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 66: June 2024

Welcome to the June edition of the Disconnected Mind Newsletter! We have had busy three months, with many exciting developments. Catch up on our latest news, including staff promotional successes and updates, new scientific publications, and knowledge exchange and public engagement events!

Update on Wave 7 of the LBC1936

The first LBC1936 participant returning for MRI scan on 18 April, with the radiographers at the Wellcome Trust Clinical Research Facility

We are delighted to report that Wave 7 of the LBC1936, which began on 21 March 2024, has been progressing very well. The team have now seen 35 participants for cognitive appointments at the Wellcome Trust Clinical Research Facility (WTRF) at the Western General Hospital and 18 participants have now returned for an MRI brain scan at the Edinburgh Imaging Facility at the Royal Infirmary of Edinburgh, with the first participant, depicted in the above photo, attending on 18 April. The cognitive testing team now comprises of Dr Janie Corley, Sabela Mendez, who joined the team in September, and Alison Pattie who is well known to many of the participants from previous waves and has returned to assist with the Wave 7 data collection. In addition, our new study coordinator, Dr Sarah McGrory, who joined the team in April, will soon complete her training and start testing later this month! We are thrilled to have Sarah and Alison on board and are looking forward to reporting on the Study's progress in the next issue!

Staff Updates

Celebrating promotional successes in the LBC team

Dr Simon Cox at the LBC reunion in May 2023

We are delighted to announce that the LBC Study Director, Dr Simon Cox has been promoted to professor and will take up his Personal Chair in Brain and Cognitive Ageing in August. Simon received his PhD in 2012 at the University of Edinburgh, examining how the brain facilitates complex cognitive abilities, and how and why people differ in their abilities across the life course. Since December 2020, Simon is the Director of the Disconnected Mind project and the Lothian Birth Cohorts and currently holds a Sir Henry Dale Fellowship by the Wellcome Trust and The Royal Society. He has led the Disconnected Mind Phase 4 funded by Age UK, and is Principal Investigator on the core LBC grant, jointly funded by the BBSRC and ESRC. Congratulations on this fantastic and well-deserved achievement, Simon!

Dr Sarah Harris at the LBC reunion in September 2019

This Spring we also celebrated Dr Sarah Harris' promotion to the post of Senior Research Fellow. Sarah joined the team in 2003 as the LBC geneticist and has contributed to over 200 scientific papers using LBC data. She is a current LBC Co-Investigator and is leading a grant application to fund a large-scale longitudinal proteomics study in the LBC. Congratulations, Sarah!

The Lothian Birth Cohorts have a new study coordinator

Former LBC study coordinator, Adele Taylor (left) and new LBC study coordinator, Dr Sarah McGrory (right)

This Spring our team said goodbye to LBC Study Coordinator, Adele Taylor and welcomed a new Study Coordinator, Dr Sarah McGrory. Adele said good-bye after almost 12 years with the Study: she joined the team in 2012 as a member of the cognitive testing team for Wave 3. She was the very heart of the study, and the right hand of both founding and current during her tenure. With her knowledge, patience and professionalism she kept the team supported and the study running smoothly. Simon, on behalf of the team, thanked Adele for all her excellent work and we all were sad to see her go. Adele said: *"I was incredibly fortunate to join the Lothian Birth Cohorts on completing my undergraduate degree in Psychology. For my first job in the world of research to be with one of the most successful and long-running studies of cognitive ageing in the world was a dream come true. Over almost 12 years I've learned an incredible amount from experienced and talented colleagues, as well as from the participants of the LBC1936 who have been a pleasure to get to know. My time with the study has been rewarding and fun, and I wish the study and all its contributors every success."* Adele was a fantastic colleague and friend, and we will miss her but wish her all the best on her new adventure travelling to the Indonesian Archipelago!

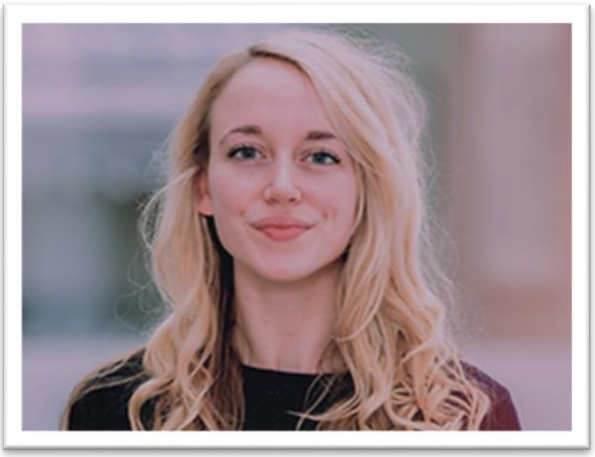
In April, we welcomed Dr Sarah McGrory as the new Study Coordinator. Sarah has a background in psychology and has previously worked on the LBC1936 Study as a post-doctoral research fellow. Sarah is returning to academia following a few years in industry and is keen to resume research into cognitive ageing and how and why people differ in their abilities across the life course. She said: *"I am delighted to be back working on the LBC1936 study and am looking forward to meeting the wonderful participants as they return for this 7th wave of cognitive testing."* A very warm welcome back to the team, Sarah!

Welcome back, Alison Pattie!

Alison Pattie with a participant at the Western General Hospital

We are also delighted to have Alison Pattie returning as a member of the cognitive testing team for this 7th wave. Alison has been a core member of the LBC studies since their inception in 1998. After her retirement in Spring 2019, Alison came back in October 2021 to help the LBC1936 team to complete Wave 6 in good time after the COVID-19 delay, and has once again demonstrated her commitment to the study and its participants by returning for this current wave of testing. Welcome back, Alison!

Dr Eleanor Conole starts a post at Oxford

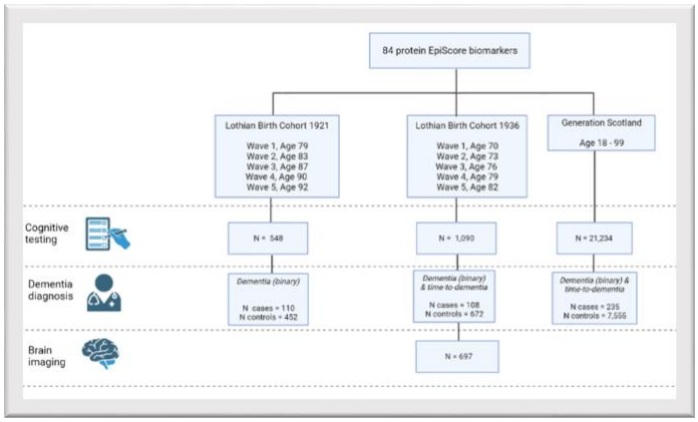


Dr Eleanor Conole

At the end of April, Dr Eleanor Conole left the team to take up a position at the University of Oxford as a research fellow in Applied AI. Eleanor joined the LBC1936 team in 2019 for a PhD in Translational Neuroscience funded by the Wellcome Trust. She's published on topics on neuroinflammation, epigenetics and brain ageing, working on questions related to how chronic inflammation relates to aspects of brain health across the lifecourse. Eleanor is not only an excellent scientist, but also a great science communicator, supporting complex ideas and research findings with beautiful illustrations. We are extremely sad to see her go and she will be missed by the entire LBC team, but we wish her all the very best in this exciting next step in her academic career. Eleanor will continue collaborating with the LBC team in her new post at Oxford. Congratulations, Eleanor!

Scientific Highlights

Discovering biomarkers of general cognitive function and brain health in DNA methylation



Study overview from Smith et al. (created with BioRender)

Hannah Smith is a PhD student working with Dr Simon Cox, Professor Riccardo Marioni and Dr Joanna Moodie as her supervisors. Her thesis examines the relationship between several risk factors, epigenetic and proteomic data with measurements of brain health in large patient groups. The aim is to discover biomarkers of brain health that will help to identify individuals at risk of neurological disorders and cognitive decline. In her recent article published in Clinical Epigenetics, Hannah focused on epigenetic changes in blood protein levels associated with general cognitive function and brain ageing. Epigenetics refers to chemical modifications to DNA that do not affect the underlying sequence. These chemical modifications can be added to the DNA sequence and turn genes up or down. One such 'epigenetic' modification is DNA methylation. We can use methylation information from multiple positions across the genome to predict protein levels in the blood – protein Epigenetic Scores or EpiScores. These EpiScores have previously been associated with disease outcomes and measures of brain health, highlighting their potential usefulness as clinical blood-based markers. In this study, we examined 84 previously published protein EpiScores as possible blood-based markers of cross-sectional and longitudinal measures of general cognitive function and brain health, and incident dementia across three independent cohorts: Generation Scotland (GS) and the Lothian Birth Cohorts 1921 and 1936. We found several EpiScores associated with general cognitive function level and brain health imaging measures, including an EpiScore for a previously identified protein marker of Alzheimer disease to be associated with incident dementia in GS and general cognitive function in a meta-analysis of all three cohorts. This study highlights that protein EpiScores may help us identify individuals at risk of poor general cognitive function, brain health, and dementia.

Smith, H. M., et al. (2024). Epigenetic scores of blood-based proteins as biomarkers of general cognitive function and brain health. *Clinical Epigenetics*.

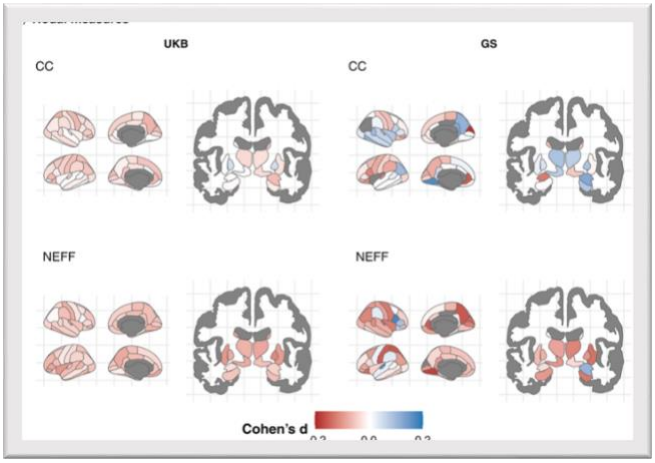
LBC1936 data contribute to a large study to better understand genetics associated with reduced lung function

LBC1936 participants taking the spirometry test

Good lung function is important for maintaining a healthy life at all ages. Smoking, obesity and other life-style factors are associated with poor lung function, but it is also partly heritable. Poor lung function may occur due to narrowing of the airways in conditions like asthma and chronic obstructive pulmonary disease (COPD). However, about 10% of the general population have reduced lung function that is not caused by a narrowing of the airways. This known as preserved ratio impaired spirometry (PRISm). Up to 50% of people with PRISm later develop COPD, whereas for others their lung function returns to normal. Little is known about the causes of PRISm although it is associated with being overweight or underweight, smoking and increased mortality, and is more common in women than men. LBC1936 contributed to a genome-wide association study designed to identify genetic variants associated with PRISm. Twenty-two regions of the genome were found to be associated with PRISm and the genetic risk factors for PRISm were shown to be shared with those for asthma, COPD, type 2 diabetes, BMI, hypertension and myocardial infarction. This is the first GWAS to report genome-wide significant SNPs for PRISm, four of which are novel for lung function. Genetic factors associated with PRISm are strongly correlated with risk of both other lung diseases and extrapulmonary comorbidity. In the future, specific biological pathways that contribute to nonobstructive impaired lung function may be identified that could potentially lead to prevention or treatment for this common problem.

Higbee, D. H., et al. (2024). Genome Wide Association Study of Preserved Ratio Impaired Spirometry (PRISm). *European Respiratory Journal.*

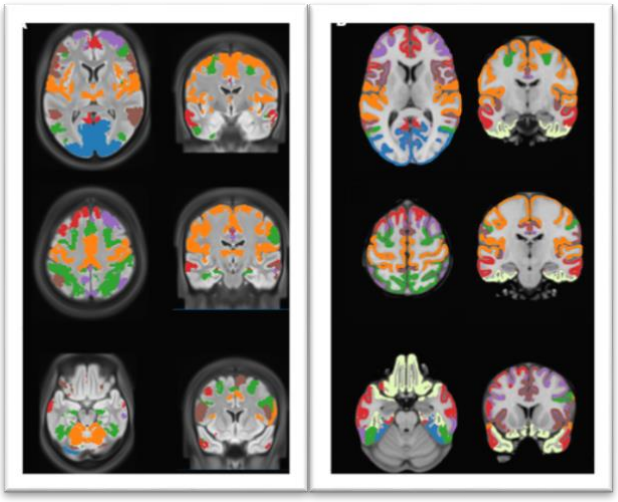
Disconnected white matter tracts across brain regions associated with Major Depressive Disorder



Neuroimaging studies on Major Depressive Disorder (MDD) have mostly focused on individual brain regions, but the brain is innately structured as a network with brain regions linked together by anatomical white matter tracts (i.e., a connectome). As a complex network, the brain exhibits non-trivial organisational properties, such as having a “rich club” core consisting of key brain regions that are strongly connected together to function as the central backbone of brain communication. MDD is thought to be associated with structural disconnectivity, where network architecture, such as the rich club core, is thought to be disrupted. However, studies adopting connectomic approaches to study these questions have been few and limited by sample size, resulting in low reproducibility. Hence, this study leveraged structural connectome data from the UK Biobank (N=5,104) and utilised graph theory to compare the connectomes of MDD cases and healthy controls from the global network level down to the individual connections. While the rich club core remained robust in MDD, there were subtle reductions in efficiency (i.e., a measure to reflect the efficiency of information transfer between brain regions) across the brain, which added up in the order of the connectome hierarchy to affect an overall reduction in global network efficiency in MDD. These results were generally consistent in the replication sample from Generation Scotland (N=725). As such, brain structural connectomic differences in MDD do not consist of large effects confined to one or two brain regions, but rather involve subtle effects that are distributed across the whole brain.

Thng, G., et al. (2024). A comprehensive hierarchical comparison of structural connectomes in Major Depressive Disorder cases v. controls in two large population samples. *Psychological Medicine*.

Brain scans provide clues to understanding depression



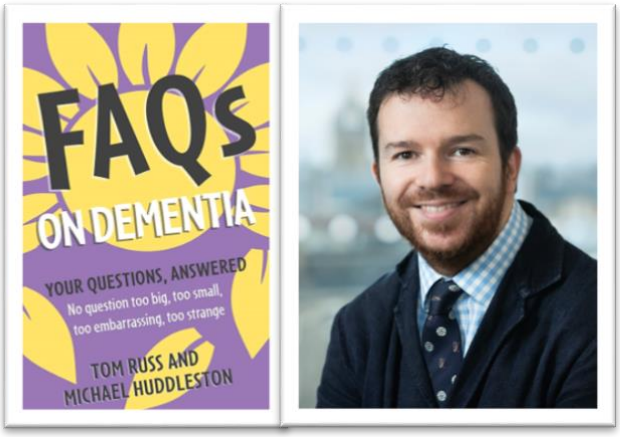
Functional subnetworks identified in the current and previous work

A former PhD student of Dr Simon Cox and later a postdoc working with the LBC team, Dr Hon Wah Yeung, led another paper examining how depression relates to aspects of brain health in middle- and older-aged adults. The study focused on major depressive disorder (MDD), a psychiatric condition affecting around 5% of the population that can greatly impact a person's life, causing persistent feelings of sadness, hopelessness, and loss of interest in activities. By analysing brain scans and different definitions of MDD together with taking into consideration experience of childhood trauma as a known risk factor, the study aimed to improve how MDD is diagnosed. With the expertise of the LBC team – funded by the National Institute of Health – the study used a large dataset of nearly 20,000 brain scans from the UK Biobank, to derive the measurement of the connectome, which maps brain connectivity as a network, either as a structural network of physical anatomical connections between brain regions, or as a functional network of neural activity. By comparing MDD patients against unaffected participants, the study found that functional connectomes, which measure brain activity during rest, are more effective than structural connectomes for diagnosing MDD. Notably, considering childhood trauma exposure improved the accuracy of diagnosis. This suggests that there are differences in brain connectivity between those with and without childhood trauma. Specific brain networks associated with the senses, movement and vision were found to be important for predicting MDD. Overall, this study highlights the complexity of classifying MDD, which can manifest differently from person to person, and underscores the importance of understanding childhood trauma in diagnosis. Ultimately, these insights could lead to improved diagnostic methods and treatments for this for this debilitating condition.

Yeung, H. W., et al. (2024). Classification accuracy of structural and functional connectomes across different depressive phenotypes. *Imaging Neuroscience*.

Knowledge Exchange

Dr Tom Russ publishes a book on dementia



"No question too embarrassing, naive, complicated or simple – everything that's ever been asked about dementia, answered." This is a subtitle for a new book "FAQs on dementia", co-authored by Dr Tom Russ – an LBC Co-Investigator and Principal Medical Consultant, Director of the Alzheimer Scotland Dementia Research Centre at the University of Edinburgh. We are delighted his book has been included on the updated Reading Well for Dementia list. This is a list of recommended books chosen by people living with dementia, carers and health professionals. The booklist provides reliable information, advice and support as well as personal stories. The new booklist is targeted at people living with dementia, carers and family members including younger children to help them understand more about dementia. The list was launched during the Dementia Action Week in May and suggests titles for public libraries across England and Wales to stock. One of the reviewers on Amazon said about the book: *"A concise, eloquent, and thought-provoking overview of a complex topic. Highly recommended."* Congratulations, Tom!

Dr Simon Cox at University of Cambridge

In early May, Dr Simon Cox visited the University of Cambridge to talk at the Zangwill Club (Psychology departmental seminar series). He spoke about a combination of recent findings and new research-in-progress using methods to combine cognitive-neuroimaging with other, new sources of information about the brain. He said, *"I thoroughly enjoyed the opportunity to discuss our newer findings with the highly engaged group of researchers in Cambridge – and I appreciated two interesting aspects of the trip: first, it was apposite that, having trained in neuropsychology, I was able to talk about relations between brain and behaviour in a club named after Oliver Zangwill, whom many consider to be the father of modern British neuropsychology. Second, it was almost exactly 20 years since Ian Deary spoke to the Zangwill Club, which would have made it 2004 – the time when the LBC1936 would have been going into field for the first time (much has happened over the past 7 waves of testing!)."*

Lothian Birth Cohorts at Edinburgh Science Festival with The Game of Life

Volunteers with a display of activities at The Game of Life at Edinburgh Science Festival in April

How do your brain and thinking skills develop and change throughout your life? How important are your genes or is it all about how you choose to live your life? These were some of the questions raised at *The Game of Life: Who gets to be 100?* workshop at this year's Edinburgh Science Festival. The LBC team, joined by S5 pupil volunteers from the Boroughmuir High School, delivered three sold-out workshops at the National Museum of Science, attended by over 40 children and their parents. The workshop was designed around a boardgame inspired by LBC-related research on cognitive and brain ageing. The participants – between eight and eleven years of age – enjoyed the opportunity to create a DNA bracelet as they reviewed basic concepts from genetics, speculated what factors influence healthy brain ageing while exploring 3D-printed brain models and played a boardgame which took them on a journey from birth to old age, learning how our genetic make-up and lifestyle choices influence cognitive and brain ageing. As the players went through 'life', they encountered a range of conditions and factors that either increase (e.g., smoking) or decrease (learning a new language, playing a musical instrument, being physically fit) their risk of dementia. While children took part in these activities, their parents were introduced to the Lothian Birth Cohorts studies to provide the context for the children's activities and were invited to explore LBC resources that supported the session (AR glasses, 3D brain models, brain scans as well as art inspired by LBC research) and could test their knowledge about brain and cognitive ageing in a quiz. One parent said: *"The team did a great job. The children were all engaged and learning life skills while having fun."* Another commented: *"We really enjoyed the workshop. It was educational and fun for the kids. Also, I enjoyed that they engaged the parents. We also got useful information that helps us to shape our life and our kids' future better. Thank you!"* We look forward to offering the workshop to many others!

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

Baranyi, G., *et al.* (2024). Life-course neighbourhood deprivation and brain structure in older adults: The Lothian Birth Cohort 1936. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-024-02591-9

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

Hatton, A. A., *et al.* (2024). Genetic control of DNA methylation is largely shared across European and East Asian populations. *Nature Communications.* https://doi.org/10.1038/s41467-024-47005-0

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

Thng, G., *et al.* (2024). A comprehensive hierarchical comparison of structural connectomes in Major Depressive Disorder cases versus controls in two large population samples. *Psychological Medicine.* https://doi.org/10.1017/S0033291724000643

Accepted/ In press:

Gibbon, S., *et al.* (in press). A method for quantifying sectoral optic disc pallor in fundus photographs and its association with peripapillary RNFL thickness. *Translational Vision Science & Technology.* https://doi.org/10.1167/tvst.13.5.20

Page, D., *et al.* (accepted). Examining the neurostructural architecture of intelligence: The Lothian Birth Cohort 1936 Study. *Cortex.*

Contact

You can contact the LBC team by email and keep up with our latest news on our website and Twitter.

If you no longer wish to receive our newsletter, please email lbc.ke@ed.ac.uk to unsubscribe from the Disconnected Mind mailing list.

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NIH National Institutes of Health

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