# 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 63: September 2023

Welcome to the Autumn 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.

## Update from the LBC1936 team

In our previous Newsletter we shared the news from the last LBC reunion that celebrated the successful completion of the LBC1936 Wave 6 data collection. Since May, when the reunion took place, the LBC1936 team has been busy processing the new Wave 6 data and preparing them for future analyses. This task involves many hours of collaborative effort from the testing team before the data can be made available for new scientific discoveries. By one estimate, it will take almost 600 hours before the data from Wave 6 (~847 data points per participant), is ready to be cross-checked for accuracy by our database manager, Paul Redmond. Other members of the team have also been working hard on the brain MRI data, deriving and carefully checking an array of important markers of brain structure. *"Making sure that the data are accurate is of paramount importance. It's a very time-consuming but very important task; the integrity of the data is critical for the forthcoming research from both our team and our collaborators,"* said Dr Janie Corley.

At the same time as the team are processing the data from Wave 6, they have begun preparing for Wave 7 of data collection, aiming to start in early 2024. The study director, Dr Simon Cox, said: *"The team has been working hard during the summer months, and has made an excellent progress in preparing the data for future analyses. At the same time, they've been busy getting ready for the next wave and I am looking forward to welcoming the LBC1936 participants back in early 2024 for a seventh – yes, seventh – wave of testing!"*

## Staff Updates

**Welcome to the team, Sabela!**

We are delighted to introduce Sabela Mendez who has joined the LBC1936 team as a new Research Assistant. Sabela will be working alongside Adele Taylor, Dr Janie Corley and Paul Redmond to support the smooth running of the LBC1936 study and conduct the cognitive testing in the upcoming LBC1936 Wave 7. Sabela has a background in medicine and psychology, and previously worked at the Scottish Cancer Research Network as a Clinical Trials Coordinator. Sabela is interested in research into healthy cognitive ageing and overall wellbeing in old age. She said: "*I feel very privileged to be starting this new role with the LBC study. The team have been very welcoming, and I am inspired by everyone's passion for developing our collective knowledge into the ageing process.*" A very warm welcome to the team, Sabela!

## Celebrating the team's achievements

### Personal Chairs for three LBC Co-Investigators

Professors Mark Bastin, Michelle Luciano and Susan Shenkin

We are delighted to announce recent promotional successes of three of the LBC Co-Investigators!

Professor Mark Bastin has been appointed Personal Chair of Brain Imaging. Mark's primary research interest is in the development of MRI acquisition methods and image processing techniques and their application to the study of white matter in the brain. He has collaborated with the LBC team on over 150 publications and is a co-investigator on a BBSRC grant supporting the LBC Waves 6 and 7.

Professor Michelle Luciano has been appointed Personal Chair of Behavioural Genetics. Michelle's research focuses on environmental and genetic factors contributing to cognition, personality, mood, well-being and brain MRI measures. She was a co-investigator on an ESRC-funded project on lifetime musical experience and healthy ageing in LBC1936 with Professor Ian Deary and Dr Judy Okely, and has co-authored over 70 LBC publications on many aspects of ageing.

Professor Susan Shenkin has been appointed Personal Chair of Healthcare for Older People. Susie has been working as a clinical academic in geriatric medicine at the University of Edinburgh and NHS Lothian since 2011, with main interests in cognitive ageing, delirium and dementia, and the health and care of residents and staff of care homes. Susie has maintained close ties with the Lothian Birth Cohorts since her Medical Research Council Training Fellowship investigating lifecourse influences on cognitive ability and cerebrovascular disease in older age under the mentorship of Professors John Starr and Ian Deary.

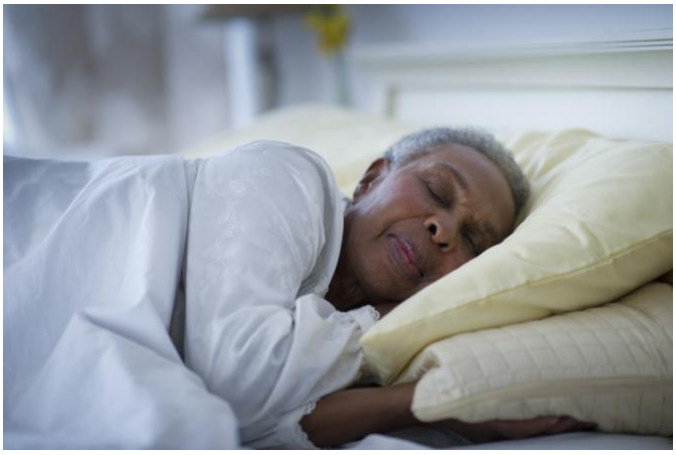
Congratulations to our colleagues on their promotional success!

### Arish Mudra Rakshasa-Loots: BNA Scholar and 3MT winner

Arish Mudra Rakshasa-Loots joined the Lothian Birth Cohorts as a PhD candidate in Translational Neuroscience to work with Dr Simon Cox on neurobiological mechanisms that may explain the significant burden of mental health issues faced by people living with HIV. He is currently completing his degree, supported by the Wellcome Trust. Earlier this year, the British Neuroscience Association selected Arish as one of seven 2023 BNA Scholars, a prestigious award offered annually by the Association to students and early career researchers from underrepresented ethnic groups to thrive in neuroscience, and to build a supportive community through networking opportunities, bursaries and mentorship. Arish, in addition to his accomplishments in neuroscience research, is a passionate activist and educator committed to the eradication of HIV/AIDS, which disproportionately affects marginalised populations such as the LGBTQ+ community. In June 2023, he took part in the University of Edinburgh's Three Minute Thesis Competition. The 3MT Competition requires doctoral researchers to deliver an engaging research presentation, concisely and effectively, to a non-specialist audience, in just 3 minutes and one slide. It is based on a concept developed by the University of Queensland in 2008, and has since gone global. Arish impressed the judges and the audience with his presentation *'When HIV meets Depression'* and became the Winner of the University's Final, clearly demonstrating his talent for communicating science. Congratulations on another fantastic achievement, Arish!

## Scientific Highlights

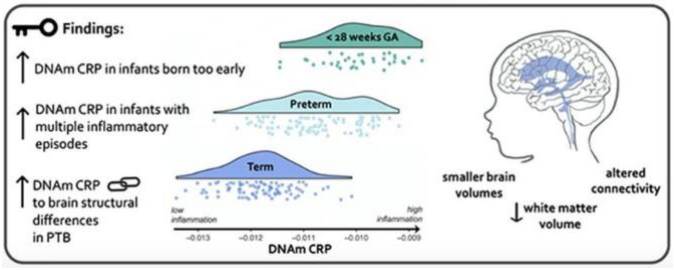
### LBC1936 brain imaging data offer insights into the role of sleep in maintaining brain health



Sleep plays an important role in brain health and general wellbeing. Research suggests that sleep promotes maintenance processes that enhance the brain's physiological health, such as clearance of metabolic waste, proteins, and cell debris that accumulate during daytime brain activity. However, how sleep affects the brain in older age over many years is not well understood. This study investigated the relationship between sleep habits and structural imaging markers of brain health in older adults. The study analysed brain magnetic resonance imaging (MRI) data collected over six years from the LBC1936 participants between ages 73 and 79. The authors explored associations between sleep duration and sleep quality with markers of brain health identifiable on brain MRI scans, including perivascular spaces (PVS), brain atrophy and white matter hyperintensities (WMH), as well as vascular risk factors. Results showed that poorer night-time sleep and increased daytime sleep were associated with markers of poorer brain health. The study suggests that sleep impairments are associated with faster loss of healthy white matter and the progression of WMH, and perivascular-space burden is a portent of those changes. These findings are consistent with the proposed role for sleep in brain waste clearance, which helps maintain its health.

Aribisala, B.S. et al. (2023). Sleep quality, perivascular spaces and brain health markers in ageing – A longitudinal study in the Lothian Birth Cohort 1936. *Sleep Medicine.*

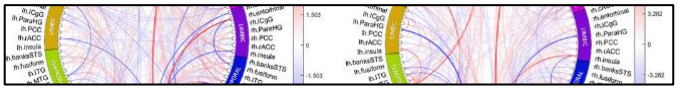
### Can inflammation-related DNA-methylation give insight into brain dysmaturation in preterm birth?




Inflammation has been linked to neuroimaging hallmarks of preterm birth. Looking for epigenetic modifications, such as those captured in DNA methylation (DNAm) signatures, offers a new way to assess the cumulative impact of maternal, fetal, and postnatal inflammatory exposures. DNAm can be analysed from various tissues like blood and saliva. Prior work has compared traditional inflammatory proteins against DNAm-based measures in relation to brain health outcomes. LBC researchers previously examined whether a DNA methylation signature of C-Reactive Protein (DNAm CRP) was more strongly associated with brain structure and function than a typical blood-based measure of CRP in older adults from the LBC1936 study. In this new study, led by Dr Eleanor Conole, the authors applied this same approach to a neonatal cohort to investigate the impact of chronic inflammation in the perinatal period, using DNAm from saliva samples to index inflammation. The epigenetic signature of inflammation was higher in preterm infants than term infants, and was related to the number of inflammatory episodes experienced by these infants. It also showed significant associations with aspects of brain structure. The findings suggest that sustained inflammation may be a key driver of neurodevelopmental disruption related to prematurity. DNAm taken from saliva could offer a non-invasive way to predict and monitor susceptibility to inflammation and its consequences, which could ultimately optimise approaches in neonatal care.

Conole, E.L.S. et al. (2023). Immuno-epigenetic signature derived in saliva associates with the encephalopathy of prematurity and perinatal inflammatory disorders. *Brain, Behavior, and Immunity.*

## AI in brain research: Keep it simple?



We often hear about artificial intelligence (AI) and machine learning (ML) for analysing large datasets. There's an expectation that advanced ML methods, when applied to brain scans, will reveal differences in the human brain related to health and disease that might not be evident with simpler statistical methods. For example, ML involves advanced computational methods that can discover complex patterns, such as those in brain scans that predict who is more likely to get a specific disease in the future, even when these patterns are challenging for humans to spot. In contrast, simple statistical methods, like linear regression rely on more basic mathematics to find relationships. In a recent study, the LBC team, who has been at the forefront of applying computational methods to study how the human brain is connected and organised, compared several ML methods to explore how brain connectivity relates to sex, age, thinking skills, and mental health. They used a large dataset of structural connectomes constructed from over 8,000 brain scans in the UK Biobank. The connectome represents brain connectivity as a network, offering a comprehensive map of how the human brain is interconnected via its white matter fibres. Lead author Dr Hon Wah Yeung put various methods to the test by directly comparing their ability to predict sex, age, and more complex variables, such as cognitive ability and mental health based on these brain networks. Surprisingly, the more complex ML methods did not outperform predictions from simpler statistical methods. Both ML and simple linear models ranked the importance of features in a similar way, suggesting that complex models might not help in finding relationships between brain connectivity and complex traits, at least for the current UK Biobank data. Dr Colin Buchanan, a co-author of the study, said: *"Machine learning shows promise, but increased statistical complexity doesn't necessarily lead to a better understanding of how brain connections shape who we are. These findings have practical implications for streamlining research approaches and reducing the need for computationally expensive methods. However, this doesn't rule out the potential for advanced machine learning to be more informative in other cases."*

Yeung, H.W., et al. (2023). Predicting sex, age, general cognition and mental health with machine learning on brain structural connectomes. *Human Brain Mapping.*

## Addressing the neuroimaging replication crisis with lessons from complex trait genetics


The replication crisis in science has become a concern of many scientific fields. Brain research, particularly neuroimaging studies, has been grappling with the issue. Research teams struggle to replicate previous discoveries. New datasets fail to yield converging findings. Diversity in methodological approaches contributes to reported discrepancies. How can we fix it? In her Viewpoint article, Dr Anna Fürtjes, who has recently joined the Lothian Birth Cohorts team as Research Associate in Statistical Genetics, suggests that solutions to address these issues in neuroimaging can be adopted from the field of genetics. She reviews research practices that have been firmly established in genetics research over the past 15 years and shows how they could be used to overcome some replicability concerns in neuroimaging studies. She draws on striking parallels between the two fields and derives five major lessons that include:

- abandoning attempts to map individual brain regions onto certain behavioural traits;
- increasing sample sizes;
- using mass-univariate testing that considers the whole brain rather than individual brain regions;
- sharing summary-level association data;
- and using existing 'multivariate' statistical techniques originating from genetics studies.

Dr Fürtjes proposes that adopting such genetics techniques could accelerate the evolution of neuroimaging research without the need for developing new statistical tools. She concludes that modern science requires more interdisciplinary mindsets and collaborations that encourage researchers to put these changes into practice.

Fürtjes, A.E. (2023). Lessons from complex trait genetics may help us overcome the neuroimaging replication crisis. *Cortex.*

## Knowledge Exchange

### LBC neuroscientists at an international conference in Montreal, Canada

Anna Fürtjes, Jo Moodie, Colin Buchanan and Simon Cox in Montreal

The Organisation of Human Brain Mapping (OHBM) is an international society dedicated to using neuroimaging to discover the organisation of the human brain. Every year, the society brings together 3,000 neuroscientists to share their latest research. In July, four members of the LBC team – Drs Simon Cox, Colin Buchanan, Anna Fürtjes and Jo Moodie– joined the OHBM annual meeting in Montreal, Canada. The team presented their work investigating the links between brain structure and cognitive ability based on data from about 40,000 participants from three different cohorts, including the LBC, the UK Biobank and Generation Scotland's STRADL database (Stratifying Resilience and Depression Longitudinally). Dr Colin Buchanan presented the results of his recent meta-analysis focused on the relationship between structural brain networks (the 'connectome') and general cognitive ability. Colin showed that our cognitive abilities rely on a widely-distributed white matter network involving all brain lobes, primarily concentrated in frontal, temporal, parietal and subcortical regions. Dr Jo Moodie presented on neurostructural associations of cognitive functioning and their spatial correlations with different neurobiological cortical profiles, including gene expression and neurotransmitter systems. Dr Anna Fürtjes's study showed the importance of study designs. She illustrated that study results substantially differ when researchers subdivide their participants' brain images into 'brain regions' according to one so-called 'brain atlas' over another. The team noticed increased interest in multiple facets of ageing in comparison to previous years and rising recognition of the role genetic factors play in brain health.

### Musical training in earlier life for healthy mind in older years

In the last newsletter, we brought to your attention a new study on lifetime experience of playing a musical instrument. The study, led by Dr Judy Okely and published in the journal *Psychology and Aging*, confirmed previous findings that lifetime musical experience in earlier life is linked to cognitive benefits in later life. Specifically, while all LBC1936 participants' test performance tended to decline during ageing, those with more experience playing a musical instrument showed sustained, slightly higher performance levels on tests of processing speed and visuospatial reasoning in the 8$^{th}$ and 9$^{th}$ decade of life, even after taking into consideration factors such as health status, years of education and childhood cognitive ability. While the results do not prove that musical training enhances cognitive skills, since unexplored factors, such as other enriching childhood experiences, might have contributed to the findings, Dr Okely said: *"We see these results as an exciting starting point for further investigation into how musical experience from across the life course might contribute to healthy ageing, and, as our study suggests, playing a musical instrument seems a clear candidate activity that might contribute to staying sharp in later life."* The results have drawn significant attention of the public and were covered as part of a special edition of the Today Programme that was guest edited by a community music group in Glasgow (BBC Radio 4 - Today, 19/08/2023) and were picked up by national and international news outlets, including The Daily Mail, The Sun, and New York Post. As well as reporting the results of the paper the authors have announced the launch of a new research volunteer database for people with musical experience who would like to contribute to future research and since its launch on 19 August, they have already recorded over 900 members!

Okely, J.A., et al. (2023). Cognitive aging and experience of playing a musical instrument. *Psychology and Aging.*

## Dr Simon Cox at the Scottish Parliament for ‘Neuroscience Matters’


World-leading neuroscience research in Scotland as a key to future health was the theme of ‘Neuroscience Matters’, a meeting organised by the British Neuroscience Association (BNA). The BNA is the largest UK organisation connecting, representing, and promoting neuroscience and neuroscientists across the globe. The organisation has over 300 members in Scotland, and the current BNA president is Professor Tara Spires-Jones, Deputy Director of the Centre for Discovery Brain Sciences at the University of Edinburgh and a close LBC collaborator. ‘Neuroscience Matters’ was held on 28 June at the Scottish Parliament and aimed to show how neuroscience research and those working within neuroscience in Scotland play a critical role in tackling some of the key health challenges of the future. The event showcased world-leading neuroscience research across Scotland, including the development of new treatment of Rett Syndrome, molecular approaches to neurodegenerative diseases like Amyotrophic Lateral Sclerosis, as well as Lothian Birth Cohorts being the longest study of human cognition in the world. The LBC study director, Dr Simon Cox, was invited to join the event and meet with the Members of the Scottish Parliament and stakeholders to explain first-hand the importance of continued funding for research on brain and cognitive ageing that will so significantly influence future Scotland. Simon said: *“It is testament to the hard work and productivity of the team, and the sustained interest the LBC studies have generated, that we were a featured research item at this meeting. It was a fascinating evening, and I found it encouraging to hear strong support for neuroscience research in Scotland from MSPs; there was enthusiasm and recognition for the fact that both basic and applied research have important roles to play in improving lives in Scotland.”*

## Lothian Birth Cohorts at the Fringe Festival


Dr Thomas Bak yet again wowed the crowds at the Edinburgh Fringe Festival this August with two sold-out shows on an LBC-related theme. In ‘Old dogs need new tricks’ – performed at The Cabaret of Dangerous Ideas on 21 and 27 August – Thomas took the audience on a journey of life-long learning as life-long discovery with an important message: no-one is too old for learning something new. On the contrary, he argues, the older we get, the more important it becomes for our brain and mental health and wellbeing that we cultivate curiosity, open-mindedness and a passion for learning new things! As usual, Thomas engaged the audience with interesting facts, questions and unexpected connections, including what his three roles (a cognitive neuroscientist, a university lecturer and a tourist guide) have in common, leaving the crowd highly entertained and inspired! Thomas said*: “The atmosphere was incredible, it's something one can never take for granted in live events; every show is different and unpredictable.”* Thomas complemented his show with a couple of new free *BrainEd* walks on the theme of life-long learning and discovery for brain health, each attended by 20 people. *“It was a busy weekend,”* he said. “*I fell exhausted into my bed afterwards, but very satisfied too!”*

Dr Thomas Bak at the Cabaret of Dangerous Ideas this August

## Publication update

**Published:**

Aribisala, B. S., et al. (2023). Sleep quality, perivascular spaces and brain health markers in ageing—A longitudinal study in the Lothian Birth Cohort 1936. *Sleep Medicine*. https://doi.org/10.1016/j.sleep.2023.03.016

Chundru, V. K., et al. (2023). Rare genetic variants underlie outlying levels of DNA methylation and gene-expression. *Human Molecular Genetics*. https://doi.org/10.1093/hmg/ddad028

Conole, E. L. S., et al. (2023). Immuno-epigenetic signature derived in saliva associates with the encephalopathy of prematurity and perinatal inflammatory disorders. *Brain, Behavior, and Immunity*. https://doi.org/10.1016/j.bbi.2023.03.011

Fürtjes, A. E., et al. (2023). General dimensions of human brain morphometry inferred from genome-wide association data. *Human Brain Mapping*. https://doi.org/10.1002/hbm.26283

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Mullin, D. S., et al. (2023). Identifying dementia using medical data linkage in a longitudinal cohort study: Lothian Birth Cohort 1936. *BMC Psychiatry*. https://doi.org/10.1186/s12888-023-04797-7

Mur, J., et al. (2023). Anticholinergic burden in middle and older age is associated with lower cognitive function, but not with brain atrophy. *British Journal of Clinical Pharmacology*. https://doi.org/10.1111/bcp.15698

Yeung, H. W., et al. (2023). Predicting sex, age, general cognition and mental health with machine learning on brain structural connectomes. *Human Brain Mapping*. https://doi.org/10.1002/hbm.26182

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

**Advanced online publication/Ahead of print:**

Okely, J. A., et al. (2023). Cognitive aging and experience of playing a musical instrument. *Psychology and Aging*. https://doi.org/10.1037/pag0000768

## Contact

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