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 55: September 2021

Welcome to the Autumn 2021 Disconnected Mind newsletter. This issue includes news about the Disconnected Mind/Lothian Birth Cohorts (LBC) team, our latest publications, and recent events.

For further information or to contribute to a future issue, please contact us using the details on page 8.

Staff news

LBC1936 young researchers' successes

The Disconnected Mind project/LBC has a long history of attracting talented young researchers to the project; and we are proud to offer such fertile ground for important research training, and future career preparation. In this special section, we celebrate the work of our brilliant young researchers, and their many and varied successes.

We begin by congratulating Dr Federica Conte, Dr Olivia Hamilton and Dr Emily Wheater, who each successfully defended their theses, recently, and have already begun their next roles in research – Dr Conte and Dr Hamilton to postdoctoral positions in Milan and Glasgow, respectively, and Dr Wheater to work for the BBSRC. All three included studies based on LBC data which continues to be a treasure trove for new scientific discoveries.! We include a message from each of them next. We want to thank them for being fantastic colleagues, and wish them luck in their next steps!

"*Some of my PhD was spent with the LBC analysing data on birth weight and brain structure in late life, supervised by Dr Simon Cox. This formed a major part of my thesis. Some LBC1936 participants were born in hospitals around Edinburgh, and had their birth weights recorded on birth records. This was unusual for the time; most people were born at home, and do not necessarily have accurate records from the time of birth. Previous work led by LBC Co-Investigator Susie Shenkin digitalised the records, so that they could be linked with the incredibly rich information from later life gathered as part of the LBC study. In LBC1936, larger birth weight was associated with having a larger brain in late life, but was not associated with age-related change such as atrophy. My viva examiners were really enthusiastic about this rare, historic data, that allows us to delve a bit deeper into the early life origins of late life brain health.* Emily Wheater, PhD

"*It has been such a pleasure to spend the last four years learning what happens to our brains as we get older. During my PhD, I used data from the LBC1936 to explore associations between vascular changes in the brain and cognitive abilities. One of our main findings was that dysfunction of the brain's small vessels is associated with declining ability in all major cognitive domains. My work benefitted hugely from the range of brain and cognitive data available in the LBC studies and from the support of the brilliant LBC team. I feel very fortunate to have worked with such a skilled and friendly group of scientists and will miss working in the 7 George Square corridor (or the digital equivalent) very much!*" Olivia Hamilton, PhD

"*Defending my dissertation on 'Personal and situational determinants of lifetime cognitive trajectories' was among the most satisfying moments of my adult life. I used LBC1936 data to explore how cognitive abilities change across the lifespan from age 11 to 82, and how earlier change trajectories might be used to predict greater cognitive decline in older age. Looking back, I believe that my experience with the LBC team allowed me to approach it with particular self-awareness and appreciation. Being a visiting student in Edinburgh has undoubtedly boosted my research skills. However, Professor Ian Deary, Dr Simon Cox and the rest of the team also taught me, by example, a lot about how I want to live my life as a researcher. In October, I will start a Post-Doc at the University of Milano-Bicocca, where I completed my PhD. I have a lot to look forward to, but I especially hope there will be opportunities to keep working with these fantastic people in the future."* Federica Conte, PhD

PhD student **Miles Welstead** has focused his thesis on how and why frailty changes over time. He has recently published two LBC1936 papers on frailty, in The Gerontologist and Experimental Gerontology. He has recently returned to complete his PhD following an internship with the Scottish Government.

Ellen Backhouse completed her PhD in 2018, supervised by Prof Joanna Wardlaw. Her thesis focused on early life risk factors and brain changes associated with stroke. Ellen is now a Research Fellow in cerebrovascular disease, and often uses LBC1936 data in papers: most recently, she examined associations between early life factors and markers of small vessel disease. We include a summary of her paper later in this newsletter, in the Scientific Highlights section.

Danni Gadd, PhD student with the Marioni Group, our close collaborators who work on genetic and epigenetic data, is using biological data from the blood to predict and better understand the onset of dementia and its associated comorbities. With LBC1936 epigenetic data, she recently created scores for protein levels in the blood, and used these to predict onset of Alzheimer's Dementia and other diseases including diabetes and stroke over a follow-up of 14 years, providing new insights into early markers of disease. The paper is under review for publication.

Dr Daniel McCartney, Bioinformatician for the Generation Scotland team, joined the university as a postdoctoral researcher in 2018 with the Marioni Group. Now, he manages and analyses biological data from approximately 20,000 volunteers. He recently published a large genetic study of biological ageing rates in over 40,000 people, including LBC1921 and LBC1936, which identified 137 genes related to the rate of biological aging, and found common underlying genetics between biological aging rates and parental lifespan, and lifestyle factors such as smoking.

Rob Hillary submitted his PhD with the Marioni Group in July, and started his new job with them as a Research Fellow. Rob's PhD was focused on finding blood based biomarkers for Alzheimer's dementia risk. The final chapter of his thesis is online as a pre-print; he conducted genome- and epigenome-wide studies on plasma levels of 281 proteins linked to Alzheimer's disease, and found 61 independent genetic and 32 epigenetic loci were associated with the expression of these proteins.

Research Associate **Dr Jo Moodie** first used LBC data during her MSc to explore associations between brain asymmetry and cognition, resulting in a publication in *Intelligence*. After finishing her PhD, she re-joined the LBC team, funded by Dr Simon Cox's Henry Dale Fellowship. She aims to characterise connections between biological, brain and cognitive ageing, and is currently investigating links between cortical gene expression and brain correlates of cognition, using LBC1936 data alongside other cohorts.

PhD student **Jure Mur** has been exploring environmental factors associated with health and disease in later life. He is currently working on researching anticholinergic drugs, which block the action of neurotransmitter acetylcholine in the brain, and their relationship with health-related outcomes. He recently published a paper which showed that in a sample from UK Biobank, there was a significant increase in anticholinergic burden between 1990 and 2015, despite previous research linking the drugs with some negative outcomes.

PhD student **Eleanor Conole** is interested in the impact lifestyle has on brain structure, and her first paper (pre-print) is now in press in *Neurology*. She showed that a DNA methylation marker of inflammation is up to 4-times more strongly associated with brain structure and cognitive functions than a protein measure taken from blood.

Finally, two team members have been studying towards an MSc in their spare time while working full-time with the LBC1936 study. Both will be writing up their theses for publication soon. Study Coordinator, **Adele Taylor**, just completed her MScR in Psychology. She used LBC1921 and LBC1936 data to examine cohort effects: differences in certain attributes that occur over time for similar-aged groups of people, defined by shared experiences. Using a range of variables, measured using identical methods when both cohorts were age 79, she examined whether there were differences in cognitive ability, non-cognitive psychology variables, and physical fitness measures between the two cohorts who were born 15 years apart.

Research Assistant **Danielle Page** is about to complete her MSc in Human Cognitive Neuropsychology in September. Her dissertation aims to solve a theoretical problem that makes interpreting associations between brain structures and cognitive abilities in neuropsychological studies more difficult. By extracting scores for domains of cognitive ability, and a score for general intelligence or '*g*', from LBC1936, she was able to map which structures in the brain are related to each domain, or to *g*, and which overlap.

Lothian Birth Cohorts News

New NIH grant to understand the genetics of cognitive ageing

In an exciting new development for the Disconnected Mind team, LBCs Director Dr Simon Cox will be leading the UK part of a new $3.5M grant from the US National Institute on Aging (NIA). The Principal Investigator is long-time collaborator Professor Elliot Tucker-Drob from the University of Texas at Austin. This 5-year project will employ cutting-edge statistical methods to understand the genetic underpinnings of cognitive changes. Dr Cox explains: "*We have led international efforts to understand how genes relate to differences in cognitive levels, but understanding cognitive changes is also vital. Particularly when peak levels of cognitive function are high, cognitive declines may go undetected for decades before individuals present with impaired levels of functioning. Thus, understanding differences only in cognitive levels dilutes and biases conventional genetic study designs. Huge numbers of participants are needed to reliably detect small genetic contributions, and until recently the technical difficulties in integrating people from different cohorts with disparate cognitive test batteries has made genetic analyses of cognitive changes difficult to achieve. The novel approach was the brainchild of Elliot and Ian, and it is a hugely exciting prospect for novel discoveries.*"

The project's primary goal is to conduct the first large-scale consortium-based genome-wide association study (GWAS) of continuous rates of longitudinal aging-related cognitive change prior to dementia onset. This will offer novel insights into genetic profiles of those at greatest risk of cognitive ageing. Alongside providing support for Co-Investigators in our team, including Professor Ian Deary, Dr Gail Davies, and Dr Riccardo Marioni, it will support an additional post-doctoral researcher in the Disconnected Mind team for the duration of the project. Congratulations Dr Cox & team!

The LBC-CCACE Cluster Evolves

Over the past decade, the research carried out by the LBC team has evolved beyond all recognition. Ten years ago, we might have analysed just a few genetic variants or a few hundred brain imaging scans, but now, we might be analyzing millions of genetic variants for hundreds of thousands of people and brain imaging data on tens of thousands of people. We have been at the forefront of these leaps forward in the possibilities of 'big data', and this latest development is critical to that continuity. At the core of our ability to handle this data is our bespoke compute and storage computer cluster. The cluster started in the basement of 7 George Square, but as the storage and analysis requirements of the team grew, we outgrew this space and the cluster migrated to a larger server room in the Dugald Stewart Building. The cluster has continued to grow as greater and greater volumes of data are analysed by the LBC team, including not only the LBC datasets but much larger datasets such as UK Biobank and Generation Scotland. The server gives immediate access to team members and key collaborators, offering critical compute power and storage resources for increasingly complex high-end analyses.

The New Cluster housing in the King's Buildings server

We have again reached the need for a step-change with the onset of large cohort genomic sequencing and major longitudinal brain imaging data collection. To enable the team to efficiently process these larger datasets, the cluster has recently been relocated again to a specialist University of Edinburgh server facility at King's Buildings. This move enables us to house the cluster in an ultraclean environment, be at less risk from disruption to power supply, and greatly improve the movement of data to and from our global research collaborators. In addition to the relocation, we continue to expand the storage capacity within the cluster. This marks the beginning of our plans for expansion and evolution that will be required over the next five years of research and will facilitate our ability to remain at the forefront of global cognitive and brain imaging research.

Scientific Highlights

Early life risk factors for small vessel disease

Cerebral small vessel disease is a major cause of stroke and dementia. Previous research has shown that small vessel disease is influenced by early life factors such as childhood IQ, education level and childhood socioeconomic status but it is unclear whether these relationships are independent of each other, of adult socioeconomic status or of vascular risk factor exposures.

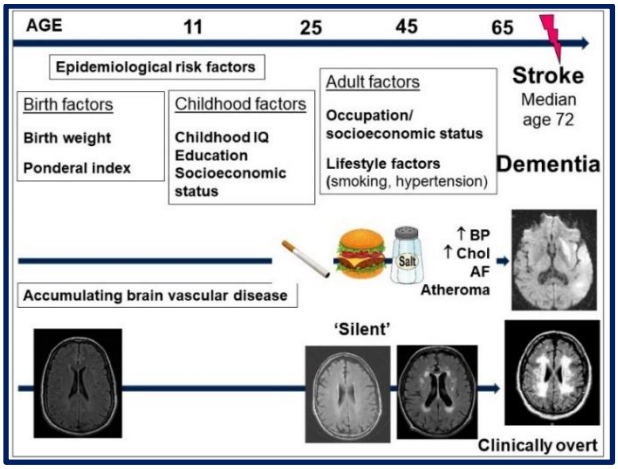


Figure from Backhouse et al (2021) showing the life course perspective of the risk of small vessel disease and stroke.

In a paper recently accepted in *Brain*, Dr Ellen Backhouse and colleagues used MRI brain imaging data from wave 2 of the LBC1936, when participants were mean age 73, and three other longitudinal birth cohorts (total N = 1,925), to test associations between early life factors and markers of small vessel disease in the brain. Lower birthweight, lower childhood IQ and less education were associated with worse small vessel disease in later life, independently of each other, and of vascular risk factors and adult socioeconomic status. These findings suggest that risk for small vessel disease may originate in early life. This may explain the association between early life factors and risk of stroke and dementia and suggests that investing in early child development may contribute to improved lifelong brain health to prevent dementia and stroke in older age.

Birth weight is associated with brain tissue volumes seven decades late

Dr Emily Wheater's paper using LBC1936 MRI brain scans and hospital birth records was recently published in *NeuroImage: Clinical*. This paper explored associations between birth weight and brain structure at 73 years old. In a subset of LBC participants who had birth weight data from hospital birth records, greater birth weight was associated with larger brain volumes and greater regional cortical surface area in later life. However, it was not associated with markers of white matter microstructure, nor with MRI markers of ageing-related changes, such as brain tissue atrophy and white matter hyperintensities (a visible marker of white matter damage). The findings suggest that being born larger, which often means having a larger head in adulthood, has long-standing effects for how much grey matter you have in older age, but does not appear to alter how quickly your brain ages.

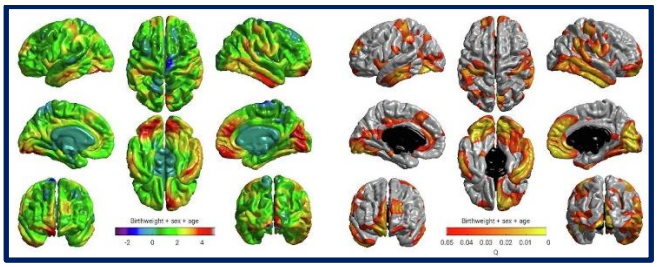
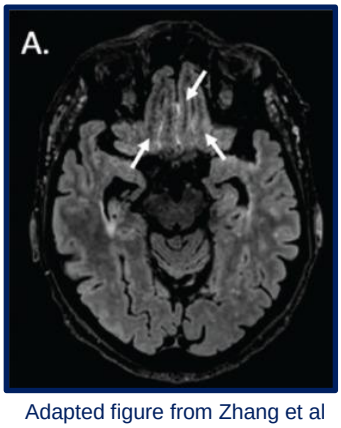


Figure from Wheater et al (2021) showing regional associations between birth weight and cortical surface area. Left: T map showing associations, Right: FDR q values showing significant associations.

Inferior frontal sulcal hyperintensities in LBC1936

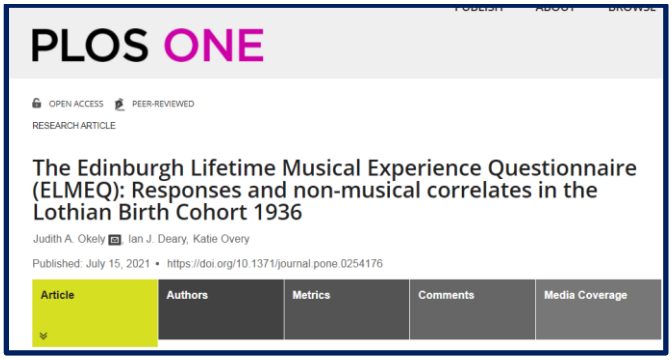
MRI images usually show cerebrospinal fluid (CSF), the fluid surrounding the brain and spinal chord, as a dark colour, but the presence of protein, blood or cell debris in CSF can increase the signal picked up by MRI, making it show up brighter, or 'hyperintense' in the image. In a recently published paper in *Neurobiology of Aging*, Dr Jun-Fang Zhang, of the University of Edinburgh's Centre for Clinical Brain Science, and colleagues noticed that in routine MRIs, these hyperintensities were commonly noticed in the inferior frontal sulci, a region of the frontal lobes, particularly in older people. To explore the clinical relevance of these hyperintensities, the authors used data from 3 cohorts including the LBC1936 to develop a scale to rate the level of IFSH in the brain. They also examined correlations with demographics, vascular risk factors, and imaging markers of diseases such as small vessel disease, including enlarged perivascular spaces (PVS): enlargement of the fluid-filled spaces which surround arteries and arterioles in the brain. They found that IFSH was associated with older age, and with enlarged PVS in stroke patients. They concluded that IFSH may be a marker of impairment of brain fluid drainage, and that future research should continue to explore IFSH associations in other cohorts.



Adapted figure from Zhang et al (2021) showing examples of IFSH

The Edinburgh Lifetime Musical Experience Questionnaire (ELMEQ): Responses and non-musical correlates in the LBC1936

At Wave 5 of the LBC1936 study, participants completed a new questionnaire designed by Dr Katie Overy (Reid School of Music) and the LBC1936 team: the Edinburgh Lifetime Musical Experience Questionnaire, or ELMEQ for short. Team member Dr Judy Okely, who is leading an ESRC funded project on Lifetime musical experience and healthy ageing in the LBC1936, along with Prof Ian Deary and Dr Katie Overy, recently published a paper detailing responses to the questionnaire in journal *PLOS ONE.*



In the paper, they describe the content of the ELMEQ, designed to assess a range of musical experiences including lifetime experience of playing a musical instrument and singing, reading musical notation and listening to music. They also describe LBC1936 participants' responses to the ELMEQ and identify some of the non-musical correlates of greater lifetime musical experience; these include a more affluent childhood environment, more years of education, a higher childhood cognitive ability, female sex, and higher scores on the personality trait extraversion. This publication also includes a copy of the ELMEQ which is freely available for other researchers to use in future.

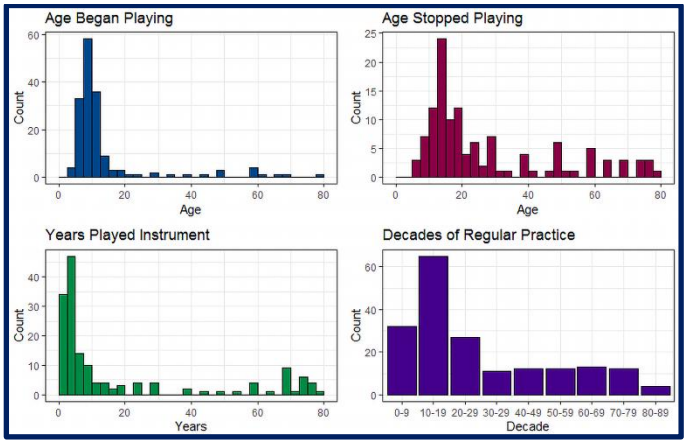


Figure from Okely et al (2021): histograms showing LBC1936 responses to the ELMEQ

KE & Impact

Who gets to be 100?: The podcast celebrating centenarians of the Lothian Birth Cohort 1921

This year marks a very special occasion for our LBC1921 participants, who are celebrating their 100th birthday. With support from PPLS Knowledge Exchange and Impact fund and the Medical Research Council Festival Open Award, the LBC team collaborated with Pennie Latin and Dan Holland of Adventurous Podcasts to create a series of podcasts to celebrate this incredible milestone. The LBC1921 and LBC1936, and their remarkable history, were also featured in Edit, the annual magazine for alumni of the University of Edinburgh.

In the first podcast, we introduced two of our LBC1921 participants, Anne and Margaret. They described their childhood and growing up in Edinburgh, as well as their memories of the 1932 Scottish Mental Survey which formed the basis for the LBC1921 study, and subsequent re-sit of the same test in 1999 at the University of Edinburgh as they began their participation in the LBC1921 study, the longest study of cognitive ageing in the world. In episode 2, Professor Ian Deary described the beginning of the cohort; how he and Professor Lawrence Whalley discovered forgotten school ledgers with the 1932 intelligence test scores from thousands of Scottish 11-year-olds, and the subsequent journey of connecting the neatly written names recorded in the notebooks to real people decades later. We also hear from research associate Alison Pattie, who worked closely with the cohort for 20 years before her retirement in 2019. In the final episode, we had a whistle-stop tour of LBC data and findings, including exploring the role of genes in cognitive ageing with Dr Sarah Harris, and new LBCs director, Dr Simon Cox, who discussed current findings and the future of the study.

The podcasts are available online on our website, as well as on Anchor, Spotify, and other podcast hosting sites.

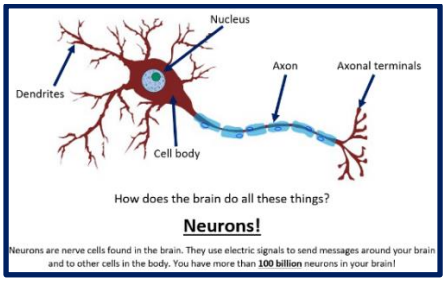
Keeping your brain sharp from age 11 to 85: Widening Participation P7 workshop

On 22nd June, team members Danielle Page and Barbora Skarabela delivered an exciting new workshop as part of the University of Edinburgh's Widening Participation (WP) team's 'Primary Initiative' project. The WP team aim to address educational inequalities and patterns of under-representation in Higher Education through a range of projects working with young people aged 11 to 18.

Danielle Page delivers the LBCs Primary School workshop

Danielle led 60 P7 children from Craigour Park Primary School, Edinburgh, through an online session designed to get them excited about Psychology. Danielle explained her role as a researcher, why the LBC1936 is so interesting, and what the LBC1936 has taught us about the brain and how to keep our thinking skills sharp. As well as learning about neurons and the brain, the children also made hypotheses about whether their thinking skills would be better or worse than an 85-year-old, and took part in some cognitive tests from the LBC1936 study to test their hypotheses. The hypotheses started some lively debates: particularly about whether an LBC1936 participant would have better memory because they had had more years of practice, or worse because their thinking skills had slowed down a little since they were 11!

The workshop was great fun for the presenters and children, and the P7s had some great thoughts and questions about thinking skills and the brain. Following great feedback, the LBC team has already been invited to deliver the workshop again for the P7 classes in 2022; we can't wait!



Screenshot from P7 work booklet: labelled figure of a neuron

Judy Okely presents LBC1936 musical experience findings at APS virtual convention and Neuroscience and Music conference

Dr Judy Okely certainly made the most of the online conference season this year by presenting her recent findings on lifetime musical experience and healthy ageing at not one, but two conferences: first, the APS virtual convention at the end of May, and then the Neuroscience and Music conference in mid June.

Judy said "*It was exciting to meet with researchers in Psychology and Music from around the world, albeit in a virtual environment, and to share findings from our two most recent studies using LBC1936 data, both of which point to a positive relationship between learning to play a musical instrument and some cognitive abilities in older age. I particularly enjoyed discussing these findings with other researchers working on interventions studies to test whether learning to play a musical instrument in later life might help to protect individuals from cognitive decline.*"

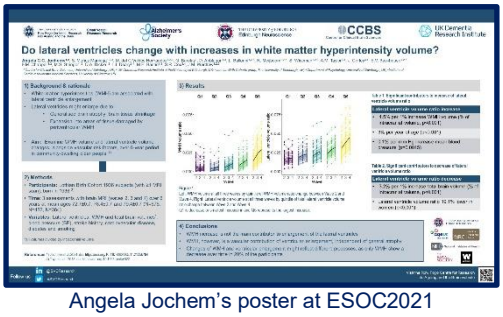
Judy virtually attends the Neuroscience and Music conference via the online platform Gathertown

Alan Gow at the Cabaret of Dangerous Ideas

The Edinburgh Festival Fringe was back in August with a mix of in-person and online events. Professor Alan Gow, LBC collaborator, featured in a double bill at a Cabaret of Dangerous Ideas show, where academics are invited to present the latest research at The Stand comedy club, with a local comedian compering their non-traditional lecture. At the show, Alan explored "marginal brain gains", the idea that there might be dozens of factors that are good for keeping us sharp as we get older, as also described in a paper by team member Dr Janie Corley. The show was in-person and broadcast online, and is now available to watch on demand.

Una Clancy and Angela Jochems at the 7th European Stroke Organisation Conference

Two collaborators recently presented work involving LBC1936 at the online European Stroke Organisation Virtual Conference, in September. Angela Jochems presented a poster on her research, which used LBC1936 data from waves 2-4, when participants were aged 73-79, to examine whether changes in lateral ventricles, cavities filled with fluid, are related to changes in white matter hyperintensities (WMH). We see WMH, signs of damaged tissue often caused by diseased small vessels and related to stroke and dementia, on brain scans. The brain shrinks and lateral ventricles become larger with aging, and is more severe in dementia. Angela wanted to see if ventricles grow by taking up the space of the WMH next to the ventricles. She found that changes in lateral ventricle size show a different pattern than changes in WMH size. However, growing WMH do play a role in the enlargement of the lateral ventricles.



Angela Jochem's poster at ESOC2021

Dr Una Clancy, clinical research fellow in cerebral small vessel diseases, won Best Rapid Oral Communication Award at the Cognition and Pathophysiology section of the conference for her presentation including LBC1936 data. The data, which also come from wave 2-4 MRI scans and questionnaires, looked at how subtle brain changes on MRI and mood symptoms could be inter-related over a six-year timeframe. Supervised by Prof Joanna Wardlaw and Dr Fergus Doubal, and overseen by other researchers from the LBC team, Una is completing a PhD on detecting subtle clinical features associated with brain changes on MRI scans. This might help us to predict which individuals are most likely to develop brain changes over time.

Una Clancy presents at ESOC2021

Unlock & Revive project evaluation

Earlier in 2021, the LBC team participated in the Unlock & Revive Programme, a cross-disciplinary project initiated by the University of Edinburgh Museum Services Manager, Ruthanne Baxter. The aim of the project was to support the wellbeing of people and communities living with dementia through online heritage and cultural engagement activities. We joined the initiative with a series of six online singing sessions delivered in partnership with singer and choir director Heather McLeod. We also contributed to the evaluation of the programme, to identify the key elements for accessible, inclusive, and engaging online events specifically designed for community care partners and their clients.

The project has now produced a rich dataset that captures feedback from people with dementia, carers, and instructors. The evaluation highlighted an overwhelmingly positive effect of these online sessions for the participants. Carers and users acknowledged that the sessions helped them relieve stress and find joy in the online activities, highlighting their positive effect for mental health as well as positive social benefits, with clients and community organisers noting new friendships and closer ties among participants. The online nature of the sessions proved to be an especially useful aspect of the series, as it eliminated travel, reducing the time investment for each session, and allowing those with mobility barriers to join and those with health conditions to easily leave the session if they felt fatigued or overwhelmed. Online sessions also meant they attracted a more diverse group of people, were more accessible and more comfortable for attendees.

The team are currently working on the full report and executive summary, with key recommendations for event organisers and healthcare professionals, which will be available in late September.

Contact

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

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www.ed.ac.uk/lothian-birth-cohorts

Some new publications

Accepted/In press

Backhouse, E., Shenkin, S. D., McIntosh, A. M., … Wardlaw, J. M. (2021). Early life predictors of late life cerebral small vessel disease in four prospective cohort studies. *Brain*.

Epub before print

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Hamilton, O. K. L., Cox, S. R., Okely, J. A., … Deary, I. J. (2021). Cerebral small vessel disease burden and longitudinal cognitive decline from age 73 to 82: The Lothian Birth Cohort 1936. *Translational Psychiatry*, *11*(1), 376. https://doi.org/10.1038/s41398-021-01495-4

McCartney, D. L., Min, J. L., Richmond, R. C., … Marioni, R. E. (2021). Genome-wide association studies identify 137 genetic loci for DNA methylation biomarkers of aging. *Genome Biology*, *22*(1), 194. https://doi.org/10.1186/s13059-021-02398-9

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Taylor, A. M., Page, D., Okely, J. A., … Cox, S. R. (2021). Impact of COVID-19 lockdown on psychosocial factors, health, and lifestyle in Scottish octogenarians: The Lothian Birth Cohort 1936 study. *PloS One*, *16*(6), e0253153. https://doi.org/10.1371/journal.pone.0253153

Zhang, J., Lim, H. F., Chappell, F. M., … Wardlaw, J. M. (2021). Relationship between inferior frontal sulcal hyperintensities on brain MRI, ageing and cerebral small vessel disease. *Neurobiology of Aging*, *106*, 130–138. https://doi.org/10.1016/j.neurobiolaging.2021.06.013