GCPH Seminar Series 10
Seminar 3
14 January 2014
Summary Paper

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Healthy Cognitive Ageing

Overview

Prof Ian Deary is Director of The Centre for Cognitive Ageing and Cognitive Epidemiology at the University of Edinburgh. In this seminar he talks about healthy cognitive ageing and principally about the work done by his team with the Lothian Birth Cohorts of 1921 and 1936.

The seminar covers

1. The Scottish Mental Surveys of 1932 and 1947
2. The Lothian Birth Cohort recruited from these surveys
3. Four different areas that might be helpful in learning about healthy cognitive ageing: lifestyle factors, biomedical factors, brain imaging and genetics.

The Scottish Mental Surveys

Scotland is unique in having twice measured the IQ of the entire population at age 11. On Monday, June 1st 1932 almost every child born in 1921, and attending school, took the same mental ability test, using the same instruction, at the same time. A total of 87,498 children were tested using the 'Moray House Test No.12'. This was part of an international project exploring different ways of testing children. No country had done this before. Ninety-five per cent of the population was tested and the results published in a book 'The Intelligence of Scottish Children'. The test was repeated in 1947 with children born in 1936.

It is clear that the world is experiencing demographic changes and that people are living longer. Age is a risk factor for dementia. However, when thinking about dementia, it is also useful to study normal, healthy cognitive ageing. Prof Deary heard about the Scottish Mental Surveys in the 1990s and discovered that all the data had been retained. He and colleagues realised that the surveys had the potential to provide information that is often missing from cognitive ageing studies; people's 'original' or childhood cognitive ability. Scotland is the only country in the world where we have this information for the whole population of people of the same age. It was agreed that it would be worthwhile to try and identify and revisit the people who took part in the survey when they were 11 years old. Work was done in Aberdeen and Edinburgh but this seminar focuses on the data and findings of Lothian Birth Cohorts of 1921 and 1936.

The Lothian Birth Cohorts of 1921 and 1936

In 1999/2000 Prof Deary and his team recruited 550 people born in 1921, who had taken the test in the Lothian area in 1932, to take part in the study. This group is known as the Lothian Birth Cohort of 1921. The team has followed these people ever since the year 2000 recalling them at ages 83, 87, 90, and 92. They are still in

touch with 100 members of the cohort, now aged 92, and have just completed brain scans on 52 of these participants.

In 2006 the team recruited a further 1,091 people who were born in 1936 and took the test in 1947, again in the Lothian area. This is the Lothian Birth Cohort of 1936. This group of people have been followed since the age of 70 to the present day.

Both cohorts were studied in a range of ways including 16 cognitive tests, brain scans looking at white and grey matter, genetic testing and a questionnaire looking at a range of factors including social background, personality, home area and lifestyle factors including diet and alcohol consumption. The tests are carried out at the Clinical Research Centre in Edinburgh.

The research is undertaken by a multidisciplinary team which is augmented with expertise from interested individuals from the wider University of Edinburgh with further expertise drawn from across the world. Over the past ten years, more than 100 scientific articles based on the team's investigations of the Lothian Cohort data have been published.

Finding factors that influence cognitive ageing

So what is the secret to having good cognition in older age? The first finding was fairly predictable. There is a tendency for people who have scored well at age 11 to score well at age 79. The percentage of differences in people's cognitive ability that is stable from childhood to old age has been determined to be about 50%. This is an interesting finding but what is even more interesting is that the other 50% of differences in cognitive ability are therefore unstable, and that there must be factors that influence this. The team is trying to identify what these factors are. They have looked at a number of factors in each of four main areas: social and lifestyle; biomedical; brain imaging; and genetics. This seminar dips briefly in to a few of these factors to give a flavour of the research in each area.

Social and lifestyle factors

A whole range of things have been suggested that appear to boost or buffer healthy cognitive ageing including: alcohol; caffeine; other dietary intakes; body mass index (BMI); smoking; cholesterol; activities/engagement; occupation; education; and bilingualism.

The team have found that one of the biggest contributors to healthy cognitive ageing is physical fitness. Being physically fit on its own makes a significant contribution, even when you take in to account cognitive ability at age 11, sex, social class and genetic status.

The team has also explored the impact of alcohol. At a first look, alcohol (particularly red wine) appears to have a small but significant positive effect on healthy cognitive ageing. People who consume more alcohol seem to have better general thinking, faster processing and a better memory. Previously this finding might have been published at this stage. But with the benefit of the Scottish Mental Survey, to further explore this association, the team undertook a further analytical step and adjusted for cognitive ability at age 11. They found that the effect disappears. So rather than

alcohol having a casual effect on healthy cognitive ageing, it appears that children with better cognitive function scores at age 11 drink more when they are older.

Recently some work has been undertaken looking at the effect of bilingualism on healthy cognitive aging, building on work that was previously done in India which suggests that bilingualism is protective against dementia. In the Lothian Birth Cohort and controlling for original cognitive ability, bilingualism appears to be protective for healthy cognitive ageing.

In summary the team have tested a number of social and lifestyle factors which appear to contribute to boosting healthy ageing in small ways. However, they have also found that other factors, that were thought to be protective (including caffeine, alcohol, BMI and activities/engagement), turn out not to be protective when original cognitive ability is accounted for.

Biomedical factors

A large number of biomedical factors have also been examined by the study team. One of these was Cytomegalovirus (CMV) infection. Two thirds of the 1936 cohort had this infection which was probably picked up in childhood. Previous studies have suggested that being infected with CMV is a risk factor for poor cognitive ageing so this infection was tested for within the Cohort. In Lothian they found that people with the CMV infection have a poorer memory and thinking skills compared to those who were infection free. However, on adjusting for childhood overcrowding (a marker of social background) then the effect of CMV almost disappears. In addition, if you adjust for childhood IQ, the effect disappears completely.

Another factor which the team looked at was 'allostatic load' or, in lay terms, the 'wear and tear' on the body[1]. This builds on work done by Prof Bruce McEwen who was a speaker in Seminar Series 3. Inflammation, metabolic syndrome and high blood pressure are all signs of a body with a high allostatic load. The Edinburgh team have found that people who have one of these symptoms tend to have all three. As predicted by Prof McEwen, the team found that a high allostatic load is associated with a decrease in total brain volume and a reduction in general cognitive function.

Brain imaging

As part of this study the team have undertaken *multi-model structural imaging* of the brain. They are testing the brain in as many different ways as possible.

For example, a new way of showing iron deposits in the brain has been developed by a member of the team. Iron deposits are thought to be partly due to very small bleeds that otherwise have not been detected. They found that people with more iron deposits have slightly impaired cognitive function than you would expect from their childhood ability. But also, interestingly, they found a second effect; the children who scored better at age 11 had less iron in their brain at age 73.

[1] Allostatic load is "the wear and tear on the body" which grows over time when the individual is exposed to repeated or chronic stress.

The brain is made up of two components known as grey and white matter. White matter contains the hundred of billions of connections in the brain. It is possible to measure the integrity and connectivity of white matter areas in the brain. That is, the number of blockages or damage to the nerve cells in a person's white matter and their connections can be measured. The Lothian Birth Cohort is one of the largest samples that has been tested using this method. The people who had better connections had better thinking skills in older age above what would be expected from their cognitive function in childhood. Therefore key to healthy cognitive ageing is keeping good white matter connections so that the 'wiring' is still intact and still able to pass messages quickly and accurately from one area of the brain to the other.

So how can this connectivity be maintained? As part of the study, intellectual, social and physical engagement have been examined. Only engagement in physical activity was associated with better cognitive ageing. People with good cognitive function did tend to be more intellectually engaged but it was all explained by their childhood IQ. Children who scored well at age 11 tend to be more intellectually engaged in old age, but this factor is not enhancing their cognitive ability in older age. People who reported taking more physical exercise did better in assessments of cognitive function but were also noted to have better white matter integrity and less atrophy or shrinkage of the grey matter. Adjusting for IQ at age 11 does not remove this effect even when social class and disease are taken in to account.

In Montreal, Canada a special technique has been developed for measuring the thickness of grey matter. It has subsequently been reported that in certain areas of the brain if the cortex (grey matter) is thicker, then people have reportedly better thinking skills. So it would appear that for healthy cognitive ageing thicker brain cortex would be beneficial. However, if you adjust for childhood IQ, the effect disappears.

A final example of the findings from the brain imaging tests concerns smoking. The team have found that people who smoke or used to smoke have thinner grey matter. Even 20 years after giving up smoking the recovery is not complete (unlike cardiovascular effects). This is a striking new finding.

Genetics

A final area the team has investigated is the impact of an individual's genetic make-up on their cognitive function. They have looked at things that were already thought to be interesting and also have done a battery of tests to see if anything new is thrown up.

For example, a key finding concerns the gene Apolipoprotien E (*APOE*). This gene appears to have a role in cholesterol transport and repair of nerve cells. A variant of this gene, *APOE* e4, is present in 25% of people in the general population. Previous research has shown that people with this version of the gene have a small increased risk of developing dementia and specifically Alzheimer's disease. The team in Edinburgh found that, at age 11, there was no difference in cognitive function between people with or without the e4 variety of the *APOE* gene. However, at age 80 there was a significant difference with people with *APOE e4* showing a decline in

cognitive function while those without remained at the same level of cognitive functioning as at age 11. In addition in the ninth decade of life people with the e4 gene displayed a significant decline in memory (excluding everyone with dementia) compared to those without the e4 variety.

Finally, a battery of 620,000 genetic tests has been done for each Lothian Birth Cohort participant. This testing for thousands of genetic markers has allowed an estimate to be made of the genetic contribution to people's differences in cognition. This is the first study in the world to report an estimated inheritability of cognition in older age based on DNA testing. It is estimated that 40-51% of people's differences in cognition seem to be down to genetic influences.

Prof Deary highlighted that he is particularly interested in how much cognition changes from childhood to old age. The genetic tests have allowed the team to make the broad estimates that 75% of changes in cognition between childhood and adulthood are as a result of the environment and 25% of these changes are the related to genetics.

The team are now testing for epigenetic[2] changes. A key epigenetic marker is the number of methyl groups associated with a gene. The older we get the more methyl groups there are, so much so that we have a chronological age and also a DNA methylation age (or biological age). Our DNA might be older or younger than our birth age. The Lothian Birth Cohorts have been studied to see whether the difference between participants chronological and the methylation age affects how long people live. The prediction was that people with an older methylation age would die sooner, and this assumption is being observed in practice. The study has identified a new indicator of human mortality based on epigenetics.

Prof Deary concluded by pointing out that cognition is not everything. As we get older we also want to be healthy and have a good quality of life. The study team asked their Birth Cohort participants about these issues as well. The final slide of the seminar demonstrated that at age 90 the majority of the participants responded that they are 'satisfied 'or 'very satisfied' with their lives.

[2] Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence