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 50: June 2020

Welcome to the Summer 2020 Disconnected Mind newsletter. This issue includes news about the Disconnected Mind/Lothian Birth Cohorts (LBC) team, our latest publications, and the events we have participated in recently. A message from our colleagues at Age UK is also included on page 8.

For further information about this newsletter or to contribute to future issues, please contact us using the details on page 10.

This is a special newsletter. Disconnected Mind Director Professor Ian Deary said, "This is the 50th Disconnected Mind Newsletter since our first Newsletter in February 2008. That appeared just after our grand official launch at Buckingham Palace with our Royal Patron Prince Philip, the Duke of Edinburgh (see picture below). In my most optimistic predictions, I should not have anticipated the quality and variety of the discoveries that have been made using the LBC1936 data, nor its current vitality and diversity. It's great to see the huge spread of the project's coverage into different areas of ageing, and scientists who are establishing young themselves in this important field, again with LBC1936/Disconnected Mind as their foundation."



Ian Deary with Prince Philip, the Duke of Edinburgh, at Buckingham Palace

Lothian Birth Cohorts News

Wave 6 Update

Due to the COVID-19 outbreak, Wave 6 of LBC1936 cognitive testing, planned to begin in April 2020, is temporarily on hold. We are disappointed not to be seeing our participants as soon as we had hoped, but it is safe to say the team have not lost momentum.



Above: Database Manager, Paul Redmond, works on data requests with his daughter, Josie, and Molly the dog. Below: Geneticist Dr Sarah Harris, working on an LBC1936 paper.



More than nine weeks ago we collected our belongings from the LBC offices in 7 George Square and embraced our new working environments, setting up our laptops and computers in our kitchens, living rooms, bedrooms or closets. We are all fine and well. As you can see from our #wfh photos, and will read in this newsletter, we are still busy with plenty of Disconnected Mind/LBC work.

We continue to write and publish papers, process and release data, and we're about to launch our new online LBC1936 survey, which you can read about later in this section. We also continue to work on knowledge exchange and public engagement activities online. You can see all our #wfh updates on twitter.

Libby Archer retires from Age UK

It is with sadness and gratitude that we note our colleague, Libby Archer, retired from her role as Senior Research Manager with Age UK in April. Libby was a great and hard-working champion of the Disconnected Mind project at Age UK for more than a decade, and the team owes her a great deal for her inspiring commitment to the project. As well as a tireless and enthusiastic champion of the Disconnected Mind, she became a friend to many of us.

Libby said to lan: "It's been, as you know, a privilege and pleasure for me to have had the opportunity to work with you and the team on a project that has such profound significance for cognitive, brain and ageing science and for older people, and that always goes above and beyond.



Libby Archer with LBC1936 participants at 2010 Reunion event

You, the team and the amazing work you do have been a constant highlight of 11 years at Age UK. What you do in Edinburgh and beyond has lifted my heart and mind. Visits to Edinburgh have always left me breathless, and one of many enduring memories will be the frequent 'rabbits out of hats' moments when you've had yet another huge scientific finding.

I'm more grateful than I can say for the way you've all worked with Age UK and me, giving generously of your time and expertise. You've all made it an absolute pleasure. A particular joy has been seeing so many talented people 'grown' in the project succeed and move from triumph to triumph. Having The Disconnected Mind project under my wing from day 1 at Age UK was just the luckiest thing.

Thank you lan and everyone. I leave knowing the LBCs studies will go from strength to strength."

We will miss Libby greatly, and want to thank her on behalf of the Disconnected Mind team, past and present. We wish her the very best for the future. Ian said, "Libby was an extraordinary Research Manager. She bound Age UK and University of Edinburgh together in a productive symbiosis. She deserves much credit for the success of the project and the great relationship between Age UK and UoE."

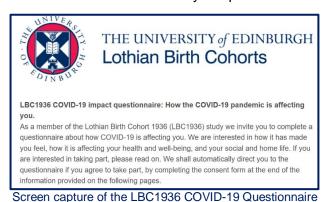


Libby Archer with her retirement gifts from the Disconnected Mind/LBC team

LBC COVID-19 online questionnaire

An exciting recent development has been the launch of our new LBC1936 COVID-19 questionnaire. Being in their 80s, LBC1936 participants are amongst some of those deemed to be at highest risk during the COVID-19 pandemic, and are likely to be following some of the strictest social distancing guidance and for the longest. The testing team have developed an online questionnaire to assess the impact of COVID-19 on LBC1936 participants.

In the 30 minute questionnaire, we ask questions about over 20 different themes and topics, covering subjects such as physical and mental health, their knowledge and feelings about COVID-19, and how it has impacted their daily activities. We included a lot of new questions, and importantly some which participants have answered before, like questions on exercise, sleep, social support, and attitudes to ageing, so we can examine how participants' answers have been affected by the pandemic.



Since the LBC1936 are such a unique group, and we have such a vast amount of data from previous waves, the responses from the questionnaire will make a valuable and unique contribution to current research on COVID-19 across the UK.

Mild Cognitive Impairment screening in LBC1936 participants

Mild Cognitive Impairment (MCI) is typically defined by a noticeable decline in an individual's memory and thinking abilities compared to another person of the same age and comparable education, but not to the extent that it interferes with their independence. Although someone with an MCI diagnosis can return to normal over time, they may also be at higher risk of developing Alzheimer's disease or other types of dementia. However, it is debated whether an MCI diagnosis provides meaningful information on what might happen to a patient, and there are no standard measurement tools. There is still much to be learned.

One of the many benefits of the wealth of information collected in the LBC1936 study is that, with the emergence of new areas of interest, we can often derive new measures we did not originally plan. Using recent guidelines on MCI criteria, Disconnected Mind PhD student Miles Welstead has been working with our Co-Investigator and Director of the Alzheimer Scotland Dementia Research Centre, Dr Tom Russ, to derive a measure of MCI from existing LBC data. This measure can then be used to assess LBC1936 participants for MCI, and to conduct future studies exploring predictors and consequences of MCI identification in the cohort. This is an exciting new project for the LBC1936 team, which we hope will shed light on current debates, and allow further exploration and understanding of MCI in later life.



Participants at reunion events. Above: 2010, Below: 2019.



Staff news

Susan Shenkin joins LBC1936 team

We are delighted to say that our long-standing research collaborator, Dr Susan Shenkin, will be taking a more hands-on role in the next wave of the LBC1936 study, providing expert clinical opinion advice as study medic, alongside Dr Tom Russ. Susie has worked with us for 20 years on both LBC1921 and LBC1936 cohorts, and we are excited to work with her even more closely in her new role.



By way of introduction, Susie said: "I am a clinical academic in Geriatric Medicine. I spend half my working time with frail older people admitted to the Royal Infirmary of Edinburgh, and half my time on research. My medical degree 'the Simpsons Study' explored the importance of very early life factors like birth weight on later thinking skills and brain health. I've stayed very interested in problems with thinking skills particularly when people are admitted to hospital. These problems can be due to delirium (acute confusion often caused by medical illness) or dementia. I'm also interested in whether people also develop physical problems (frailty), and how they adapt, particularly when they need more support or care, including moving into care homes.

I've been very privileged to see the huge impact that the LBC1921 and LBC1936 has had in the scientific community, and the interest from newspapers and television over the years; it really is a unique study, and all the participants are so appreciated. I'm delighted to join Dr Tom Russ as study medic, answering questions that need clinical input, and look forward to working with everyone to continue to answer important questions about ageing."

David Hill is awarded, twice!



Disconnected Mind statistical geneticist, Dr David Hill has been awarded a five year fellowship from the MRC to conduct his own programme of research and to employ a post doc. This research programme is titled "From genetic sequence to phenotypic

consequence: genetic and environmental links between cognitive ability, socioeconomic position, and health" and will examine the genetic and environmental links with intelligence, and what this means for our physical and mental health.

David has also been awarded the "The Journal of Intelligence Young Investigator Award 2020", for his work in conducting the first well powered genome wide association study examining intelligence differences, and his work finding that rare genetic variants contribute towards differences in our level of cognitive functioning. Congratulations, David!

The LBC team welcomes Samuel Gibbon

We'll soon be welcoming a new PhD student, Samuel Gibbon, working under the Tom supervision of Dr MacGillivray, from the Centre for Clinical Brain Science, and co-supervised by Prof. Emanuele Trucco the University of Dundee.



Samuel studied Psychology at the University of Edinburgh in 2013, and has since been working at the University of Cambridge in infant development. His research leverages deep learning, the same technology used to power driverless cars, to find patterns in the EEG (brainwaves) of babies, which might predict later language difficulties. With the LBC team, he'll be applying similar methods at the other end of the development span, through looking at the retina (a piece of nerve tissue at the back of the eye) and its' relation to cognitive decline.

The retina can be thought of as a "window" to the brain, as they share the same blood supply. This means that changes in the retina should reflect changes in the brain. His particular focus will be on the health of small blood vessels, which when damaged can leak material into the brain, causing numerous problems, including cognitive decline.

Samuel is funded through the EASTBIO partnership of Scottish universities, and his work will feed into the VAMPIRE project. Welcome, Samuel!

Scientific Highlights

Generation of 24 induced pluripotent stem cell lines from members of the LBC1936

Data from Lothian Birth Cohort 1936 is helping scientists understand the neurobiology of cognitive ability and why this declines for some people as we age while others retain their abilities. This is a dauntingly complex undertaking, requiring a multifaceted and interdisciplinary approach. We recently added another tool to the toolbox for understanding cognitive ageing by generating induced pluripotent stem cells (iPSCs) from donated blood samples from 24 LBC1936 participants, grouped by whether they had good or poor performance on cognitive tests across the testing waves.



In a paper published in the scientific journal <u>Stem Cell Reports</u>, we show data from stem cell lines from each of the 24 subjects that confirms all of these cells are true pluripotent stem cells, meaning they can be programmed to become any cell type in the body. The lines have also been registered on the European Stem Cell registry and alongside the data in the new paper, this is a phenomenal resource for the global scientific community.

In our Edinburgh labs, we have started programming these cells to become neurons, the brain cells important for cognition. This will allow us to study the molecular mechanisms inside the cells that are important to vulnerability to cognitive decline and resilience in the face of these processes. We will be able to compare the cell data with all of the other measurements that participants contribute to including brain imaging, data from donated brain tissue samples post mortem, and of course cognitive data. Many thanks from the team working in the labs with these cells for your continued donations and participation. This resource will help push the boundaries of our knowledge of the human brain and ageing further!

An update: the Marioni Research Group

The Marioni Research Group, led by our colleague Dr Riccardo Marioni, have been very busy lately! Here, we will hand over to Riccardo to give us an update:

"Dr Daniel McCartney (postdoc) has led an international consortium project (including both LBC studies) exploring the genetics of six measures of biological ageing (how old we look based on our biology relative to our chronological age). The 'biology' in question is DNA methylation (chemical additions to DNA that help turn genes on and off) in our blood. The paper, which includes >42,000 participants from 31 cohorts, will be submitted for peer-review in the next couple of weeks.



The Marioni Research Group catch up at an online meeting. Clockwise, from top left: Danni Gadd, Dr Riccardo Marioni, Anna Stevenson, Rob Hillary, Dr Daniel McCartney.

Anna Stevenson (final year PhD student) had led the analysis of DNA methylation in the LBC brain bank. In collaboration with Prof Tara Spires-Jones, she has characterised DNA methylation in five different brain regions and has related this to the biological hallmarks of dementia. In addition to writing this up for publication (her 5th first author paper from an incredibly productive PhD!), Anna has also been mentoring our PhD rotation students Danni Gadd and Sarah Kent. Danni will have some exciting LBC methylation-brain-lifestyle findings to report in the near future!

Rob Hillary is approaching the mid-point of his PhD in which he has been exploring the link between genes, DNA methylation, protein levels and brain health in LBC and Generation Scotland. He has been using advanced statistical approaches to analyse these large datasets simultaneously. This has resulted in two published papers with another two under review. He is also busy building an online tool to help translate his findings to the general public."

Causes of loneliness differ between generations



Loneliness is a growing public health issue in the developed world. Among older adults, loneliness is a particular challenge, being comorbid with many physical and mental health issues. In a recent study, published in Psychological Medicine, Dr Drew Altschul and colleagues analysed over 4000 participants from four cohorts of older individuals, including LBC1936. They used state-of-the-art machine learning techniques, as well as traditional statistics, to identify and replicate associations between loneliness and a variety of psychological and social factors. They found similar levels of loneliness in both younger and older participants, and higher emotional stability, the inverse of neuroticism, was associated with lower loneliness in all groups. In the older group (70 and older), social circumstances such as living alone were also associated with higher loneliness, and this was even more acute in men. In the younger group (55 to 69), extraversion's association with lower loneliness was the only other confirmed relationship. The results suggest older and middle aged people are equally lonely, but different individual and social differences might underlie loneliness differences in different age groups.

The paper was featured in a high profile <u>blog</u> in Psychology Today.

Psuchology Today

Drew M. Altschul Ph.D.

Reverse Causation



LONELINESS

What Puts People at Higher Risk for Loneliness

Which factors are related to loneliness in middle-age and older people?

Posted Apr 22, 2020



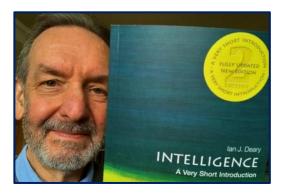
'Narrating future selves': 6-Day Sample Study

In a recent paper, accepted by scientific journal Anthropology & Aging, Professor Jane Elliot and Dr JD Carpentieri aimed to find out more about the many ways that older people think about themselves and their future, how they incorporate this into their decision making and planning, and how this supports their wellbeing. To study this, they interviewed a subgroup of 33 individuals from the 6-Day Sample study cohort, all born in 1936 and who took part in the Scottish Mental Survey of 1947 (which the LBC1936-ers took part in). They asked questions about topics such as future plans, health, physical capabilities, interests and activities. After examining themes from the interviews and two case studies, they discuss the many lenses through which participants view themselves and their futures, including when looking at topics such as care needs, frailty, and death. This study is important in investigating themes which might not be fully explored and quantified through more structured, quantitative scientific studies. The full paper, 'Narrating future selves: perspectives on ageing from a Scottish cohort born in 1936', is due to be published in Autumn 2020.

Knowledge exchange and Impact

Intelligence: A very short introduction

In March, we celebrated the publication of Professor lan Deary's second edition of 'Intelligence: A very short introduction'. The book, published by Oxford University Press, explores intelligence in ten key questions, helping the reader understand why some people's brains and thinking skills age better than others, what more intelligent brains look like, and, in a brand new chapter, what research shows about how childhood intelligence relates to later health and survival (using Scottish Mental Survey data). Ian said, "About 80% of the book is new in this edition, and I was delighted that so many chapters featured Scottish Mental Survey/Lothian Birth Cohorts data". The book was featured at the Edinburgh Science Festival in April in a 60 second science video. Ian spoke about the book at the Cheltenham Science Festival @ Home on 4th June, which you can now watch on YouTube!



LBCs on BBC Two Horizon episode: 'The Great British Intelligence Test'

In our last edition, we told you all about the BBC visiting the Lothian Birth Cohorts in February to film an episode of Horizon all about intelligence.



Above: Dr Simon Cox filming with Dr Hannah Fry and Bobby Seagull. Below: Dr Michael Mosely with LBC1936 participants, Mr Patrick Forsyth and Mrs Audrey Mackie.



The special BBC Two show was watched live by 1.4 million viewers on the 4th May. Dr Michael Mosely and Dr Hannah Fry demonstrated cognitive tests on volunteers, much like those undertaken by LBC1936 participants, and revealed the results of the Great British Intelligence Test: an online series of cognitive tests designed by researchers at Imperial College.

The programme showcased the LBCs' unique history and contribution to cognitive ageing research. Our LBC1936 participants, Mrs Audrey Mackie and Mr Patrick Forsyth, explained to Dr Mosely what they thought kept them sharp, such as regularly physical activity like cycling or playing golf. Professor Deary was shown reviewing some key insights into successful cognitive ageing, and Dr Simon Cox explained links between thinking skills and features of the brain, such as brain size, and the importance of white and grey matter health.

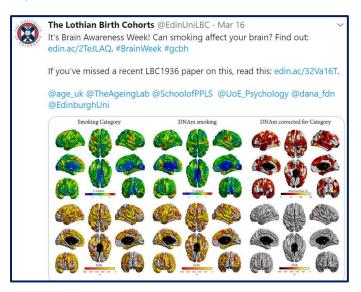
The show also featured segments from the radiographers at Edinburgh Imaging Facility, and from former team member, now LBC collaborator, Professor Alan Gow of Heriot Watt University.

If you missed the episode, you can catch up on BBC iPlayer <u>here</u>, and you can still have a go at the Great British Intelligence Test <u>here</u>.

Brain Awareness Week

We celebrated the Brain Awareness Week between 16 and 20 March, together with Age UK, in a series of tweets related to key messages from the Global Council on Brain Health's <u>recent report</u> on the brain and heart connection. Each tweet focused on one particular aspect of the brain-health connection in older age was posted daily. The tweets asked how factors like smoking, exercise, sleep, diet, and heart health affect brain health, linked to relevant LBC papers, and included a link to Age UK's Staying Sharp pages, where readers could find the answers.

Despite this year's Brain Awareness Week falling on the first week of the UK Covid-19 lockdown, when everyone's attention was focused on the Corona virus, our tweets generated a lot of interest. Over 3,000 users visited the Staying Sharp pages during the week, particularly pages on Smoking and Exercise. Our tweet on smoking, with a link to a recent paper by Dr Janie Corley and colleagues, attracted over 13 thousand impressions on Twitter, becoming the Disconnected Mind's top tweet of the month!



The Lothian Birth Cohorts' tweet about smoking during Brain Awareness Week



When science turns into art

Our neuroscientist, Dr Colin Buchanan, uses tractography, a 3D modelling technique used to represent nerve tracts, to model data collected by diffusion magnetic resonance imaging (MRI) of a healthy middle-aged adult. These beautiful images, shown below and on the next page, represent healthy white matter fibre tracts showing connections across the brain.

You can also see a 3D animation of the model on our <u>twitter</u>, where it is now our 'top tweet', with over 37 thousand impressions and growing, overtaking our tweet from Brain Awareness week. Enjoy!



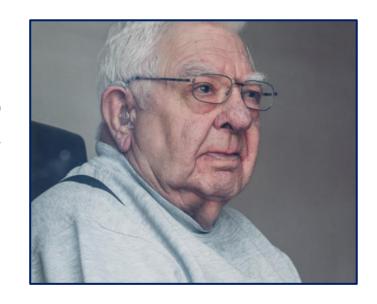




Age UK News

Greetings from Age UK! This has been a strange spring, with the Covid-19 pandemic having a big impact on us all. At Age UK that means that we're all working from home, to try to help reduce the spread of the virus. We have all seen how Covid-19 is particularly dangerous for older people so we're channelling all our efforts towards helping the older people who need us most, be that with information and advice or with food parcels, and by working to influence the government and other organisations to protect older people during the epidemic.

To find out more about how Age UK is supporting older people, please visit our website: https://www.ageuk.org.uk/



Some new publications

Accepted

Cadar, D., Robitaille, A., Pattie, A., Deary, I.J., Muniz-Terrera, G., (2020). The long arm of childhood intelligence on terminal decline. Psychology and Aging.

Colicino, E., Marioni, R., Ward-Caviness, C., Gondalia, R., Guan, W., et al., (2020). Blood DNA methylation sites predict death risk in a longitudinal study of 12,300 individuals. Aging.

Ma, J., Rebholz, C.M., Braun, K.V.E., Reynolds, L.M., Aslibekyan, S., et al., (2020). Whole blood DNA methylation signatures of diet are associated with cardiovascular disease risk factors and all-cause mortality. Circulation: Genomic and Precision Medicine.

Toombs, J., Panther, L., Ornelas, L., Liu, C., Gomez, E., et al., (2020). Generation of twenty four induced pluripotent stem cell lines from twenty four members of the Lothian 4 Birth Cohort 1936. Stem cell research.

E-published ahead of print

Altschul, D., Iveson, M., Deary, I.J., (2020). Generational differences in loneliness and its psychological and sociodemographic predictors: an exploratory and confirmatory machine learning study. Psychol. Med. 1–10. https://doi.org/10.1017/S0033291719003933

de las Fuentes, L., Sung, Y.J., Noordam, R., Winkler, T., Feitosa, M.F., et al., (2020). Gene-educational attainment interactions in a multi-ancestry genome-wide meta-analysis identify novel blood pressure loci. Mol Psychiatry. https://doi.org/10.1038/s41380-020-0719-3

Lund, J.B., Li, S., Baumbach, J., Christensen, K., Li, W., et al., (2020). Weighted gene co-regulation network analysis (WGCNA) of promoter DNA methylation on all-cause mortality in old-aged birth cohorts finds modules of high-risk associated biomarkers. The Journals of Gerontology: Series A glaa066. https://doi.org/10.1093/gerona/glaa066

Published

Alonso, N., Larraz-Prieto, B., Berg, K., Lambert, Z., Redmond, P., et al., (2020). Loss-of-function mutations in the ALPL gene presenting with adult onset osteoporosis and low serum concentrations of total alkaline phosphatase. J Bone Miner Res jbmr.3928. https://doi.org/10.1002/jbmr.3928

Published (continued)

Beaudet, G., Tsuchida, A., Petit, L., Tzourio, C., Caspers, S., et al., (2020). Age-related changes of Peak width Skeletonized Mean Diffusivity (PSMD) across the adult life span: A multi-cohort study. Frontiers in psychiatry.

Biton, A., Traut, N., Poline, J.-B., Aribisala, B.S., Bastin, M.E., et al., (2020). Polygenic Architecture of Human Neuroanatomical Diversity. Cerebral Cortex bhz241. https://doi.org/10.1093/cercor/bhz241

Graham, E.K., Weston, S.J., Gerstorf, D., Yoneda, T.B., Booth, T., et al., (2020). Trajectories of Big Five Personality Traits: A Coordinated Analysis of 16 Longitudinal Samples. European Journal of Personality. https://doi.org/10.1002/per.2259

Grasby, K.L., Jahanshad, N., Painter, J.N., Colodro-Conde, L., Bralten, J., et al., (2020). The genetic architecture of the human cerebral cortex. Science 367. https://doi.org/10.1126/science.aay6690

Li, S., Lund, J.B., Christensen, K., Baumbach, J., Mengel-From, J., et al., (2020). Exploratory analysis of age and sex dependent DNA methylation patterns on the X-chromosome in whole blood samples. Genome Med 12, 39. https://doi.org/10.1186/s13073-020-00736-3

McLachlan, K.J.J., Cole, J.H., Harris, S.E., Marioni, R.E., et al., (2020). Attitudes to ageing, biomarkers of ageing and mortality: the Lothian Birth Cohort 1936. J Epidemiol Community Health jech-2019-213462. https://doi.org/10.1136/jech-2019-213462

Seeboth, A., McCartney, D.L., Wang, Y., Hillary, R.F., Stevenson, A.J., et al., (2020). DNA methylation outlier burden, health, and ageing in Generation Scotland and the Lothian Birth Cohorts of 1921 and 1936. Clin Epigenetics 12, 49. https://doi.org/10.1186/s13148-020-00838-0

Taylor, A.M., Ritchie, S.J., Madden, C., Deary, I.J., (2020). Associations between Brief Resilience Scale scores and ageing-related domains in the Lothian Birth Cohort 1936. Psychol Aging. https://doi.org/10.1037/pag0000419

Westerman, K., Fernández-Sanlés, A., Patil, P., Sebastiani, P., Jacques, P., et al., (2020). Epigenomic Assessment of Cardiovascular Disease Risk and Interactions With Traditional Risk Metrics. JAHA 9. https://doi.org/10.1161/JAHA.119.015299

Wu, Y., Qi, T., Wang, H., Zhang, F., Zheng, Z., et al., (2020). Promoter-anchored chromatin interactions predicted from genetic analysis of epigenomic data. Nat Commun 11, 2061. https://doi.org/10.1038/s41467-020-15587-0









More #wfh photos. Left, from top: Disconnected Mind Director Professor Ian Deary; Study Co-ordinator Adele Taylor; Research Associate Dr Janie Corley; Senior Research Associate Dr Simon Cox with his new office-mate, Sam, his four-year-old son. Right: Research Assistant Danielle Page; PhD student Miles Welstead with his dog Phoebe.





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