10 years of CCACE

Director Ian Deary reflects upon the progress of CCACE as it enters its 10th anniversary year

As CCACE has matured, its confidence and reach has improved. The collective force of our members has produced excellent results and resources, and our influence has been noted internationally.

We’ve had a clear mission from the start, and we’ve stuck to it: “CCACE’s aim is to understand the reciprocal influences of cognition and health across the human life course and between generations.”

Professor Ian Deary, Director CCACE

Much of this is thanks to the support of our excellent CCACE core staff, post-docs, PhD students and clinical fellows. CCACE brought us together, and united us under common aims, yet we retained the flexibility to respond to opportunities as they arose.

All of this together has allowed us to take leadership roles in, for example:

- **Dementias Platform UK**: work packages, experimental medicine projects, and capital infrastructure.
- **Lothian Birth Cohorts**: adding multi-omics (whole genome sequencing, DNA methylation, gene expression, lipidomics, and stem cells).
- **Generation Scotland**: leading the cognitive and personality work.
- **Cognitive testing in the Healthy AGing In Scotland** (yes, HAGIS) study.
- **Producing large-scale knowledge exchange resources**, e.g. with Age UK.
- **Administrative Data Research Centre**: leading work packages.
- **Dementia Research Institute CCACE** was prominent in the successful bid for the centre coming to Edinburgh.
- **Large international CHARGE cognitive function GWAS meta-analyses**.
- **Conducting scarily-large and ambitious big-data linkage projects** on cognitive ability and health.
- **UK Biobank**: improving the cognitive tests and producing large-scale genetic and phenotypic results.
- **Generating large-scale knowledge exchange resources**, e.g. with Age UK.
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There are more examples, and your favourite one might be missing. But they make the point that a Centre and its resources can do something much more than a research project or even a research programme. It provides communality of purpose and the freedom to address new problems or attack new possibilities.

The fruit of all this may be glimpsed in the groups’ reports, and even more so in the 2080 peer-reviewed papers and 262 collaborations we returned in researchfish (the annual RCUK output reporting system).

Thank you to everyone who has contributed to our success over the last 10 years.

Professor Ian Deary
As we near the start of the third quinquennium of CCACE, what have we achieved and where do we go from here?

**Achievements to date:**
- 262 national and international collaborations,
- 29 postgraduate students,
- 2080 publications

Multiple influences on government, social and health policy.

**Big Data**

**The mood is changing**

In the last two years, CCACE publications on mood related traits have grown. Beginning at the inception of CCACE with neuroticism (negativity), we continue to use our genetic and brain imaging data, to find linkages to traits such as cognition and depression.

**The future is longitudinal**

UK biobank and other longitudinal cohort studies are providing us with a vast amount of genetic data. With increased computing power and new analytical measures, we can further explore the reciprocal and causal relationships between cognition, personality and mood.

**The future is young**

Through collaborations with James Boardman and colleagues in Clinical Psychology, CCACE has been able to extend our life course perspective to earlier ages, even before birth!

**What next?**

- We build on the environment created by our MRC centre.
- We grow through new funding awards, fellowships and strategic grants.

**Building towards ‘Lifelong Resilience’**

The next generation of researchers from psychology and medicine will help us build towards a new centre, based on the key areas of cognition, mood and health and united by the common theme of ‘lifelong resilience’.

**New life from the LBC1936!**

Taking a tangent from CCACE, The Dementia Research Institute1, will use Lothian Birth Cohort data, brain tissue and stem cells to search for new treatments for dementia.
How old is your brain?

Although two people may be exactly the same age, the biological influence of age might affect them quite differently.

We used a set of statistical techniques called “machine learning” to calculate a “brain age” for each individual Lothian Birth Cohort participant. This told us the difference between their calendar (chronological) age and the age of their brain.

We found that individuals whose “brain age” was younger than their calendar age were healthier and were more likely to be alive at later waves of the study.


Pathways of ageing

Scientists at CCACE undertook the most comprehensive study to date on ageing and the brain’s connections. They analysed brain scans from more than 3,500 people in middle and older age.

The brain connections that showed the poorest health with advancing age were those linked to complex thinking skills.

Conversely, those supporting functions like movement and hearing were relatively preserved.

This is one of the first results to be reported from the UK Biobank’s database of brain images.


Health inequalities

A small part of the association between health and socio-economic status might be due to shared genetic influences, a new CCACE paper finds.

Using data from the UK Biobank, we found that 21% of the variation in an area-based deprivation measure and 11% of the variation in household income could be accounted for by common genetic variants. We also found that these measures had many genetic correlations with physical and mental health, and with cognitive functions.

David Hill said, “As expected, the large majority of people’s differences in area-based deprivation and income appeared to be environmental in origin. There were small genetic contributions to both, which might arise owing to shared genetic influences with factors such as ill health, cognitive ability, and personality. The individual genetic influences on socio-economic status appeared to be miniscule.”

David and the team emphasise CCACE’s mission to understand and address inequalities in health, and they also understand that finding any, even a small, genetic contribution to these social factors is surprising. Therefore, a briefing document and FAQ are available on the CCACE website.


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And when it comes to the Lothian Birth Cohorts, the members address Ian like a close friend! No-where was this more evident than at the 2017 reunion – held 70 years to the day since the 1936 cohort sat their childhood intelligence test (see image on the right).

The key role of the differential group in CCACE is to describe and explain why some people’s thinking skills and brains age better than others. Many of their results have been described in Age UK’s new online resource, ‘Staying Sharp’ (www.ageuk.org.uk/stayingsharp).

The team also have a wider remit, to consider individual differences in intelligence and personality traits. “This year, we realised an aim I’d had for the whole of CCACE’s duration” says Professor Deary “linking almost all ‘Scottish Mental Survey 1947′s’ childhood intelligence data to death records in older age”.

Scotland now has the only whole-population description of which causes of death are associated with intelligence scores at age 11. “It’s that rara avis, a definitive, whole-population study” And the answer? Almost all causes of death, except non-smoking related cancers.

The team are now delving into the functional importance of these genes.

Just like their research, the success of the group is largely due to individuals and their talents. “I enjoy seeing junior staff develop impressively,” says Professor Deary. “Sometimes we collaborate with experts to do new things, and sometimes we learn to do those things ourselves. CCACE provides a great environment for the broadening of skills”.

From individual differences to the ‘power of many’, it is collaboration and hard work that has been the key to the success of this group.

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From the large cohorts of volunteers, to the cohesive ‘individual differences’ team, it is clear that CCACE has offered a platform for each individual to play their part.

The best thing about CCACE is the staff. Having core staff permits us flexibility, and the gang of talented researchers work closely together to address problems says Professor Ian Deary

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From individual differences to the ‘power of many’, it is collaboration and hard work that has been the key to the success of this group.
Since its inception in 2008, CCACE has become a global leader in the field of intelligence genomics. The output of over 100 papers in just 10 years speaks volumes for the collective productivity of a small, closely knit team says Professor David Porteous.

Exploding out the starting blocks
In the first 5 years (phase 1), the teams 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. “These unique features have made the LBC data the ‘go to’ place for several international consortia” (ENIGMA, CHARGE, SSGAC etc).

In phase 2 of CCACE, the group recognised the need for ever larger studies, so committed their support to several international consortia and to Generation Scotland (GS). GS has the benefit of scale; 24,000 participants in 7,000 family groups, all with a detailed history. Research outputs from this data have included a 2011 paper (Davis et al’) which linked 40-50% of the variation in human intelligence to common genetic variants, each of small effect.

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 health to other mental or physical health conditions (Hagenaars et al 2016). One of our most significant papers demonstrated that the same genes, which had previously been linked to educational attainment, could predict longevity (Marioni et al 2016). “This UK Biobank exercise is being repeated as we speak, following the full data release [500,000 members] this summer.”

Achieving results
Over the last 10 years, some of our results have been provocative, such as the evidence supporting a correlation between height and intelligence. Others results have significantly moved the field forward, e.g. our study on the genetic overlap between cognitive traits and cardiometabolic traits [risk of cardiovascular disorders and diabetes]. “We have also seen diverse spin offs, such as the genetics of male pattern baldness”.

Although the primary remit of CCACE is cognition, significant contributions towards a genetic understanding of major depressive disorder, neuroticism, stroke and dementia have been made along the way.

Future challenges
With the help of projects such STRADL (Stratifying Resilience and Depression Longitudinally), CCACE is starting to broaden its focus to include more psychiatric aspects.

“The challenge for the future is to join up all the dots; to reveal the hidden biological mechanisms, and to translate this for individual and societal benefit.”

Davis et al, 2011
This study alone has been cited over 300 times in last 6 years.

The mosaic of life

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

The Cognitive Epidemiology group research the causes (aetiology) of chronic diseases in later life. “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, 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 risk1. This particular set of findings received wide coverage in the media and has been cited in a WHO report1. It is our hope that it will go on to help inform public health policies in the future.

We also found that a diagnosis of mental disorder in early adulthood puts people at an increased risk of developing heart disease3. This indicates that 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 lower mortality rates4. This is something we are continuing to investigate.

Many of these investigations are possible, thanks to the multi-disciplinary character of CCACE. “Owing to the composition of staff and its members, a multitude of scientific disciplines are represented by the Centre” says Professor Batty.

“This gives us the data and expertise that we need to investigate the wide range of factors that could be influencing health in later life”.


Stress: A tale of two enzymes

Over the last 10 years, 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 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 also 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.

Animal studies offer important opportunities for CCACE to test specific hypotheses about the biological basis of ageing. They are an important step in the road towards clinical interventions.

“The best thing about CCACE is the cross college community, discussing science from many different viewpoints.” Says Professor Holmes.

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; for example the finding that lower IQ in youth, leads to an increased number of WMHs in later life.1

The group also discovered a general factor of ‘white matter integrity’2. 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”.3

Recently the team has begun to use novel image analyses techniques to study the connections between all cortical regions (known as connectome) and to look at shape deformations in structures like the hippocampus. “These new techniques open new avenues for us to understand how the brain changes with age”.

From neo-natal imaging to multiple sclerosis, the imaging group are involved in a diverse range of studies. With methodologies that take account of genetics associations, health, lifestyle etc, theirs is a truly multi-disciplinary approach.

We have worked extensively on the development of image analysis techniques for the study of these features says Professor Wardlaw

Without our collaborations with other CACCE members, these studies and discoveries would not have been possible.

1 Maria del C. Valdés Hernández a, c, Tom Booth et al (2013) Brain white matter damage in aging and cognitive ability in youth and older age. Neurobiology of Aging. Volume 34, Issue 12, Pages 2740-2747


IQ at 11 accounts for more than 2/3rds of the association between IQ and cortical thickness in older age, in many of the brain regions associated with intelligence differences.
From research to clinic

Patients in the early stage of AD have problems dealing with multiple sources of information, for example, tracking who said what in a conversation. This form of memory is called temporary binding. “We discovered that temporary binding is greatly affected by Alzheimer’s disease, but is not affected by healthy ageing, chronic depression or by other types of dementia,” says Professor Sergio Della Sala.

Temporary binding is an important part of our ‘working memory’ system, which holds information for a few seconds, before updating it. This helps us reason, think, solve problems, navigate, hold conversations and generally interact with the world from moment to moment. “A breakdown in this ability can undermine independent living” says Professor Robert Logie.

In the laboratory, volunteers had to keep track of both colour and shape, and say whether the next image matched the previous one or not (see figure 1). This is a simple test that could be performed in a GP surgery. Importantly, the test was also able to identify carriers of an early onset Alzheimer’s gene (E280A), 10 years or more before the onset of symptoms. Such an early diagnostic test could give people more time to understand their condition, have access to drugs and to plan their future. It could also prove invaluable for future research efforts and recruitment to clinical trials.

Misinformation lingers in memory

A CCACE study compared three commonly used pro-vaccination strategies, all of which backfired!

1. Attempting to correct vaccine myths with facts “Countering false information in ways that repeat it appears to amplify and spread the misconception, making it familiar and therefore more acceptable”, say researchers.

2. Comparing potential complications of diseases with side effects of vaccines “this resulted in less damage but did not bring any effective result”.

3. Showing images of unvaccinated children suffering from the disease “This inspired the strongest belief that vaccines had harmful side effects”.

“These findings offer a useful example of how factual information is misremembered. Even after a short delay, facts fade from the memory, leaving behind the popular misconceptions” says Professor Della Sala.

Figure 1. Test for temporary memory of two shapes, of two colours, or of two-coloured shapes. From: Logie et al 2015"
Developing a simple test for delirium and making it widely available to clinicians has been a major focus for Professor Alasdair MacLullich and his team.

Delirium is a syndrome of acute deterioration in mental functioning that affects one in eight hospitalised patients. It is a common complication of dementia and independently predicts negative outcomes such as the need for a care home, permanent decrements in cognitive functioning and even mortality.

A simple paper based test

Prof MacLullich and his team developed a simple bedside test for the diagnosis of delirium, which takes less than 2 minutes and does not require any special training. It consists of 4 ‘A’s: alertness, Abbreviated Mental Test 4 (age, date of birth, current location and year), attention (months of year backwards) and acute change (changes to mental state over last 24 hours).

“This test is now used internationally as a standard instrument for delirium detection in clinical care (estimated millions of uses per year) and is included in many international guidelines and policy documents.”

Delbox ‘computerised’ Test

The Delbox is a simple visual test. It has two buttons which flash on and off. Patients are asked to either count how many light flashes the device produces over a short period of time or to press a button each time they see one of the buttons light up. The Delbox has a simple and objective scoring system and provides a more precise measure of inattention in delirium than conventional tests of attention.

Crucially, Delbox has been designed to differentiate between delirium and dementia. Patients with dementia are able to focus their attention for longer periods, and score better than patients with delirium on this test.

Recently the Delbox has been shown to be effective at both detecting delirium and monitoring its severity in critically ill patients within an intensive care unit.

Delapp – Smart phone App

The team at CCACE, including project lead psychologist Dr Zoë Tieges, is now taking this diagnostic test one step further by designing a smart phone app. Known as Delapp, the software incorporates a visual acuity test, a brief arousal assessment and a graded counting task to measure attention. The findings from this research will be released within the next few months.

“This will be an exciting time as it represents the culmination of many years of work” says Prof MacLullich.

As a medical doctor, CCACE has greatly facilitated ongoing interactions with colleagues active in psychology research.

LBC on BBC again!
The BBC 1 series ‘Holding Back The Years’ featured five much loved celebrities, attempting to get to the bottom of the key aging concerns that affect the public.

On Friday 31st March 2017, the programme featured Bill Turnbull and our very own Lothian Birth Cohort 1936.

Bill Turnbull, star of BBC’s Breakfast News, returned to his student days in Edinburgh, where he set out to expose some of the fake news we often hear about aging, and explore how it can be put in to practice.

In a unique experiment that dates back to the 1940s and found out ‘how the results it is producing today could help the scientific breakthroughs of tomorrow’.

(Quotes from BBC programme description. Available on iplayer for a limited time)

‘Genes and Brains’ at Ocean Terminal
As part of the MRC Festival of Medical Research, CCACE joined up with Leith Labs and The Living Memory Association to present talks and drop in activities on ‘How to stay sharp in older age’.

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

Staying Sharp summarises ground-breaking 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 Staying Sharp www.ageuk.org.uk/stayingsharp

Informing policy

It was Chaired by Sir Mark Walport, the Chief Scientific Advisor to HM Government. There were 11 invited scientists, two of them from Edinburgh’s CCACE: Ian Deary and Richard Morris.

The seminar was the start of a process to collect the best evidence about healthy cognitive ageing, and explore how it can be put in to practice.

On the fringes
The Cabinet of Dangerous Ideas is coordinated by the Beltane Public Engagement Network

Is monolingualism making us ill?
In his Fringe show, Thomas Bak proposed that there is nothing ‘natural’ about monolingualism: it is a “disease of the civilisation”, like obesity and diabetes. In health terms he compared it to a sedentary lifestyle; the results are accelerated cognitive ageing, earlier onset of dementia and a slower recovery from stroke.

But, we can always improve our mental agility by learning languages, and it is never too late to start! “We found measurable improvements on tests of attention after just one week of intensive language courses and this in participants up to 78-years old!”

What keeps you sharp?
In his show, Alan Gow asked his audiences to consider questions including “When do our thinking skills start to decline?” and “What keeps you sharp?” Each question led to discussion of the audience responses, how those matched the nationwide survey, and then back to the latest research findings, including many references to the LBC.

Awards
• Professor Joanna Wardlaw was honoured with the Presidential Award, at the European Stroke Conference in May 2017. This is fantastic international recognition of Joanna’s contribution to stroke research - congratulations!
• Professor Mead was awarded the 2016 William Farr Medal for her world leading work in exercise after stroke.
• Dr Mario Parra Rodriguez won runner up award in the category “Outstanding early career contribution to dementia research” from Alzheimer’s Society.

PhD submission
Saskia Hagenaaers submitted her PhD a remarkable 5.5 months early and with 5 publications in high impact journals. Her results provide further evidence for genetic links between cognitive ability and health, and between negative emotions and health.

In her time at CCACE, Saskia also won the Sir William Darling Memorial Prize (based on academic merit).

Saskia has now moved to London to undertake a 3-year post doctoral Fellowship at King’s College London.

Creative Engagement
From cakes to knitting, CCACE members got creative to raise money for Age UK.

It’s a sell out
Talks by Professor Ian Deary are always in high demand, and this year has been no exception. Highlights included a sell out talk to over 250 University of the Third Age (U3A) members at The Royal Society in London, and 2 shows in one day at the Edinburgh International Science Festival (EISF).

SAVE THE DATE
St Andrews Day Special Invited Seminar
28th November 2017
Professor Paul Matthews OBE Division of Brain Sciences, Imperial College London.

5.00pm, venue to be confirmed. This seminar is open to all. No booking required.
Bridging the gap

CCACE bridges the research gap between ‘healthy’ and ‘non-healthy’ cognitive ageing.

Most people do not get dementia, but they do experience the effects of cognitive ageing says Professor John Starr, Co-director CCACE

Over the last 10 years, CCACE has trained “a cohort of now internationally esteemed researchers”.

This training legacy began as a postgraduate certificate in research methods, and branched out into supporting clinical research fellows and PhD students.

The centre complements its research into ‘healthy cognitive ageing’ with that addressing ‘non-healthy’ states like dementia. This is evidenced by CCACE’s significant contribution to the Dementia Platform UK and its close involvement with the Alzheimer Scotland Dementia Research Centre.

“Sometimes I think of CCACE like a football team. Players come and go, but the management structure has remained remarkably stable. I’m not sure if Ian would prefer to be likened to Alex Ferguson or Arsene Wenger, but he has certainly led a successful team over an extended period!”

1 Cognitive Ageing Research Methods for Medical Scientists (CARMMS), Postgraduate Certificate by Distance Learning, University of Edinburgh
2 www.dementiasplatform.uk
3 www.alzscotdrc.ed.ac.uk

1 in 6 people over the age of 80 have dementia, which means 5 in 6 people do not.

(Figure from Alzheimer’s society, 2017)
A lasting legacy

From a team of just 4 people who were interviewed by the research councils, CCACE has grown into a large interdisciplinary centre, with a wide reaching impact on society.

CCACE is at the forefront of the emerging cognitive epidemiology field, and has been very successful in creating new knowledge. “If one has to pick out highlights, then clearly the Lothian birth cohort has been world leading in its ability to encourage us to understand the life-course approach to ageing,” says Professor Jonathan Seckl, Co-director CCACE and Vice Principal, University of Edinburgh.

CCACE was careful to make sure that the public were deeply engaged throughout. “This has been one of the genius moves that Ian led us through”.

CCACE has also encouraged politicians and funders to realise that cognitive ageing is an important issue that needs to be addressed. Indeed, normal human ageing is now included as a proposed target for the UK Government’s ‘Industry Strategy Challenge Fund’.

I believe CCACE will have a lasting legacy for decades to come, as we deal with the demographic challenges of an ageing population.

Professor Jonathan Seckl, Co-director CCACE and Vice Principal University of Edinburgh