Issue eight
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Alzheimer's Society
Leading the fight against dementia

Careandcure

The Alzheimer's Society research magazine

Hunting for genes

A source of new insights into dementia

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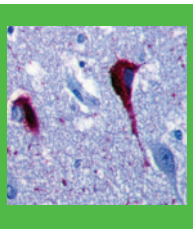

Targeting tau tangles
Positive results despite clinical trial failure.

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APOE4 gene may affect brain development.

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What's in this issue of Careandcure

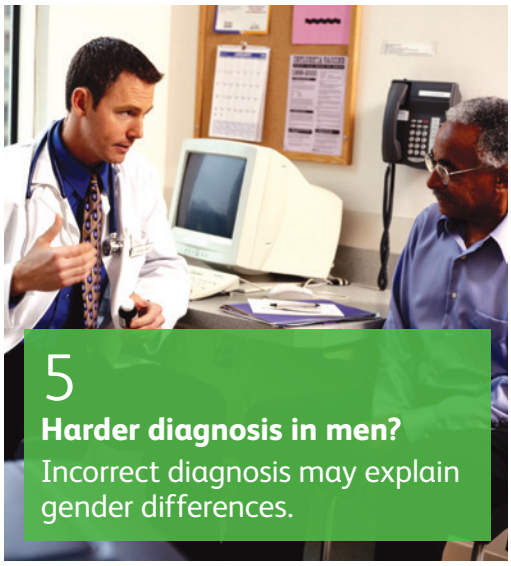
After nearly two years as editor of Care and cure, I am sad to say that this will be my last issue. The aim of this magazine is to make news and information about dementia research more accessible to a wider audience, and I hope we have done this. I am very proud of the response we have had from you, our readers, with over 2,000 Friends of Research signed up to receive the magazine by email.

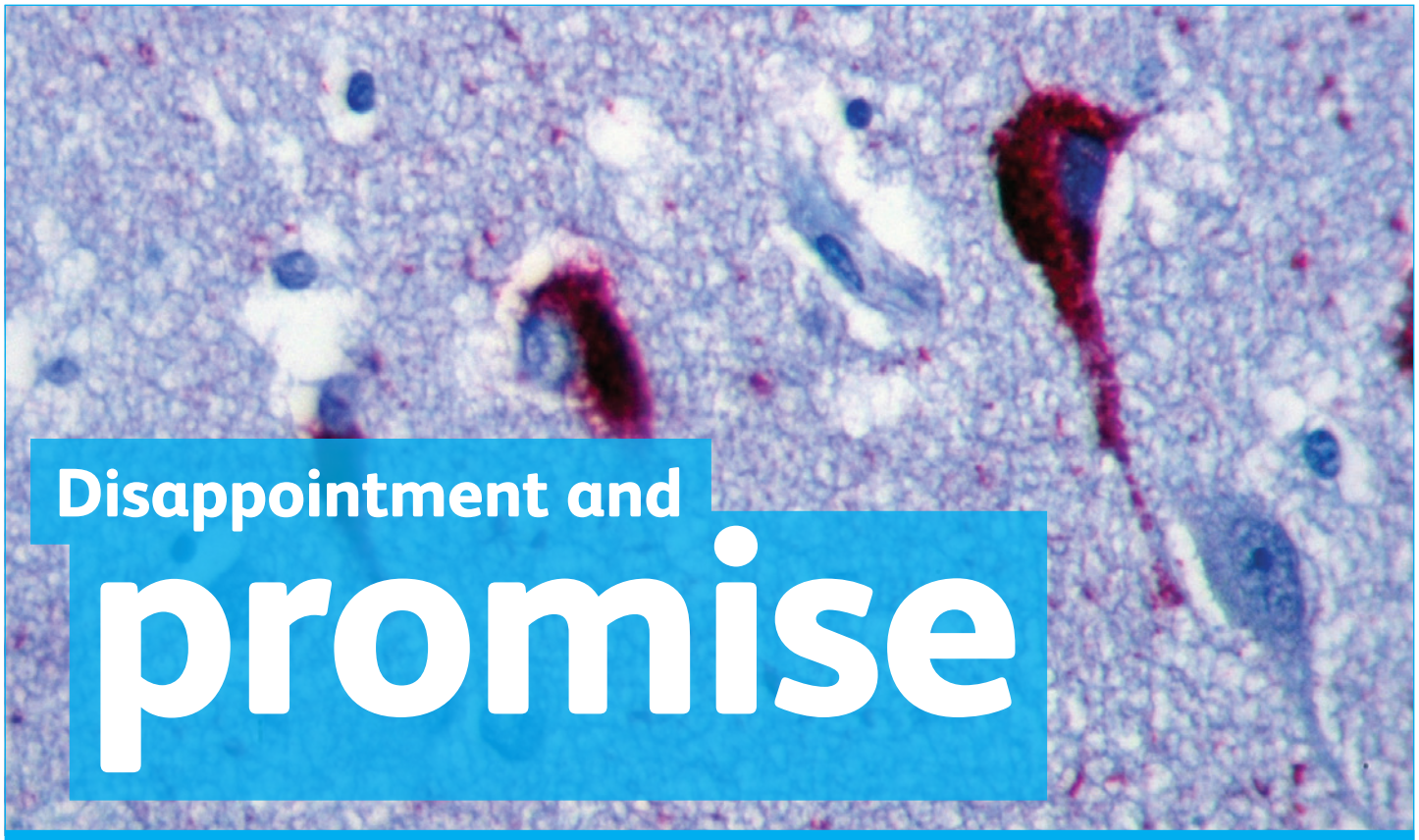
As dementia research gains a higher profile, the demand for more information grows. We now provide our expert opinion in the media on a daily basis, reach out through more public events and recruit more people to take part in research. For too long, dementia research has been underfunded relative to the condition's cost to society and increased attention provides hope that this will change.

However where there's hope, hype can quickly follow. Each week, headlines in newspapers proclaim new cures or sure-fire ways to prevent dementia and these can do more harm than good. We will always try to explain the limitations of new research, put it in context and say what it might mean for the future. Giving hope, without the hype.

Thank you for reading.

Ian Le Guillou
Editor
Careandcure





Disappointment and promise

First drug to target tau tangles fails in clinical trial but produces intriguing results.

Several neurodegenerative diseases involve the production of toxic clumps of proteins that cause damage to nerves. In Alzheimer's disease, the protein culprits are amyloid, which forms large build-ups called plaques, and tau, which forms harmful tangles inside brain cells.

For a long time, amyloid has been the main target of drugs designed to treat Alzheimer's disease. However, several of these drugs have failed once they are tested in clinical trials. Focus has shifted onto targeting tau in the hope that this will be more successful. This summer, the results of the first clinical trial to target tau were announced.

The trial was for a drug called LMTX and involved almost 900 people with mild to moderate Alzheimer's. The participants took either LMTX or a placebo pill twice daily for 15 months. Disappointingly, the overall results were negative – the drug failed to improve memory and thinking performance or to affect brain shrinkage compared to the placebo over the course of the trial.

'There are still lots of questions to answer before we know how promising this new treatment could be.'
Dr Brown

However, when the researchers examined the findings in more detail, there was a silver lining. A small subset of people on the trial – those who were not taking any other Alzheimer's medications – did show positive results.

'While it's disappointing to see another large clinical trial for Alzheimer's disease fail to meet its goal, there appears to have been some striking improvements for the subset of people who took the drug on its own,' said Dr Doug Brown, Director of Research and Development at Alzheimer's Society.

For the people who took LMTX alone, there was a reduction in brain shrinkage by 30–40 per cent. This group also saw significant improvements in memory and thinking tests, and in their ability to get on with day-to-day tasks such as dressing, cooking and using public transport.

'There are still lots of questions to answer before we know how promising this new treatment could be, such as why it doesn't appear to work in those who are already taking other medications for Alzheimer's disease,' said Dr Brown.

The number of people who took the drug on its own was small – only 82 people – and so these results will need to be verified in a larger study before it could even be considered for approval as a new treatment. A second study of LMTX in people with mild Alzheimer's disease is due to report its results in December and we will keep you updated with any news.

Complex jobs and resilience

Working with people may help to increase the brain's resilience.

The Alzheimer's Association International Conference is one of the main events in the dementia research calendar, where experts from around the world gather to discuss the latest news, progress and insights.

Several sessions at the 2016 conference focused on how the way we live our lives can influence our risk of dementia. Of particular interest was a concept called 'cognitive reserve'. This is a theory that if you do things throughout your life that challenge certain parts of the brain, it may help your brain cells to be resistant to damage caused by dementia. This is supported by the fact that if you have a high level of education, it appears to have a protective effect.

A particularly interesting conference presentation looked at whether having a complex job could also help your brain to be more resilient

to dementia. Researchers from Wisconsin in the US scanned the brains of 284 people at a high risk of dementia to look for signs of 'white matter hyperintensities', which may indicate damage to the brain due to dementia. They also asked participants about their jobs and put this information into three categories – working with people, data or things.

The researchers found that people who had complex jobs that involved working with people had more white matter hyperintensities, but performed as well as their peers on tests of memory and thinking. This indicates that their brains are more able to sustain the damage caused by dementia. It adds weight to the idea that keeping the brain active and challenged may help to protect against dementia.

Dr Doug Brown, Alzheimer's Society's Director of Research and Development, said, 'It's incredibly positive to see that there are things we can do in life that could help our brains as they age. For many of us, the complexity of our job is not something we can easily change, so we need to see more research into other ways for people to build up their resilience to dementia.'

Risk gene at work in childhood

The APOE4 gene may have effects on the brain even in early age.

The gene APOE comes in three versions and each one has a different effect on your risk of developing Alzheimer's disease. Whereas having APOE2 is slightly protective, having the APOE4 version can increase your risk by up to 10 times.

How this gene works to influence the risk of dementia is still not understood, but it is a hot topic of research across the world. A new study, published in an American Academy of Neurology journal, looked at the gene's influence on the brain in childhood.

Children aged between three and 20 years took part in the study, which identified which version of APOE they had, tested their memory and thinking skills, and gave them brain scans.

The study found differences in brain development among children with the higher-risk APOE4 gene when compared to those with other versions of the gene. These changes were seen in areas of the brain that are often affected by Alzheimer's disease.

While this research is very interesting, it is worth noting that less than 30 of the 1,187 children involved in the study had the APOE4 gene, meaning that these results are from a small group of people and so need to be interpreted with caution.

The APOE4 gene is known to increase risk of Alzheimer's disease, but people with the gene will not necessarily develop the condition. Further research will hopefully uncover more details about the long-term effects of this gene on the brain.

Harder diagnosis in men?

Research challenges the idea that dementia is more common in women.

Researchers from the Mayo Clinic in Florida presented data at the Alzheimer's Association International Conference showing that men with Alzheimer's may be more likely to be diagnosed incorrectly with something else than women. This might explain why the disease has appeared to be more common in women.

The researchers looked at brain tissue stored in the Florida brain bank to find people who had died with Alzheimer's disease. By looking at clinical records as well, the researchers could see what symptoms the people had experienced when they were alive. Men were found to experience more unusual symptoms of Alzheimer's, such as problems with speech or movement. In contrast, women were more likely to experience problems with their memory.

One of the first areas of the brain to be damaged in Alzheimer's disease is the hippocampus, the brain's memory centre. In this study, the hippocampus was more often spared from damage in the brains of men, potentially explaining the differences in the symptoms they experience.

Differences in the age of onset of Alzheimer's were also observed. Where the disease had previously been diagnosed correctly, men were more likely to be diagnosed in their 60s, whereas women were diagnosed more often in their 70s and later.

Dr Clare Walton, Research Manager at Alzheimer's Society, said, 'Alzheimer's was first identified in a woman in the early 1900s but these results suggest there are important differences in how the disease affects men and women. More research is needed to understand how much misdiagnosis in men contributes to the observation that nearly two-thirds of people living with dementia in the UK are women.'

News in brief

Researchers have used computer models to identify a key step in the formation of the toxic amyloid clumps that are associated with the development of Alzheimer's disease. This provides important information about how we might prevent these clumps from forming in the future.

A 'risk score' based on whether someone has particular genes could help to identify people who are more likely to develop Alzheimer's. There are several genes that are known to contribute slightly towards developing the disease – understanding the combined effect of these genes could help to determine who is most at risk.

Research presented at the Alzheimer's Association International Conference found that people with good vision but a thinner nerve fibre layer at the back of their eyes were more likely to experience memory and thinking problems. Further research is needed but this could be a useful diagnostic tool in the future.

Hunting for genes

Our risk of developing dementia is a complex interaction between lifestyle and genetics. While we cannot do anything about our genes, knowing more about them can help researchers to better understand dementia and find new treatments.

The genetics of dementia is highly complicated, with dozens of genes linked to different types of the condition. Some rare genetic mutations directly cause dementia, while others might raise the risk of developing it over your lifetime.

It can be difficult to get to grips with if you are not an expert, but if you are then it is a great way to understand dementia.

'Genetics is fairly straightforward when you compare it to other fields,' says Dr Jose Bras, an Alzheimer's Society fellow at University College London. 'DNA is DNA – there aren't many things that can affect your results.'

Jose is studying the genetics of dementia with Lewy bodies (DLB), a form of dementia that has similarities with both Alzheimer's and Parkinson's disease.

'We haven't done as much research into DLB as we have into Parkinson's or Alzheimer's. When I started we didn't know much about the genetics of DLB. In the past four years, we have found four or five genes that increase a person's risk of developing DLB by a small amount. It doesn't mean that a person will develop DLB, but it raises their lifetime risk.'

Some of these genes can only increase the risk of DLB by 0.5 per cent, so it is very difficult to detect them. One of the main ways to do this is to compare large numbers of people with the disease and people without. Finding a gene that is more common in people with the disease suggests that it could be a contributing factor.

To find genes that have such a small effect, researchers need a large number of DNA samples.

'When you look at work on Parkinson's, it's about 100,000 people that are included in these studies. We currently have about 1,400 for DLB and when I started it was only 50,' says Dr Bras.

New insights

Finding these genes can reveal new insights into the disease.

'These genes for DLB are involved in Parkinson's and Alzheimer's disease, so that means they are linked not just in how they present clinically but also in their biology.

'If you can understand genetics, it opens new doors for treating the disease.'

Dr Rita Guerreiro, Jose's colleague and wife, understands this well. She previously discovered that mutations in the immune system gene TREM2

could increase the risk of developing Alzheimer's disease. Although these mutations are quite rare, only found in 2 per cent of people with Alzheimer's, the identification of TREM2 emphasised the importance of the immune system in the development of the condition.

'There are now drugs that are being tested to target the immune system to treat Alzheimer's disease,' she says.

Rather than searching through DNA samples from thousands of people, Dr Guerreiro discovered this aspect of TREM2 through a rare form of dementia found in three Turkish families where people inherited two mutated copies of this gene– one from each parent.

'They had a dementia that was similar to frontotemporal dementia, which was due to mutations in both copies of TREM2. So we searched for these same mutations in larger groups and found that having only one copy of the gene raised the risk of developing Alzheimer's disease.'

Although this TREM2 mutation triples the risk of Alzheimer's, it is too rare to have been detected by earlier attempts to screen large numbers of people. To have such a strong effect on the risk of dementia indicates that it could be an important avenue of research.

Since the discovery, Rita has been given several awards for her work, including an Alzheimer's Society Dementia Research Leader award in 2015, which Jose also won this summer (see page 11).

'I am now trying to do the same with other rare forms of dementia and we have already found two other interesting genes,' says Rita, now an Alzheimer's Society Senior Fellow.

'Finding these genes is important for the families too, so they can get a diagnosis. We work closely with clinicians in Portugal and Turkey, where the families can be underserved for genetic testing.'

Changing pace

In genetics, the pace of change in technology has been dramatic over the past few years.

'Each one of us has 20,000 genes and when we started in genetics we could only look at one gene at a time,' says Jose.

'Now we are looking at the whole genetic makeup of a person and that's quite amazing,' says Rita. 'We can now start to look at thousands of patients with this scale.'

Genomics England is aiming to do this through the 100,000 Genomes project, to understand more about the genetic causes of cancer and various rare conditions. As part of this, they plan to analyse every gene in hundreds of people with rarer forms of dementia.

This will include people who have inherited forms of Alzheimer's disease, which are very rare and account for only one in 1,000 people with dementia. This is due to a small number of mutations that directly cause Alzheimer's, often by the age of 50. The effect of these mutations is so strong that you only need to inherit one damaged copy of the gene from one parent for it to trigger Alzheimer's.

Previous studies of families where these mutations had passed down through generations have revealed a lot about how the disease develops. The first of these mutations, discovered in 1991, showed the importance of the build-up of amyloid protein – a crucial piece of evidence that focused drug development efforts to target amyloid.

This type of genetic defect was relatively straightforward to identify because of its profound impact and pattern of inheritance in a family. Today's searches are looking for much more subtle effects – it may be the total impact of dozens of genes that come together to give each person their overall risk. Advances in technology are helping us to see that bigger picture.

'It will get to a point where we each know all of our genetic makeup,' says Jose. 'But understanding it is a completely different matter.'

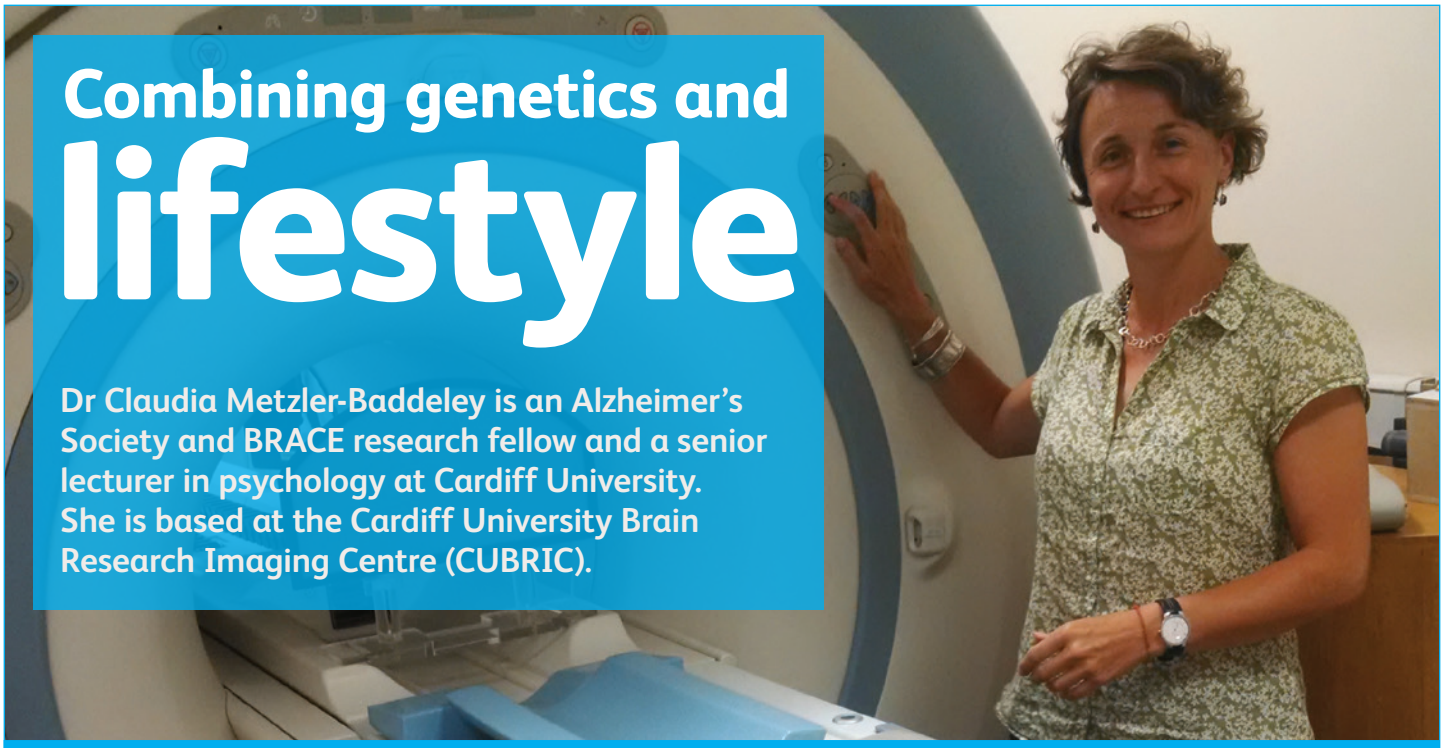
Dr Jose Bras

'Each one of us has 20,000 genes and when we started in genetics we could only look at one gene at a time.'

Dr Jose Bras

Dr Rita Guerreiro

Combining genetics and lifestyle



Dr Claudia Metzler-Baddeley is an Alzheimer's Society and BRACE research fellow and a senior lecturer in psychology at Cardiff University. She is based at the Cardiff University Brain Research Imaging Centre (CUBRIC).

I am a cognitive neuropsychologist with more than 10 years' experience of working with older adults with dementia, both in research and memory clinic settings. During this time, I have had the chance to meet many people with dementia and their relatives and carers, and to listen to their concerns and day-to-day challenges.

We are all living longer and any one of us, including our loved ones, may be affected by dementia at some point in our lives. My research into ageing and dementia is very much motivated by the need to identify risk early on and develop appropriate strategies to ensure the best quality of life for people with dementia and their families.

Since joining CUBRIC in 2009, I have been using magnetic resonance imaging (MRI) techniques to learn more about the impact of the disease on the brain. For example, my colleagues and I found that people with mild cognitive impairment – memory problems beyond normal ageing – develop specific disruptions in brain connections from the hippocampus, a region important for memory. This may help to identify the people with mild cognitive impairment who are at most risk of developing Alzheimer's.

> **'We are all living longer and any one of us, including our loved ones, may be affected by dementia at some point in our lives.'**
>
> Dr Metzler-Baddeley

However, we know that the changes leading to Alzheimer's disease develop gradually over many years. Ideally we would like to be able to see who is at risk in midlife and work out tailored interventions that may slow down or prevent the disease's development. With the support of Alzheimer's Society and BRACE, another charity, I am conducting research at CUBRIC into the impact of genetic and lifestyle risk factors of dementia in 180 healthy middle-aged adults. Both dementia and obesity are on the rise and many studies suggest they may be linked. People who are obese in midlife have a greater risk of developing dementia later on, but why this is the case remains unknown.

My research studies the impact of body fat and of the APOE4 gene – the best established genetic risk factor for Alzheimer's – on different properties of brain tissue. APOE codes for a protein that transports cholesterol through the brain. Cholesterol is needed for the repair of a fatty substance called myelin, which surrounds the brain's connections and allows different regions of the brain to communicate with each other efficiently. It has been suggested that the loss of myelin contributes to the development of Alzheimer's in an important way, and that both obesity and APOE4 may lead to damage of the brain's wiring. With MRI and blood analyses, I am studying whether myelin is reduced in obese people who carry the APOE4 gene and whether this is linked to any other changes.

I am also investigating whether changes in brain tissue may be related to mental functions such as response speed, attention and memory. The aim of my research is to identify early warning signs in midlife that may help us to reduce risk and develop ways to prevent dementia.

Feedback on research

Research studies often require a high level of commitment from participants and so it is crucial that we understand how people are willing to be involved. We hear how listening to participants led to a major grant that could help to improve the success of clinical trials in Alzheimer's disease.

One of the obstacles to finding ways to treat Alzheimer's disease is the difficulty in knowing how well a treatment is working during a clinical trial. To be able to do this, researchers want to measure some of the changes that Alzheimer's produces in the body and how these develop over time. These changes can be in the brain, blood or cerebrospinal fluid, which fills the spine and covers the brain. These are not easy to access or monitor regularly, making it harder to understand how the disease affects them.

Professor Simon Lovestone at the University of Oxford proposed a research project to test for biological changes regularly in people with preclinical Alzheimer's disease. These are people who are experiencing memory loss that wouldn't qualify as full dementia, but who do have early signs of damage in their brains. 'We needed to know whether people would be willing to take part in a study like this, requiring regular visits to the hospital for scans or lumbar punctures,' says Simon.

To show that this approach could work, he set up a test study in 2014 with 22 people who had dementia.

Matt Murray, Research Engagement Manager at Alzheimer's Society, led work to understand how acceptable these tests would be for participants.

He says, 'We recruited people with the early stages of Alzheimer's for the feasibility study, even though the full study was intended to be for people with preclinical dementia. For ethical reasons, we needed to show that someone with undiagnosed dementia would still be able to remain in the study.

'Feedback from participants encouraged the researchers to rethink aspects of the study, even the time of day for certain tests. For the electroencephalogram, or EEG, you have to wear a cap with electrodes attached. By doing the EEG later on in the day, participants didn't have to spend the day with messed-up hair.'

Although untidy hair may seem like a trivial concern, it is important to make the process as easy as possible to avoid participants dropping out of the study.

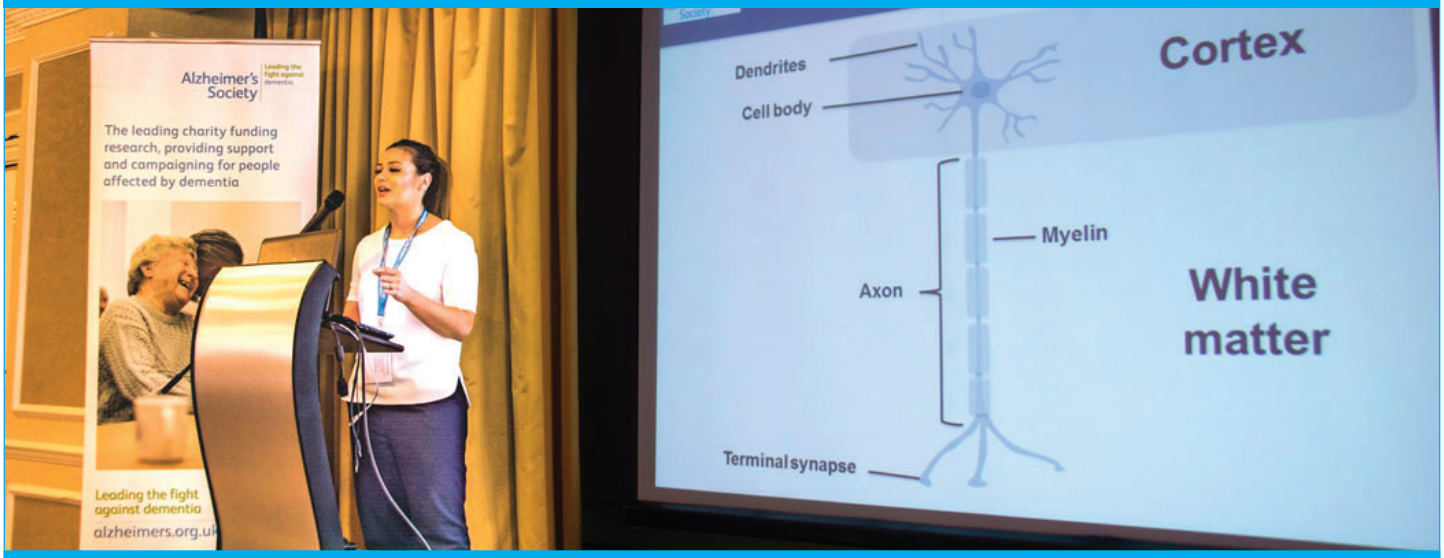
'People were mostly worried about the lumbar puncture to sample spinal fluid,' says Matt. 'So we checked people's expectations of procedures against their actual experiences. For the lumbar puncture, all but one had a better experience than they had expected. In the case where it wasn't better, this seemed to be because the person hadn't followed the doctor's instructions and was too active afterwards.'

By showing how to make the study acceptable to participants, this work has played a vital role in securing funding for the full Deep and Frequent Phenotyping study. Professor Lovestone has recently been awarded £6 million by the Medical Research Council and National Institute for Health Research to perform up to 50 tests each on 250 people in the preclinical stages of Alzheimer's disease.

'The feedback we received allowed us to improve the study and demonstrate that people are willing and able to help us to gain a unique insight into Alzheimer's disease,' says Simon.

Alzheimer's Society is supporting the new study by making videos of each procedure to make it easier for participants to see what they are agreeing to. People who take part will be offered the chance to take part in a clinical trial afterwards, as part of a partnership with the European Prevention of Alzheimer's Disease Consortium.

Highlights from our 2016 conference



One-of-a-kind research conference brings together researchers and people affected by dementia.

In June 2016, Bristol became host to over 200 dementia researchers, Research Network volunteers and Alzheimer's Society staff attending our annual research conference. This unique event is a great opportunity for researchers and people affected by dementia to come together to share ideas and hear about the latest research.

As in previous years, the conference was split over two days. The first day consisted of specialist training and workshops for the Research Network, our group of over 270 volunteers with personal experience of dementia who help us to set our research priorities and strategies. This year, the network volunteers were treated to a variety of talks including about how research knowledge is put into practice and updates on clinical trials.

The day also focused on our Dementia Research Leaders, who are researchers in the early and middle stages of their careers. This year we held sessions to help them build their leadership skills and understand how to better communicate with

audiences of non-scientists.
In the evening we held a poster session that allowed our staff, researchers and Research Network volunteers to read more about the important projects that we are funding, discuss results and share experiences and ideas.

Hope for progress

Dr Doug Brown, Director of Research and Development, introduced the second day by telling attendees about the great progress of our research programme during the last year. This included over 90 research publications from projects funded by us and the launch of our implementation grants.

Talks throughout the day covered a range of research from speakers with a variety of backgrounds and levels of experience. Keynote sessions were given by Dr Tara Spires-Jones from the University of Edinburgh and Professor Martin Knapp from the London School of Economics. Dr Spires-Jones spoke about her work to understand the effect of dementia on important connections between brain cells and Professor Knapp discussed how to assess cost-effectiveness of dementia care. Other topics addressed throughout the day included how to manage other conditions alongside dementia, caring for people with dementia in rural areas and clinical trials in the Bristol area.

The day was rounded off by Dr Brown asking everyone what the best part of the conference had been for them. The response was overwhelmingly that people were feeling positive about progress in dementia research. Much of this has been made by Society-funded researchers and we will continue to build on this throughout 2017 and beyond.

Photo credits: Peter Paniccia

Dementia Research Leaders award winners

Alzheimer's Society awards celebrate the work of early career researchers.

The 2016 Dementia Research Leaders awards were announced at our annual research conference. These recognise the achievements and progress of researchers in the early and middle stages of their careers. There were two categories this year – Rising Star in Dementia Research for PhD students and junior postdoctoral researchers, and Leader in Dementia Research for senior postdoctoral researchers and those at fellowship or lecturer level.

The judging panel was comprised of researchers from the care and biomedical fields and a member of our Research Network. The judges took into account aspects such as nominees' achievements so far, their commitment to patient and public involvement, and the way their work could benefit people affected by dementia.

The Rising Star in Dementia Research award was won by Dr Tim Shakespeare from University College London, who specialises in researching ways to better diagnose and understand posterior cortical atrophy. The judges were particularly impressed with Tim's commitment to helping the public find out more about dementia, including his online education programme, The Many Faces of Dementia.

The two runners up for the Rising Star in Dementia Research award were Dr Kirsty McAleese from the University of Newcastle and Dr Naaheed Mukadam from University College London. They were praised for their work on how dementia affects the brain and work with south Asian communities respectively.

The Leader in Dementia Research award went to Dr Jose Bras from the Institute of Neurology at University College London. Jose's work focuses on the genetics of dementia, particularly dementia with Lewy bodies. The judges praised his very strong academic publication record and dedication to mentoring other researchers.

The runner up prize for Leader in Dementia Research went to Dr Jon Rohrer from University College London, who was commended for his work on the genetics of frontotemporal dementia, including setting up an international collaborative network of scientists in order to share data.

Photo credit: Peter Paniccia

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About us

Alzheimer's Society is the leading support and research charity for people with dementia, their families and carers.

Since 1990, Alzheimer's Society has funded £30 million of cutting-edge dementia research. We aim to increase our investment in our research programme to around £10 million a year by 2017. This money funds important research that will help us to improve the quality of life of people with dementia, by tackling questions related to the causes of dementia, investigating good practice in care and treatment, and pursuing a cure.

Research Network

One distinctive feature of our ground-breaking research programme is the integral involvement of people with dementia and carers.

As part of our Research Network, volunteers with direct experience of living with dementia inform our research priorities.

If you have been a carer for someone with dementia or you have dementia and are interested in joining the Research Network, please contact Anna Grinbergs-Saull, Research Engagement Manager, for an application form or apply online at **alzheimers.org.uk/researchnetwork**

Keep up to date

Care and cure is the research magazine of Alzheimer's Society. To receive a copy of this magazine quarterly, please sign up to become a Friend of Research at **alzheimers.org.uk/friendsofresearch**

For general enquiries, email info@alzheimers.org.uk

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