISm). *European Respiratory Journal.* https://doi.org/10.1183/13993003.00337-2023

Jaggi, A. *et al.* (2024). A structural heart-brain axis mediates the association between cardiovascular risk and cognitive function. *Imaging Neuroscience.* https://doi.org/10.1162/imag_a_00063

Mei, H. *et al.* (2024). Multi-omics and pathway analyses of genome-wide associations implicate regulation and immunity in verbal declarative memory performance. *Alzheimer's Research & Therapy*. https://doi.org/10.1186/s13195-023-01376-6

Moodie, J. E. *et al.* (2024). General and specific patterns of cortical gene expression as spatial correlates of complex cognitive functioning. *Human Brain Mapping.* https://doi.org/10.1002/hbm.26641

Smith, H. M. *et al.* (2024). Epigenetic scores of blood-based proteins as biomarkers of general cognitive function and brain health. *Clinical Epigenetics.* https://doi.org/10.1186/s13148-024-01661-7

Sterenborg, R. B. T. M. *et al.* (2024). Multi-trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications. *Nature Communications.* https://doi.org/10.1038/s41467-024-44701-9

Yeung, H. W. *et al.* (2024). Classification accuracy of structural and functional connectomes across different depressive phenotypes. *Imaging Neuroscience*. https://doi.org/10.1162/imag_a_00064

Accepted/ In press:

Hatton, A. A. *et al.* (accepted). Genetic control of DNA methylation is largely shared across European and East Asian populations. *Nature Communications.*

Thng, G. *et al.* (accepted). A comprehensive hierarchical comparison of structural connectomes in Major Depressive Disorder cases versus controls in two large population samples. *Psychological Medicine.*

Contact

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