Lifelong resilience

Director, Professor Andrew McIntosh reflects upon ‘Resilience’

Dictionaries define resilience as “the ability to recover quickly from difficulties”. In our centre, we often use the term ‘psychological resilience’, to define our work on understanding cognitive age, emotions and how the brain changes over time.

“You could think of resilience as a spring. We are all born with our spring slightly stretched; perhaps by our genetics, or because our mother experienced stress or famine during pregnancy. As we go through life, additional weights are added to our spring, in the form of disease or adversity. Finally, the weight becomes so great, that we tip from being ‘resilient’ to impairment of our thinking skills or mood. That final load may be small, but when added to what we are already carrying, it prevents us from ‘bouncing back’ and recovering.”

However, resilience is not just about ‘bouncing back’; it is also about finding ways to stay well or reduce the impact of stress in the future. “With our research, we hope to find ways to help people become more resilient and improve their lifelong mental health,” says Professor McIntosh.

How do we study resilience?

Data science

Our centre deals with a very large volume of genetic and brain scan data. By creating new tools, we have been able to explore the relationships between genetics, personality and mood.

Our outlook is longitudinal

Much of the data we use comes from longitudinal cohort studies, where data is gathered from the same people over a long period of time, often for decades. This allows us to identify risk and psychological resilience factors, many years before the individual develops difficulties.
The future is young

Some of our research participants haven’t even been born yet! Using scanning technologies, we can now examine changes in the brain that occur before birth.

Building towards ‘Lifelong Resilience’

Researchers from psychology and medicine are helping us build a clearer understanding of ‘life-long resilience’.

‘Bounce Back’ – the ability to take knocks and rebound.

‘New Growth’ – the ability to grow and thrive in difficult conditions, where others would fail to flourish.

The capacity to recover from adversity.

The restoration of health in body and mind after early life adversity.
Public engagement

Resilience ceilidh

Over the last few months, CCACE researchers have been working with community groups to produce creative pieces, inspired by the concept of ‘resilience’.

In celebration of their efforts, a ‘Resilience Ceilidh’ was held on 3rd February 2018, where the groups shared their creative works with their families, the public and each other.

The event was run in association with Science Ceilidh Band (www.scienceceilidh.com)

Harmony choir

Harmony Choir is a group of singers, some of whom have experience with mental health symptoms. They were brought together to enjoy singing, appreciate each other’s company, and reduce the stigma that is so often associated with mental illness in our society.

Harmony Choir worked with Professor Andrew McIntosh to brainstorm the term ‘resilience’ and what it means to them. This inspired the creation of a brand new song – ‘Find my Way’, which had its public premiere at the Resilience Ceilidh.

The group also put together a ‘Resilience Playlist’, which can be found on the CCACE YouTube Channel (see @ccacevideo).

Find out more about Harmony Choir at harmonychoir.com

Leith SWI (Scottish Women’s Institute)

Leith SWI worked with Kristine Janson of Earthy Mindfulness (earthymindfulness.com) to create ‘Mindful Art’, inspired by the work of Xueyi Shen, on the white matter ‘wiring’ of the brain. (see page 20)

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Resilience Ceilidh Dance

Leith SWI also worked with Lewis Hou of Science Ceilidh Band, to create a new resilience themed ceilidh dance, inspired by the work of Dr Heather Whalley, on brain imaging. (see page 20)
Project Soothe

In research and psychological therapy, we know that the ability to soothe ourselves at times of distress helps us stay well. However, little is known about how people soothe themselves in everyday life.

The goal of Project Soothe is to create a bank of soothing images that we can use in future research and psychotherapy.

We are doing this by asking the public to submit images that they find soothing – and to rate those submitted by other people. View the gallery and find out more at: www.projectsoothe.com

Writing mums

Dr Stella Chan talked to ‘Writing Mums’ about Project Soothe and her work on understanding resilience. The group used this as their inspiration to create a set of poems, which were performed at the resilience ceilidh.

‘Writing Mums’ is a writer’s group from Dunbar, who originally met at the school gates. They include Hannah Lavery, Engagement Coordinator at the Scottish Poetry Library (www.scottishpoetrylibrary.org.uk)

Untangling resilience to depression (online videos)

1. ‘The Biology of Resilience’
   Professor Andrew McIntosh, (12 min)
2. ‘The Psychology of Resilience’
   Professor Andrew Gumley, (9 min)
3. ‘The History of Mental Illness’
   Professor Matthew Smith, (16 min)
4. ‘Environment and Mental Wellbeing’
   Dr Roger Hyam, (12 min)

Many people talk about ‘resilience’, but what exactly is it? What factors make some people more resilient than others? Is it their brain or their environment?

This series of four back-to-back talks explores this important issue, which affects every one of us.

View the videos at: www.edinburghneuroscience.ed.ac.uk/online-talks

Staying sharp website

Staying Sharp is a new ‘one-stop shop’ on the Age UK website.

Staying Sharp summarises groundbreaking research findings from CCACE and the Global Council on Brain Health.

It describes how key lifestyle factors can affect brain ageing and offers suggestions for ‘looking after your thinking skills’.

Find out more at www.ageuk.org.uk/stayingsharp
The mosaic of life

CCACE is about people, including thousands of volunteers who donate their data. Each volunteer is unique, but when they are brought together, new patterns are discovered.

It is the use of cohort studies, individually and via data pooling, that has allowed us to explore the links between mind and body says Professor David Batty.

“As part of CCACE, we focus on cognitive ability [thinking skills], of course, but also on personality, negative emotions (such as depression or anxiety), and psychosocial stress (such as job strain)” says Professor Catharine Gale.

For example, we have found that the more psychological distress a person experiences, the higher their risk of premature death. In fact, even mild mental illnesses (such as anxiety or depression), can put people at risk⁴. This particular set of findings received wide coverage in the media and has been cited in a WHO report⁵. It is our hope that it will inform public health policies in the future.

We also found that a diagnosis of a mental disorder in early adulthood puts people at an increased risk of developing heart disease⁶. Therefore, the physical healthcare needs of these patients should be given a higher priority.

But we are not always the bearers of bad news. We also found that a specific aspect of neuroticism, related to worry and feelings of vulnerability, seems to have a protective effect and actually lowers mortality rate⁷. This is something we are continuing to investigate.
The power of many

The Lothian Birth Cohorts (LBC) are two groups of people born in 1921 and 1936, who sat a test of mental ability at school when they were 11 years old. Many years later, Professor Ian Deary and his team traced over 1500 of these individuals (who were, by then, in their 70s).

The LBC members attend assessments every 3 years, where they repeat that mental test, as well as undertake a wide variety of other investigations (including lifestyle questionnaires, medical examinations, blood tests and brain scans). This wealth of data is invaluable to medical researchers.

“From the start of the Lothian studies, almost 20 years ago, I’ve made sure that the participants see their basic results before we report them. Of course, it’s also a happy occasion in which to have a good blether and to swap the pleasures and pains of growing older.” says Professor Ian Deary

And this feeling is reciprocal, with LBC members addressing Ian like a close friend during the 2017 reunion (see photo above).

4 Catharine R. Gale, Iva Cukic, G David Batty, Andrew M. McIntosh, Alexander Weiss, Ian J. Deary. When Is Higher Neuroticism Protective Against Death? Findings From UK Biobank Psychological Science First published date: July-13-2017
Born too soon

A baby’s head almost doubles in size between 25 and 39 weeks gestation (full term).

But what if this process occurs in an incubator (instead of in the womb)? What effect does this have on the developing brain?

These are the questions Professor James Boardman and his team would like to answer.

Preterm birth affects 7-8% of pregnancies in the UK. Studies suggest that children born prematurely are more likely to require special educational support in school, especially with skills like numeracy.

Being ‘born too soon’ also increases their likelihood of being diagnosed with autistic spectrum disorders in youth, and psychiatric disorders [mental illness] in adulthood.

But not all children are affected.

“An atlas of brain growth from 28 weeks onwards” (Serag et al, Neuroimage, 2012).
Our team use MRI scans to study the brain development of babies ‘born too early’.

Our research has highlighted the importance of the white matter ‘wiring’ of the brain. Poor connectivity leads to reduced growth in several deep areas of the brain, which are vital for thinking and learning. By contrast, ‘resilient’ preterm babies have ‘normal’ white matter and display ‘normal’ brain growth. “The brain structures that support intelligence in adulthood are already present in the newborn,” confirms Professor Boardman.

Professor Boardman’s work is centred around the Theirworld Edinburgh Birth Cohort (www.tebc.ed.ac.uk). This study will follow 400 young people from infancy to adulthood, looking at the consequences on brain development of being born too early, or too small.

“We are trying to identify the key factors (which may be medical, educational or family circumstances) that can affect a child’s growing brain. Our aim is to discover new ways of protecting the brain after preterm birth, so that children can grow to reach their full potential, despite early life adversity.”

“The developing brain shows remarkable potential for resilience, but more research is needed to discover the most effective treatments and strategies for promoting it.”

A recording of Professor James Boardman’s talk, “Born too soon: Consequences for brain development” can be found on the CCACE YouTube Channel @ccacevideo.

A new brain atlas

The Edinburgh Neonatal Atlas (ENA33) will help researchers model brain growth throughout development. This image shows the average brain anatomy of 33 healthy newborns, colour coded by brain region. It was made using a set of adult labels which have been ‘warped down’.

1 Telford, E, Cox et al (2017), ‘A latent measure explains substantial variance in white matter microstructure across the newborn human brain’ Brain Structure and Function. 06.06.2017

There are many things that can affect a baby’s growth in the womb, but Professor Rebecca Reynolds and her team are particularly interested in the impact of ‘stress’.

“When women attended their routine antenatal care clinic, we asked if they would be willing to take part in our research,” says Professor Reynolds. “Those who agreed completed questionnaires, which asked them how stressed they felt during pregnancy, and whether they had any symptoms of anxiety or depression.” We also took blood samples and collected more general health information. Using this data, the team found a link between self-reported stress (from the questionnaire) and stress hormone levels in the blood. Stress is not just a ‘feeling’; it actually causes biological changes within the body. Furthermore, the study suggested that women who were obese [very overweight] tended to be less satisfied with life, and were more likely to report symptoms of anxiety and depression.

But what the team really wanted to find out was the long-term impact of stress on the infant. “We followed up the children at age five, to see if there were any long-standing effects of stress on the baby’s behaviour, and how it develops.

One of the tests is called the ‘marshmallow test’. This is a test of self-regulation, which measures the child’s resilience to stress. “You show the child a marshmallow and say to them, ‘we are going to come back in 15 minutes, and if you haven’t eaten the marshmallow, I will give you another one as a special treat’. What the child doesn’t realise is that we film them, and grade their behaviour.” “What I can tell you from this is that all the boys eat the marshmallow almost immediately, whereas the girls are very good; they will do lots of distracting things such as poking the marshmallow, but many girls can hold out for the full 15 minutes.”

Stressful events experienced before birth can shape your health in the future. In the UK, 1 in 12 babies are born ‘too small’, that is, they weigh less than 5.5 lbs (2.5 kilos).

The first 1,000 days between a woman’s pregnancy and her child’s 2nd birthday offer a unique window of opportunity to build healthier futures.

1,000days.org

CCACE Notes - Building towards ‘Lifelong Resilience’

1,000 days

Stressful events experienced before birth can shape your health in the future. In the UK, 1 in 12 babies are born ‘too small’, that is, they weigh less than 5.5 lbs (2.5 kilos).
The results suggest that if the mother suffers from depression throughout her pregnancy, it increases the chances of her child developing ‘problem behaviours’\textsuperscript{1}, including those associated with ADHD\textsuperscript{2} [attention deficit hyperactivity disorder]. Similar results were also found for children born to very severely obese mothers\textsuperscript{3,4}.

“The knowledge that stress and obesity might impact on a baby’s development gives us an opportunity to do something during pregnancy to improve the outcomes for both the mothers and the babies,” says Professor Reynolds.

And the team are already testing a solution: “We are testing an intervention called ‘Enjoy your bump’, which can be completed on a mobile phone or other device. It encourages mothers to think about their mood, their anxiety and their stress during pregnancy, and gives them a plan for how to deal with it.”

If we can find ways to reduce the mother’s stress, control her weight and increase her resilience, then this should have a knock-on effect on the health and resilience of her unborn child. It is a win-win situation.

This work is supported by supported by Tommy’s and the British Heart Foundation.


\textsuperscript{2} Wolford E, et al. (2017) Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. PLoS ONE 12(12): e0190248


Since its inception in 2008, CCACE has become a global leader in the field of intelligence genomics.

Genomics is the study of genes and their function. The main difference from 'genetics' is that it doesn’t just look at a single gene. Genomics aims to study all the genes together; to untangle the inter-relationships between them, and to identify their combined influence on the body. To do this, genomics uses large datasets (genetic information from as many people as possible).

In this way, they can discover patterns and uncover genetic influences that may be very small.

Exploding out of the starting blocks

Our first focus was on the Lothian Birth Cohorts (LBC). The wealth of data we have on them is astounding; from health and personality details, to brain imaging and DNA analysis.

However, the researchers recognised the need for ever larger studies, so committed their support to Generation Scotland, which has the benefit of scale: 24,000 participants in 7,000 family groups, all with a detailed medical history.

Putting our experience to the test

In June 2015, the UK Biobank released its first set of genetic data from ~150,000 members. “With careful preparation and an ‘all hands on deck’ approach, the team rapidly produced a package of ‘first to publish’ manuscripts of high impact”, says Professor Porteous.

Many of our findings linked cognitive [brain] health to other mental or physical health conditions). “This UK Biobank exercise is being repeated as we speak, following the full data release [500,000 members] last summer.”

Achieving results

Some of our results have been provocative, such as the evidence supporting a correlation between height and intelligence. Others have significantly moved the field forward, e.g. our study on the genetic overlap between cognitive traits [thinking skills] and the risk of cardiovascular disorders and diabetes (cardiometabolic traits). “We have also seen diverse spin-offs, such as the genetics of male pattern baldness”.

In addition, we have made significant contributions towards a genetic understanding of major depressive disorder, stroke and dementia along the way.

Future challenges

With the help of projects such STRADL (Stratifying Resilience and Depression Longitudinally), CCACE is broadening its focus to include more psychiatric aspects.
Male pattern baldness: some CCACE authors of the study, and summary ‘Manhattan’ plot of genetics findings.

The challenge for the future is to join up all the dots; to reveal the hidden biological mechanisms of resilient emotional and cognitive ageing, and to translate this for individual and societal benefit.

1 Hagenaars SP et al (2016) Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia. Mol Psychiatry Nov;21(11):1624–1632
Brain imaging is state of the art

From state of the art techniques to hauntingly beautiful pictures, the CCACE imaging group adds a splash of colour to our research findings.

Professor Joanna Wardlaw, who leads the group has a professional interest in cerebral small vessel disease (SVD) – tiny changes to blood vessels, thought to underlie changes in our thinking skills as we age.

One way in which SVD manifests itself is through ‘white matter hyperintensities’ (WMHs) – bright spots on an MRI scan, which indicate damage to the ‘wiring’ of the brain.

Using these methodologies, the group has discovered multiple associations with cognition [thinking skills], for example the finding that lower IQ in youth leads to an increased number of WMHs in later life. This suggests that more intelligent people have more resilient brains that gather damage at a slower rate.

The group also discovered a general factor of ‘white matter integrity’. It was previously thought that individual tracts aged and were damaged at different rates. “We found that impaired cortical connection is substantially a global process, affecting various major tracts simultaneously”.

The Lothian Birth Cohorts 1921 and 1936 are the flagship studies of CCACE. Using LBC data, the imaging group have shown that the associations between cognition and cortical thickness are preserved throughout life.

“Without early-life measures of cognitive ability, it would have been tempting to conclude that preservation of cortical thickness [outer layer of the brain] in old age is the main mechanism of successful cognitive ageing when instead, it is a lifelong association.”

Recently, the team has begun to use novel image analyses techniques, to study the connections between all cortical regions (known as the connectome), and to look at shape deformations in structures like the hippocampus.

From neo-natal imaging to multiple sclerosis, the imaging group has a truly multi-disciplinary approach to their research.
These new techniques open new avenues for us to understand how the brain changes with age says Professor Wardlaw

IQ at age 11 accounts for more than two thirds of the association between IQ and cortical thickness in older age, in many of the brain regions associated with intelligence differences\(^1\).

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Would you want to know?

If you were at high risk of developing schizophrenia, would you want to know?

Schizophrenia is a mental health condition which encompasses a wide range of psychotic symptoms, including hallucinations (mainly hearing things that others don’t) and delusions (mistaken beliefs). These symptoms are often accompanied by more general symptoms, such as a lack of energy or enthusiasm.

Schizophrenia affects around 1% of the population over the course of the average lifetime. To put that in context, the number of people living daily with schizophrenia is about the same as those who live with Alzheimer’s disease. Yet we talk about it much less.

Schizophrenia often occurs in repeated cycles of symptoms and recovery. However, what makes some people more resilient to relapses, or more responsive to treatments is currently unknown.

Using MRI [brain} scans, Professor Stephen Lawrie and his team have identified key brain areas that reduce in size as schizophrenia develops. But this is not just a quirk of anatomy, these changes closely coincide with an increase in psychotic symptoms.

Recently, the team have been examining their MRI data using advanced machine learning techniques [computers that learn without being programmed]. This has uncovered distinct patterns within the brain scans that can accurately predict schizophrenia (in those who carry the genes)\(^1\)\(^2\).

Professor Lawrie’s team can now identify those at high risk of developing schizophrenia, years before their symptoms develop. Furthermore, when used on people who are already experiencing mild psychotic symptoms, the test is over 90% accurate in detecting who will go on to develop schizophrenia within the next 2.5 years, and of course, those who won’t.

“That is quite a powerful diagnostic test, and one that arguably should be available to people who have those sorts of concerns”, says Professor Lawrie.

The team hope that their findings will lead to earlier interventions and better outcomes for those with schizophrenia, and perhaps even new ways of intervening to prevent schizophrenia. But the truth is, we are not there yet.


2 Zarogianni E, et al. *Improved individualised prediction of schizophrenia in subjects at familial high risk, based on neuroanatomical data, schizotypal and neurocognitive features*. Schizophr Res. 2017 Mar;181:6-12
So, what should we do with these results?

- Should people at high risk of developing schizophrenia be put on anti-psychotic medication now? The medication can have significant side effects, such as weight gain, tiredness and impaired / involuntary movements (parkinsonism)
- At what level of risk would you want to be informed? (% chance of developing schizophrenia)
- What level of ‘false-positives’ is acceptable? (i.e. you are informed that you are at high risk, but never go on to develop the condition).
- Would the availability of preventions or treatments influence your decision?

As we untangle the puzzle of resilience, these ethical discussions are likely to continue.

A new brain atlas

Carriers of a rare genetic condition (a t1:11 translocation), are 30 times more likely to develop a major mental illness and the associated changes in the brain. However, it is important to note that not all of them will become unwell.

Professor Lawrie and his team have used their ‘machine learning techniques’ to provide proof of principle that carriers could be provided with predictive information about their risk of becoming ill.

Nevertheless, many younger family members did not want to know if they had the genetic anomaly or not, and some refused to take part in the research.

Genetic and neuroimaging technologies are allowing us to diagnose mental disorders in the same way as other parts of medicine, but until the treatments catch up, do we want to know?
Depression matters

Depression has a major impact on the lives – and brains – of those affected.

Depression is the world’s leading cause of disability and affects around a fifth of UK adults during their lifetime. Symptoms include low mood, exhaustion and feelings of emptiness.

However, what happens in the brain to trigger depression is still largely unknown. “We know that some people resist depression better than others”, says Dr Heather Whalley. “But we don’t know why?”

Recently, Dr Whalley and her team examined brain scan data [MRI] from over 3000 people – the largest study of its type to date. We discovered that people with depression have changes in the white matter ‘wiring’ of their brain.

Our data came from UK Biobank, a national research resource which holds health data from 500,000 volunteers. Within the next few years, UK Biobank aim to scan 100,000 people and make all of this data available to researchers around the world.

“However, we don’t know whether these brain changes cause depression or are a consequence of it. That would require a longer-term study” says Dr Heather Whalley.

“Our next steps are to look towards the resilient brain. We want to find out how the absence of structural changes in the brain, leads to better protection from distress and low mood”

In the future, what could people do to keep their brains healthy, or to ‘bounce back’ more quickly? What would make their brain more like a ‘naturally’ resilient one?

We discovered that people with depression have changes in the white matter ‘wiring’ of their brain.
“There is no single factor that determines resilience”, says Dr Whalley. “While this means that the research is complicated, it also means that resilience in its widest sense is not ‘fixed’. This is a positive message – it means there is capacity to cultivate resilience in all of us.”

“I particularly enjoy the materials science definition of resilience: ‘The ability of something to return to its original shape after it has been pulled, stretched, pressed, bent etc’. It makes me think of a rubber brain!”

1 WHO (2017), Media Centre – Depression Fact Sheet
Decoding depression

Machines can see patterns in health data that human researchers wouldn’t spot.

Major depressive disorder (MDD) is one of the most common mental illnesses, with 1 in 6 people developing it at some point during their lifetime.

MDD is treated using antidepressants and talking therapies. However, only 30% of patients respond well to the first treatment chosen. A further 30% fail to respond to any of the currently available treatments. Therefore, new approaches for early intervention, and indeed prevention of MDD are urgently needed.

Dr Mairead Bermingham used the power of machine learning [computers that learn without being programmed] to develop a new model, which can predict who is at high risk of developing MDD during their lifetime.

The factors that produced the most accurate predictions were family history of MDD, clinical symptoms and demographics (e.g. age, income or address).

“We hope that by accurately identifying those who will go on to develop MDD, we can boost funding and research into preventative and therapeutic interventions”, says Dr Bermingham.

Perhaps we can find ways to help people become more resilient to MDD, before the condition fully takes hold?

To explore this idea further, the team are looking into the genetics of resilience. They are interested in both individual genes and how they interact with one another. Furthermore, they want to examine how our life experiences and lifestyles interact with our genes; could our life experiences be turning ‘on’ or ‘off’ our genes [epigenetics]?

Or perhaps, instead of inheriting a ‘gene for depression’, people inherit a ‘sensitivity’ that puts them at higher risk of depression, when stressful life events occur?

Answers to these questions could help us predict how people at risk of developing depression will respond to new preventions and treatments.
The data used in this study was from Generation Scotland – a biobank who collect health information from thousands of volunteers across Scotland, and make it available to medical researchers. [www.generationscotland.co.uk]

First, the team used some of the data to ‘train’ the computer. Computers can spot trends and details across huge data sets (thousands of people), that humans would never be able to find. In this case, the computer compared those with MDD (717 people) to those without this condition (3,177), and developed a model for telling the two apart.

Next, the team ‘tested’ the model, by giving the computer a second set of data, and asking it to identify those with MDD. The team already knew whether these people had MDD or not (from their medical records), so could tell whether the computer got it right or wrong.

The computer model was able to predict who would develop MDD with approximately 70% accuracy, making it a useful tool for researchers and clinicians in the future.
Lauren is a PhD student, currently writing her thesis on ‘Psychological Resilience’.

What was your research about?

Not all individuals who inherit the genes for depression become unwell. This suggests that there are other factors which influence ‘depression genes’ to increase or decrease risk for the disorder. Recently, we examined the influence of two traits:

- **Resilience:** the ability to ‘bounce back’ from adversity. Resilience was associated with a decreased risk for developing depression, even in those who carried the genes.
- **Neuroticism:** a personality trait characterised by negative emotions and high stress sensitivity. High neuroticism was associated with an increased risk of developing depression, especially in those who carried the genes.

Further investigation suggested that resilience and neuroticism are partially independent pathways to depression, and not opposite ends of the same scale. Together, these findings are important, for both researchers and clinicians, as they may inform the development of new preventative strategies for depression.

What is your experience of resilience?

To me, resilience is the idea that despite things going wrong, you can dust yourself off and continue as normal. You may have a little moan, cry, or a wobble, but ultimately, you don’t let things get on top of you.

What did you do before your PhD?

I have always been interested in mental health research. I did an undergraduate degree in Psychology at Cardiff University. During this, I undertook a research placement year at MRC Cognition and Brain Sciences Unit, where I got involved with several studies investigating depression. After university, I worked as a Research Manager for a market research and consultancy company. This allowed me to travel and to gain experience working on very large datasets. These experiences set me up well for my PhD.

What is the best thing about being a PhD student?

The flexibility. Although it is a lot of hard work, I enjoy that I can work when I want and where I want (within reason). As someone that suffers from insomnia, I like that if I’m awake at 4am, I can start working, and if I achieve what I want that day, I don’t feel guilty if I finish early. I also enjoy the process of writing, as it consolidates my thoughts and helps my understanding.

When I’m not working, I like to travel, cook, swim, and see friends.

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1 Navrady, Lauren et al (2017). Genetic risk of major depressive disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self reported depression. Psychological Medicine. 1-10
Ella was a PhD student, who looked at the genetics of depression

What was your research about?

My research focussed on ‘treatment resistant depression’. This is where antidepressant treatments have failed, and symptoms continue or recur.

I used statistical methods to find patterns in genetic data, so it was important that I had lots of data, from lots of different people, to work with. To increase the size of my study, I examined prescription records, and identified additional people with ‘treatment resistant depression’ that we could include in our models. Although my study was still too small to detect any relevant genes, the work is now part of a larger international project into the genetics of antidepressant resistance.

My other research explored regions of the brain that are sometimes reported to be smaller than average in people with depression. I wanted to find out if the same genes that cause depression, could be causing this reduction in size. However, I did not find any evidence of an overlap, so differences in brain volume may be due to life experiences or lifestyle, rather than genes.

What does resilience mean to you?

I associate it with the ability to bounce back from adversity. Within my own life, I deal with stress by trying to resolve the cause, but also by giving myself time for social activities.

What did you do before your PhD?

I did an undergraduate degree in Pharmacology. During this, I became particularly interested in pharmacogenomics [how genes affect a person’s response to drugs]. I chose this PhD because of my existing interest in mental health conditions, and because it seemed like a great opportunity to work with data from Generation Scotland. [Generation Scotland holds biological samples and health information from thousands of volunteers across Scotland, which is made available for medical research]

Since my PhD, I have started a job at AstraZeneca [Pharmaceutical company], so will continue to do genetics research, but on a broader range of medical conditions.

What is the best thing about being a PhD student?

The best thing is probably the freedom. I was allowed to change my project to suit what I was interested in. I also worked with a really great team of people.

CCACE studies have shown that stressful life events can have a major influence on healthy cognitive ageing.

The body reacts to stress by releasing hormones. These allow you to respond in a good way; by increasing cognition [thinking skills] and activating energy. However, exposure to major stressful episodes (such as bereavement or trauma) can have long-lasting effects on the brain.

Professor Megan Holmes and her team have identified 2 enzymes (11ß-HSD) that metabolize the stress hormone cortisol. The first, (type 1) activates the cortisol and the other (type 2) inactivates it.

Levels of type 1 have been shown to increase with age, exacerbating the damaging effects of cortisol on the brain, and contributing to cognitive decline. However, CCACE researchers have shown that type 1 inhibitors can both improve cognition and decrease the strength of traumatic memories in animals. These drugs are now in clinical trials.

But it is not just older adults who should be aware of their stress levels. “We have shown that foetuses, babies and children up to puberty, are very sensitive to major stresses”, says Professor Holmes.

Nevertheless, unborn babies do have several levels of protection. The first is the presence of the type 2 (inactivating) enzymes in the placenta. This greatly limits the amount of active stress hormone reaching the baby’s blood supply. The second is the presence of type 2 enzymes in the foetal brain. These have been shown to be particularly protective against cortisol damage that could otherwise lead to depression and cognitive impairment in later life.

Maternal stress can result in a decreased birthweight and an increased risk of heart disease later in life. A recent study by Professor Holmes’ team has suggested that statins could counteract these negative effects in mice. “Although more work needs to be done to show statins are safe in human pregnancy, these results show a new way forward for the major unmet need of fetal growth retardation and potentially its consequent effects on adult cognition”, says Professor Holmes.


Three generations of Professor Holmes' family.
Making predictions

**Prediction is the first step towards prevention.**

Memory loss [dementia] is one of the most feared aspects of growing older. Alzheimer’s disease (AD) often develops slowly, over many years, and the initial symptoms can be subtle. Yet the brain changes that lead to AD are known to begin in mid-life. By the time more obvious symptoms develop, it may already be too late for interventions.

“It is therefore critical that individuals at high risk are identified as early as possible, to provide them with the best support and treatments”, says Dr Riccardo Marioni. “Our work aims to identify those at high risk of developing AD, years before their symptoms develop.”

In the immediate future, this would aid recruitment to clinical trials, as only those with the highest risk of developing the condition would take part. “This would reduce the timescale and cost of these trials, and increase the likelihood of discovering a common biological mechanism” says Dr Marioni.

In the longer term, a predictive test like this could be used in the clinic, to ascertain who would benefit most from preventative treatments.

One aspect of ‘disease risk’ comes from our genes. Recently, Dr Marioni and his team have been developing a new ‘genetic scoring system’ for AD. This is based on two factors:

1. **APOE status:** This is the greatest known genetic risk factor for AD. [APOE is a protein involved in fat transportation.]
2. **Global polygenic risk:** the additive effect of lots of small gene changes, none of which substantially increase the risk of AD on their own.

However, the team recognise that genes are just one piece of the puzzle.

“Over the next couple of years, I aim to extend the prediction element of my research by including environmental [lifestyle] data, to improve our estimation of disease risk.”

We know that stressful events and lifestyle factors (such as diet and exercise) can chemically alter genes, helping to turn them ‘on and off’. Dr Marioni and his team would like to find out what gene ‘settings’ are present in those who seem ‘resilient’ to AD; those who perhaps carry the risk genes, but never go on to develop the condition. Are there things about their diet or lifestyle that push the AD genes towards the ‘off’ position?

“For now, we don’t really know, so I’d opt for everything in moderation!” says Dr Marioni. However, our ultimate goal with this research is to unscramble the puzzle of resilience, and to help people lead longer and healthier lives.
Science studies using genetic data are often poorly reported in the mainstream media – a lot of the time the genetic effects on disease are very small, especially compared to the environmental [lifestyle] influences!

Quote from Science Media Centre [online] www.sciencemediacentre.org