



OxDARE

Oxford Dementia and
Ageing Research

NEWSLETTER

Summer 2020
Issue 10



Sheldonian Theatre; Photo Credit: Dr Michael Ben Yehuda

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*please share your views
on our new-look newsletter*

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Since OxDARE's spring newsletter, the University of Oxford has continued its impressive contribution to the understanding of COVID-19; you can find the latest news [here](#).

Sadly, the Office for National statistics confirms that the elderly - and especially those with dementia - have suffered disproportionately high death rates from COVID-19. We felt now was a good time to review where we are with our understanding of the diseases that cause dementia and consider the status of drug development research (*page 3 - 4*).

Ultimately it is access to rich data about large numbers of people over time that will advance our understanding of how the brain ages in healthy and unhealthy individuals. Researchers require clinical, genetic and lifestyle information from different sources to be brought together for such analysis. Read about one of the biggest global initiatives to do just that on *page 5*, and meet Dr Ludovica Griffanti who develops brain MRI software for the analysis of large datasets on *page 6*.

We are learning the importance of a lifelong approach to brain health, as highlighted by Dr Ruby Tsang's work on early-life adversity on *page 7*. Read about the growing research interest in mindfulness on *page 8*. Maybe the free online mindfulness sessions on *page 8* will give us all the opportunity to increase our mental wellbeing in these difficult times.

**“Our Science is better
if we are diverse.
Our workplace is better
when we are inclusive.”**

OxDARE Principal Investigator Dr Sana Suri and colleagues have invited fellow researchers to a series of conversations to discuss the backdrop of racial violence that has led to the recent world-wide protests. The aim is to highlight the importance of educating ourselves on institutionalised racism and to actively promote racial and ethnic equity in academia and science.

‘We aim to identify concrete actions to help dismantle barriers faced by aspiring Black and Brown scientists.’

We also know that despite an often greater disease burden, people from minority ethnic groups are underrepresented in clinical health and dementia research. The lack of diversity among research participants has **serious ethical and scientific implications**. These include that efficacy and safety findings cannot be generalised to the larger population and that many patients do not have access to high quality services and research innovations. OxDARE recognises that this is a moral and scientific issue and is committed to actively overcome critical barriers and to address the diversity problem.

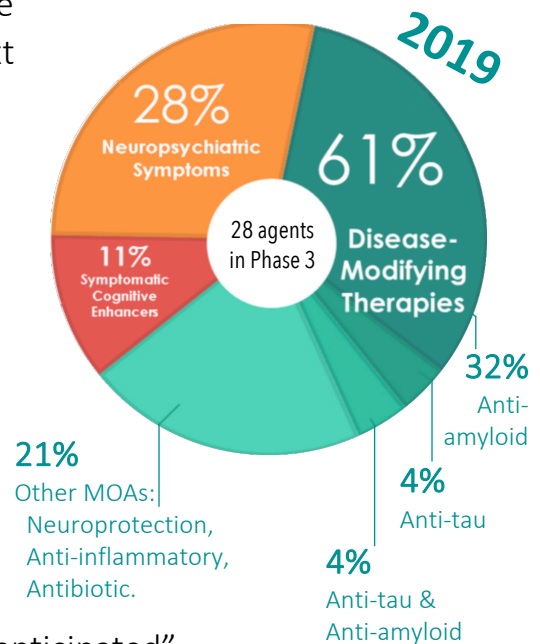
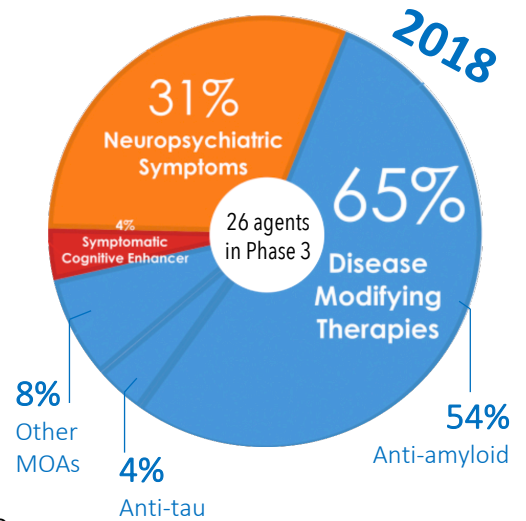
Alzheimer's Disease: Growing diversity of drug development

Each year, Dr Jeffrey Cummings, a world-renowned Alzheimer's researcher and leader in clinical trials, systematically reviews where we stand regarding the treatment of Alzheimer's disease (AD). Whilst to date, there is no drug that can reverse, slow or stop AD, the researchers note in their 2019 review that "drug development continues robustly at all phases despite setbacks in several programs in the past".

The role of the 'amyloid-β protein' in AD has received extensive research attention, and amyloid has been identified as a potential drug target. You can read more about the key underlying disease processes on the next page, which also include 'tau' and inflammation.

In 2018, over half of all drugs in late-stage 'Phase 3' trials, were targeting only one disease process - which was amyloid. One year later, there is much greater diversity among research into **disease-modifying therapies**, i.e. drugs which are intended to change the biology of AD. These include 'anti-amyloid' and 'anti-tau' agents, but also increasingly other 'mechanisms of actions' (MOAs), such as anti-inflammatory agents.

The review ends with the encouraging statement that "improvements in drug development success rate are anticipated".



How are drugs designed and developed? Clinical trial phases explained:

Pre-Clinical Research	Phase 1	Phase 2	Phase 3
Lab & Animal testing	Tens weeks - months	Hundreds months - 2 years	Thousands 1 - 4 years
<ul style="list-style-type: none"> What goes wrong in the disease and how might we correct it? Finding a drug that might work 	<ul style="list-style-type: none"> How does the drug work in the human body? Is the drug safe? Dosage? 	<ul style="list-style-type: none"> How effective is the drug? Beneficial effects? Side effects? 	<ul style="list-style-type: none"> Benefits or risks to a specific population? How does the drug compare to standard care or placebo?

What goes wrong in Alzheimer's?

A closer look in and around 'neurons', the fundamental units of the brain:

1 PRODUCING BETA-AMYLOID (A β)

In the neuron's outer layer - also called a 'membrane' - the 'amyloid precursor protein' (APP) helps the neuron grow and repair itself after injury. Like other proteins, APP gets used and recycled. If APP is cut by the chemicals ' β - and γ - secretase', then the leftovers or 'peptides' cannot dissolve. We call these leftover peptides: 'beta-amyloid' or A β .

2 A β PEPTIDES LUMP TOGETHER

A β peptides are prone to lump into small toxic groups called 'oligomers', which impair basic neuronal processes. For example, oligomers can damage the essential junctions at which neurons communicate with one another (We call these 'synapses').

3 A β PLAQUES: LARGE, STICKY CLUMPS

A β oligomers can group into large, sticky clumps known as plaques, leading to more disruption.

4 INFLAMMATORY REACTIONS

The primary immune cells in the brain are 'microglia', which can detect A β deposits outside the neuron and around the blood vessels. They respond by releasing inflammatory chemicals which can escalate the neuronal damage and increase risk of bleeding.

5 TANGLES BLOCK CELL TRAFFIC

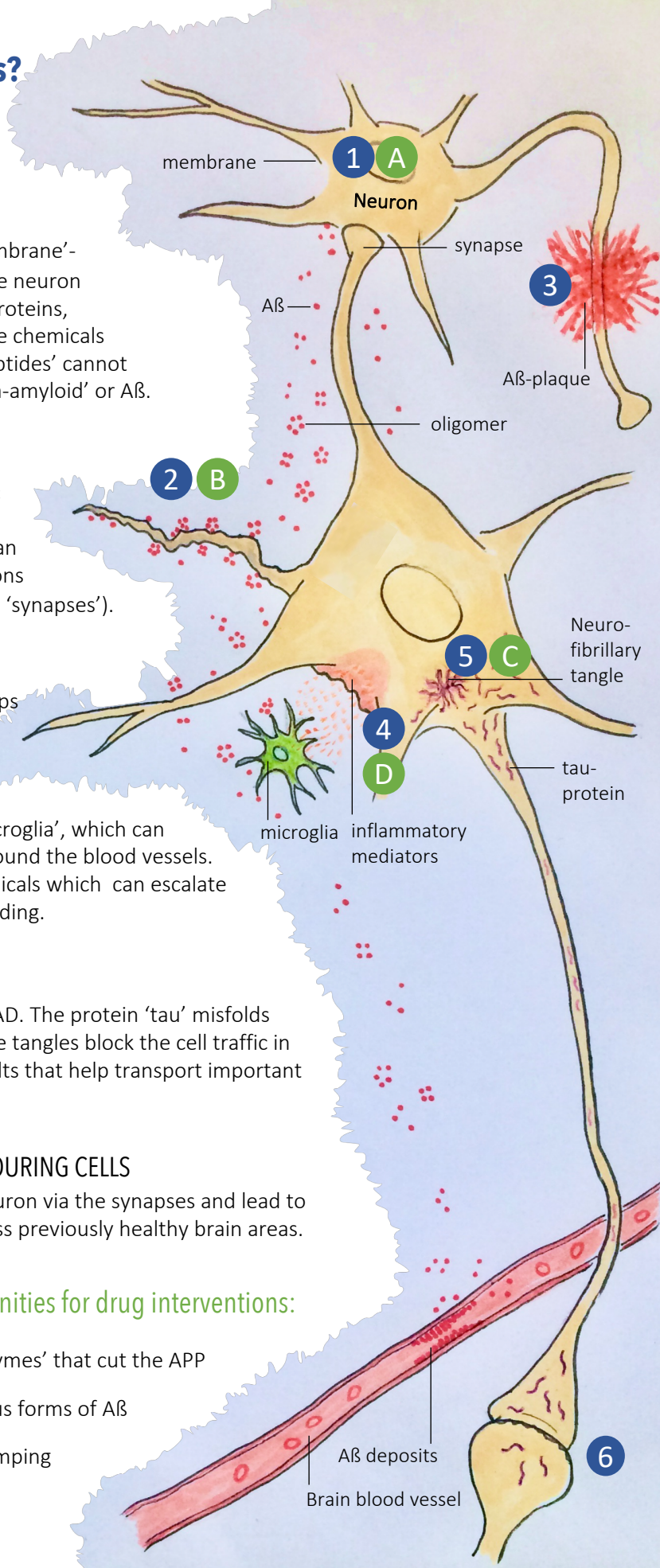
Along with plaques, tangles are a hallmark of AD. The protein 'tau' misfolds and masses into 'neurofibrillary tangles'. These tangles block the cell traffic in the 'microtubules', which are the conveyer belts that help transport important nutrients and messages within the neurons.

6 SPREADING PATHOLOGY TO NEIGHBOURING CELLS

Misfolded tau can transfer from neuron to neuron via the synapses and lead to more misfolding - thereby spreading tau across previously healthy brain areas.

How might we correct it? Opportunities for drug interventions:

- A** Interfering with the chemicals or 'enzymes' that cut the APP
- B** Artificial antibodies that bind to various forms of A β
- C** Immunotherapies that prevent the lumping and spreading of tau proteins
- D** Anti-inflammatory drugs



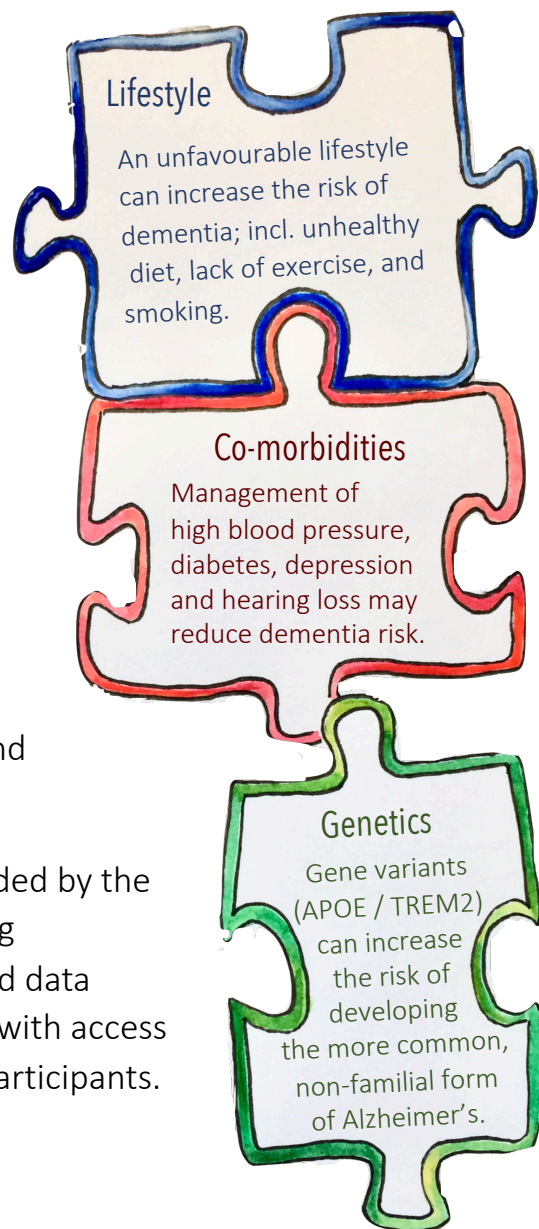
Access to big data to advance dementia research

The root causes of the diseases that lead to dementia are not yet fully understood. What we do know is that genetic, biological, cognitive and lifestyle information all play a part in solving the jigsaw puzzle.

We require observations of a person's life over many years because we know that changes occur in the brain decades before the symptoms of dementia appear. We also need such information for large numbers of people to carry out robust analyses.

The good news is that 3.5% of the UK population, across different life stages, are a member of one of many long-term health studies. The challenge is to bring that data together in a standardised format and in a secure, ethical and functional manner.

Oxford-based Dementias Platform UK (DPUK) is funded by the Medical Research Council to do just that by fostering collaborations and applying the right technology and data expertise. The result is a one-stop-shop data portal with access to information from more than 3 million research participants.



? What is being researched with DPUK data?

Researchers from academic, commercial and governmental institutions across 16 countries are already undertaking wide-ranging studies, such as:

- Deepening our understanding of how childhood adversity – such as poverty, emotional abuse and sexual abuse impact brain health across the lifespan
- Exploring how older people's living environments can influence their risk of dementia to inform WHO's work on healthy ageing
- Identifying mechanisms that may link heart health to brain health in order to find ways of protecting brain function

As a result, DPUK aims to accelerate the understanding that will lead to potential preventative strategies and treatments for dementia.

Meet Dr Ludovica Griffanti, one of the Scientists behind OxDARE



Postdoctoral researcher
Translational Neuroimaging Group

'I want to improve patients' diagnosis and care by using advanced **MRI** and engineering methods to understand brain changes due to diseases. I develop software for brain MRI analyses and apply it to large studies on ageing, Alzheimer's, Parkinson's and vascular disease, looking for early signs of neuro-degeneration and dementia. In future, I would like to make advanced brain information available in routine clinical settings.'

? Why did you decide to get involved with ageing and Dementia research?

'I have a background in biomedical engineering and I have always been interested in medical imaging, particularly of the brain. I became fascinated by the complexity of its structure and function, and even more, by its changes during ageing. There are so many things we still don't know about the most common diseases of the ageing brain and so much can be done to help diagnosis and care.'



Why is Magnetic Resonance Imaging (MRI) important for Dementia research?

MRI uses a strong magnetic field and radiofrequency signals to produce detailed images of the brain. These images can reveal small tissue damage and show us *where* structural changes are occurring. It is possible to detect brain changes in individuals who have not yet developed dementia symptoms – allowing for early intervention research. MRI can also help us track disease progression and show us if or how patients are responding to new treatments!

Most of OxDARE's imaging takes place at the *Oxford Centre for Human Brain Activity* (OHBA). Prof Clare Mackay and Radiologist Juliet Semple explain the steps of having a MRI in this [video](#).

? Can you recommend any activities for OxDARE readers shielding at home?

'In this period when we are not allowed to travel or visit a museum, many museums around the world are "virtually open". [Here](#) are some virtual tours of museums in my home country, Italy. Enjoy!'

Early-life adversity linked to decline in memory and thinking



Dr Ruby Tsang

Postdoctoral researcher
Dementias Platform UK

The Alzheimer's Research UK (ARUK) Virtual Conference allowed scientists to share their latest findings despite the COVID-19 outbreak. OxDARE researcher Dr Ruby Tsang showed that childhood experiences can have a "far-reaching and important influence" on memory and thinking skills in later life.

With use of the Dementias Platform UK (DPUK) Data Portal (more info on [page 5](#)), Dr Tsang studied 15,309 volunteers. Participants were asked about their childhood experiences, e.g. their family socioeconomic status, their own health and whether they were the victim of abuse. The DPUK data portal also holds participants' scores on various memory and thinking tests, including **verbal fluency** in mid-to later life.



What is verbal fluency?

Dementia researchers may ask you to generate a list of words that belong to a certain category or begin with a specific letter in 60 seconds. This task requires many challenging control processes, for example: accessing your mental lexicon, focussing on the task, forming useful strategies, selecting words which meet certain constraints, self-monitoring & avoiding repetition.

Dr Tsang revealed 3 memory & thinking patterns:

- 1) resilience to cognitive decline,
- 2) gradual age-related decline, and
- 3) rapid cognitive decline.

Lower education, family financial hardship and poorer health in early life predicted a greater decline in cognitive performance. Dr Tsang also reported key differences between men and women, with women more likely to be resilient to cognitive decline.

Dr Routledge, Director of Research at ARUK, said: "This research adds to growing evidence that suggests we need to protect brain health throughout life".

Read a full comment by Dr Routledge and Dr Tsang [here](#).

Oxford University offers Free Online Mindfulness Sessions

The Oxford Mindfulness Centre (OMC) is offering online **mindfulness** sessions, on the first Wednesday of each month to the general public. These sessions are led by mindfulness teachers and researchers from across the world. No prior experience is required to take part. These sessions are completely free and past recordings are available on the [OMC website](#).



What is Mindfulness?

Mindfulness means maintaining a present moment awareness of what is happening around and within you. This means paying deliberate and full attention to your thoughts, feelings, bodily sensations and surroundings - without criticism or judgement. Techniques include body scans, mindful breathing & stretching.

? Why are researchers, clinicians and the general public interested in mindfulness?

Mindfulness is beneficial to our mental and physical health; particularly for reducing anxiety, depression and stress. Mindfulness is now recommended by the National Institute for Health and Care Excellence (NICE) as a way to prevent future depressive relapses. The positive impact is not, however, confined to clinical populations.

The Oxford [MYRIAD](#) research team is investigating the effects of mindfulness-based interventions on well-being and resilience in 5700 school students. The growing interest in mindfulness is coupled with the fact that it is a low-cost, self-directed intervention that all individuals can practice without age, time and space constraints!

? Does mindfulness have an impact on healthy ageing and cognitive decline?

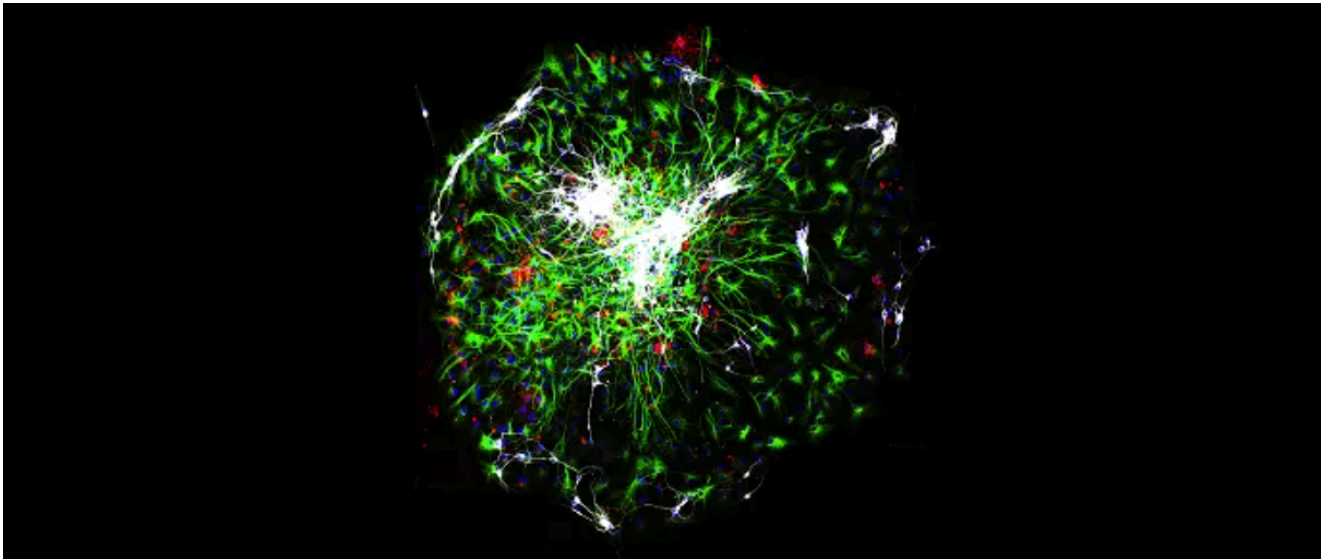
Recent research suggests that non-judgement and present-moment attention may develop naturally with time and life experience. These mindfulness qualities may become particularly important in middle and older age, as they boost flexibility in responding to age-related changes and enhance well-being.

Systematic reviews also conclude that mindfulness may potentially delay cognitive decline. The underlying biological mechanisms are still unclear. One proposed explanation, or 'hypothesis', is that mindfulness targets inflammation- and stress-related pathways, which in turn reduce the risk of developing cerebrovascular disease or depression, both found to be linked to dementia. A pilot study recently found that upon 9 months of daily mindfulness practice, older adults with mild cognitive impairment (MCI) showed improved 'biomarker' levels of inflammation. The researchers call their results "encouraging". More research is needed before mindfulness can be put into routine clinical practice for older adults with MCI.



The BRAINScape 2020 winners have been announced!

Each year, Oxford researchers are invited to submit a neuroscience, psychology or psychiatry related image to the BRAINScape competition. This year, Dr Francis Szele, Associate Professor of Developmental Biology, received joint first prize for the image: “*A neurosphere of influence*”. ‘Neurospheres’ are free-floating cell clusters that provide scientists the opportunity to study ‘neural stem cells’. Neural stem cells are self-renewing cells that generate neurons (white) and support cells (green) in the mammalian brain. The Szele group use these cells to stimulate neural repair. For more fascinating images see BRAINScape’s [2019](#) and [2020](#) winners.



Thank you to Oxford’s 76 EPAD participants!

In 2015 we secured funding to allow us to build the EPAD Longitudinal Cohort Study and follow participants for 5 years to better understand the earliest stages of Alzheimer’s Disease and test new treatments more effectively. Despite our best efforts, we have been unable to secure further funding to allow us to continue collecting this valuable data. Sadly, this means that the EPAD LCS study has come to a close.

The data we have collected continues to be an incredibly valuable resource for Alzheimer’s disease researchers across the globe. The [EPAD website](#) will continue to act as a key resource to keep everyone informed of updates and publications.

We are working closely with colleagues and other UK EPAD sites to be able to offer research opportunities to our EPAD participants in order to continue our best efforts to prevent dementia.

Solve the OxDARE Crossword Puzzle!



down

- 1.** Brain structure known to play an important role in learning and memory (11 letters). **2.** A psychological quality that allows some people to be knocked down by the adversities of life and come back at least as strong as before (10 letters). **4.** The junction at which neurons communicate with one another (7 letters). **7.** The way in which a person lives, including interests and behaviours (9 letters). **8.** The body's protective response to harmful stimuli or injury involving immune cells and mediators (12 letters). **10.** Along with plaques these are a hallmark of Alzheimer's Disease (7 letters). **12.** The action of stopping something from happening (10 letters). **14.** State of physical, mental and social wellbeing (6 letters).

across

- 3.** The primary immune cell in the brain that releases inflammatory mediators when detecting beta-amyloid (9 letters). **5.** The most common cause of dementia & the last name of a German psychiatrist (9 letters). **6.** The fundamental unit of the brain, also known as a nerve cell (6 letters). **9.** The ability to pay deliberate and full attention to what is happening around and within you without criticism or judgement (11 letters). **12.** A medical treatment or procedure designed to have no therapeutic value in a clinical experiment (7 letters). **13.** A measurable indicator of a biological state or condition (9 letters). **15.** Acronym for a medical imaging technique that uses a strong magnetic field and radiofrequency signals (3 letters). **16.** A protein found in plaques in Alzheimer's Disease (7 letters).

You will find the answers in the next OxDARE newsletter - Issue 11.

Public & Patient Involvement Opportunities

> Could people with mild cognitive impairment (MCI) get greater benefit from our gardens, libraries and museums?

We are looking for people with an MCI diagnosis to help our research. We are interested in how cultural spaces – such as museums, libraries and gardens – could help people with an MCI diagnosis; whether that is for social interaction, having fun, relaxation or giving structure to their week. We are designing a research project and would like members of the public to help us decide what topics to focus on. We are holding a series of **conversations – online and by phone** – which you can join from the comfort of your home. No special knowledge or experience of research is needed – we are interested in understanding what is important to you.

If you are interested in taking part, and have an MCI diagnosis, please contact Shona Forster before 17th July 2020 via shona.forster@psych.ox.ac.uk or 07884 063700.

> Please share your views on our new-look OxDARE newsletter!

You may have noticed the changes to this newsletter which is subscribed to by the public, researchers and clinicians. Over the years, Friends of OxDARE have provided lots of valuable feedback on our communications and we have been guided by that learning. Our aim was to broaden the scope of our articles to give you a better feeling for all that is going on in the world of dementia and ageing research. We also hope the new design will be easy and enjoyable to read!

Please let us know which articles were of particular interest to you or any topics you would like us to cover in future. Please also point out any instances where we have not explained the science clearly enough. Please contact us via OxDARE@psych.ox.ac.uk.



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Encouraging engagement
between dementia researchers,
clinicians and the general public.

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