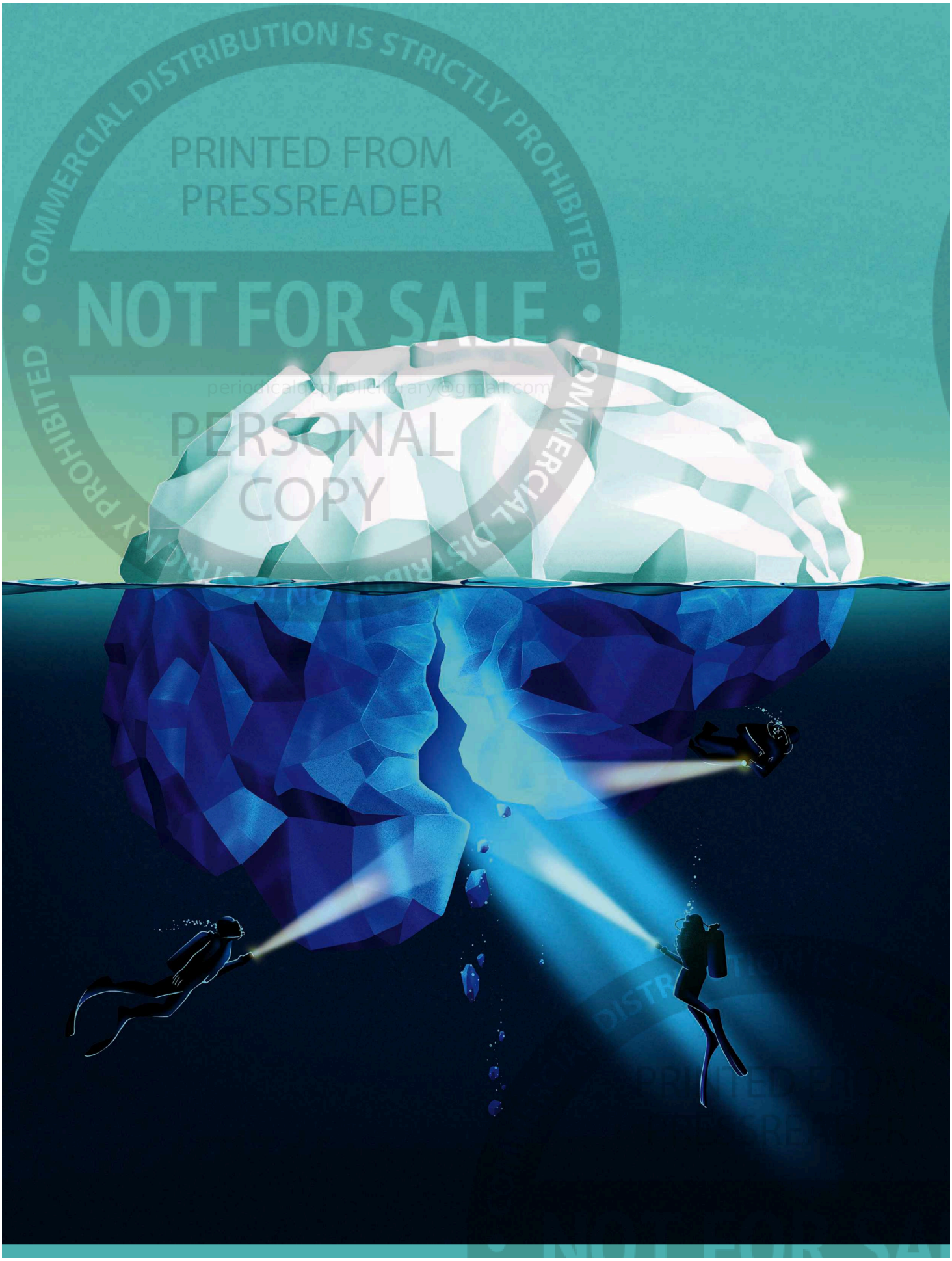
- Dementia



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DETECTING DEMENTIA

New science is uncovering how Alzheimer's could be detected decades before symptoms strike. Could it give us the head start needed to fight back and defeat the disease?

by ANTHEA ROWAN

I don't have to think very hard to remember when my mother's memory revealed the first tiniest clues that all was not well.

We were on the phone. I recounted a story of my best friend, Caroline.

"Who's Caroline?" she asked.

I had known Caroline since I was very young; she was a significant part of my life. And Mum's.

I told myself my mother's lapse was on account of the dislocation that comes with a conversation that isn't face-to-face. That my reference to Caroline was out of context. That Mum wasn't concentrating. That she was having a 'senior moment'. And then I tried to forget that Mum had ever forgotten Caroline at all.

That was 10 years before my mother died of Alzheimer's disease, the most common type of dementia. It accounts for up to 80 per cent of cases and is the slowest to develop which, perhaps paradoxically, might be to a person's advantage: it could mean that there's a window of opportunity to do something about the impact of this devastating disease that many people – including some doctors – don't yet appreciate. According to Alzheimer's Disease International's 2024 World Alzheimer's Report, 65 per cent of health and care professionals believe dementia is a normal part of ageing and 80 per cent of the public do too (up from 66 per cent five years ago). But it's not.

"DEMENTIA MAKES ITSELF AT HOME AND LINGERS IN THE SHADOWS"

Dementia might feel like a wrecking ball, but it's not simply absent one day and fully present the next. No, it settles in, makes itself at home and lingers in the shadows for 10, 15, or even 20 years.

Studies in the past have presented Alzheimer's as developing in several stages, but recent research has changed this picture. A team from the Allen Institute for Brain Science in Seattle, claims the disease develops in only two distinct phases, or 'epochs'.

The first, a slow 'stealth' phase – a time when only a few vulnerable cells in the brain are affected. It's only in the second, faster and more aggressive, phase that the characteristics of cognitive collapse that we commonly associate →

ILLUSTRATION: SARA CARNEVALE

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→ with dementia – namely functional, memory and thought impairments – start to have an effect on living standards.

It sounds alarming, but the first, so-called 'stealth', phase could present an opportunity. In fact, it could be a chance to completely alter the trajectory of this disease.

DOUBLE TROUBLE

The new breakthroughs centre on two main proteins thought to drive Alzheimer's: amyloid and tau.

Both can contribute to cognitive decline in slightly different ways. Amyloids can clump together as plaques between nerve cells, which eventually disrupt communication between them.

In turn, this disturbance can cause tau proteins to clump together, forming tangles of neural fibres that impair cell function and contribute to their death.

Together, the two proteins have been called the trigger and bullet of Alzheimer's – amyloid the trigger, tau the bullet.

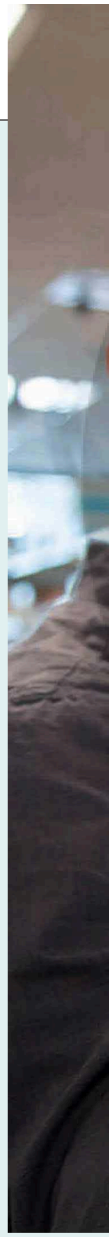
Although the build-up of these proteins can remain symptomless, early warning signs may begin to surface. As Prof Michael Hornberger – University of East Anglia dementia researcher, and author of *Tangled Up: The Science and History of Alzheimer's Disease* – explains: "The earliest accumulation of proteins, in particular tau, happens in a part of your brain that's important for, among other things, spatial navigation. This probably explains why losing your way can be among the first signs of Alzheimer's disease."

It's only when the disease affects the neighbouring hippocampus – the memory centre of your brain (responsible for both short- and long-term memories) – that people develop the classic symptoms we associate with dementia. For instance, someone might forget recent events, but have a good recall of memories from long ago.

TIPPING POINTS

Previous investigations into the development of Alzheimer's have been focused on tracking the behaviour of those proteins,





"IT'S LIKE TAKING A FOOT OFF THE BRAKE AND INSTEAD PRESSING BOTH FEET DOWN HARD ON THE THROTTLE"

ABOVE A coloured MRI scan of the brain of a patient with Alzheimer's disease

ABOVE RIGHT Drs Kyle Travaglini and Mariano Gabitto examining brain tissue samples in a lab at the Allen Institute

TOP RIGHT An illustration of amyloid plaques on a brain cell

RIGHT A diagram showing how Alzheimer's disease affects the tau proteins in the brain

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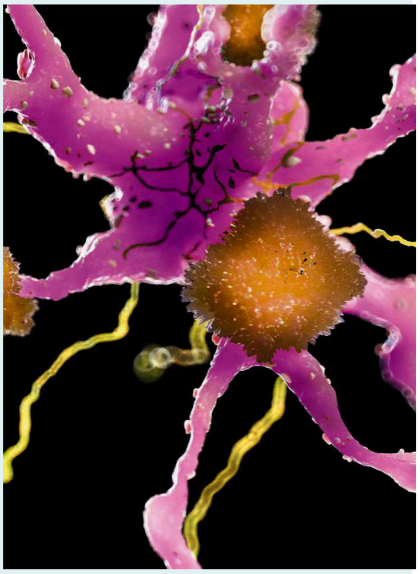

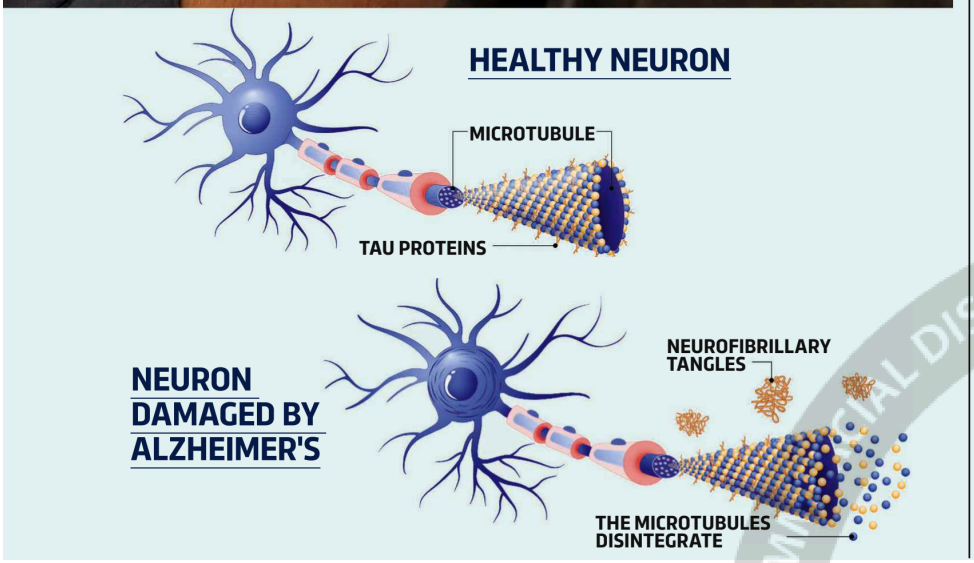

seeing how amyloid plaques cemented, and how tau tangled itself together. But the Allen Institute for Brain Science research worked slightly differently.

It saw a team of scientists studying the brains of donors (average age 88 years old) post-mortem with the assistance of machine learning. From this, they were able to assess the levels of tau and amyloid in a subject's brain.

Drs Mariano Gabitto and Kyle Travaglini, the lead authors of the study, explained that some donors' brain tissue showed evidence of early stages of the disease – small amounts of problematic tau and amyloid were present in the brain. Yet even in brains presenting low levels of the proteins, there were already signs that a number of crucial 'inhibitory' neurones were being lost.

It's difficult to understate how important these cells are. Your brain's cells exchange billions of signals every second, and two types of synapses – excitatory and inhibitory – are essential for maintaining optimal communication.

The excitatory ones ramp up activity, whereas the inhibitory neurones, as the name suggests, calm things down. For the brain to function at its best, these two types must work in harmony, maintaining a delicate balance.

But, for instance, when excitatory neurones are overactive and inhibitory neurones are lost, it's like taking a foot off the brake and instead pressing both feet down hard on the throttle. →

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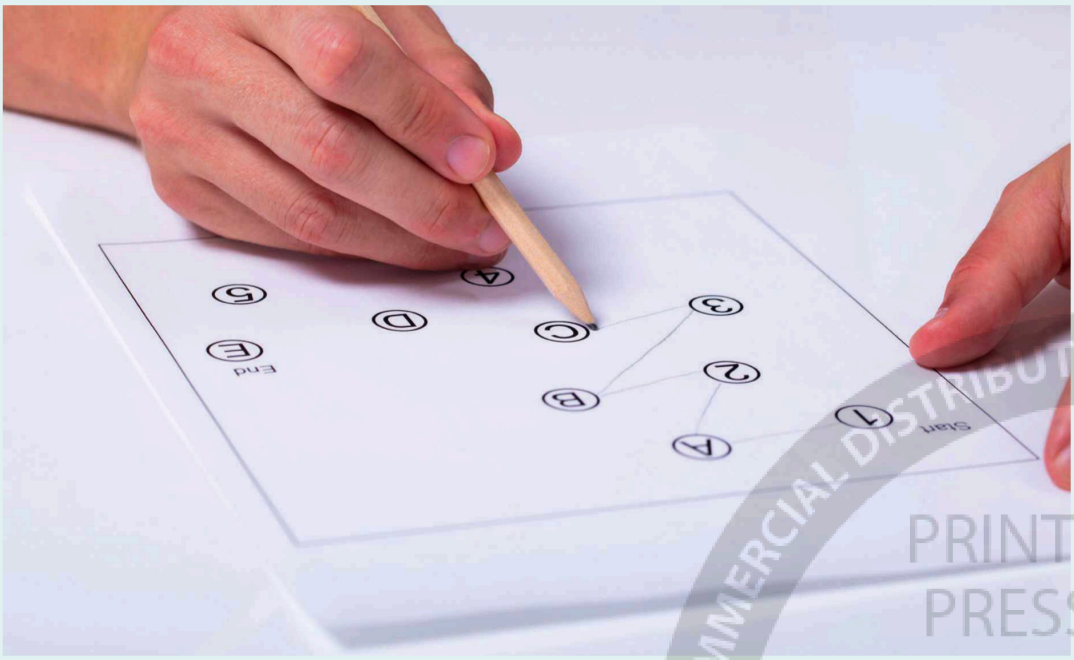
→ Slightly offsetting the equilibrium of your brain neurones – as tau and amyloid can – may only have a small impact initially, but this could compound over time. As Travaglini theorises, "Early inhibitory neuron loss would disrupt these circuits partially, but not completely. And their loss may make it easier for further disruption to occur."

These findings are worrying, to say the least. But they also represent a significant breakthrough in uncovering what we should think of as the "cellular canaries" of the disease. As Gabitto puts it, "Identifying the earliest neurones lost could be crucial for developing therapeutic interventions to protect them and prevent further cognitive decline."

It's important to note that early damage to your inhibitory and exhibitory neurones doesn't always lead to dementia, but it can be a good early warning sign. And as Dr Igor Camargo Fontana, director of scientific conference programming



TOP LEFT A coloured MRI scan showing white matter fibres in the hippocampus of a brain belonging to a patient with Alzheimer's disease. The hippocampus is one of the first areas to be affected by Alzheimer's

LEFT A sample page of a cognitive function test for dementia

ABOVE RIGHT A structural model of the apolipoprotein 4 (APOE4) gene, which can be used as an indicator of a person's potential dementia risk

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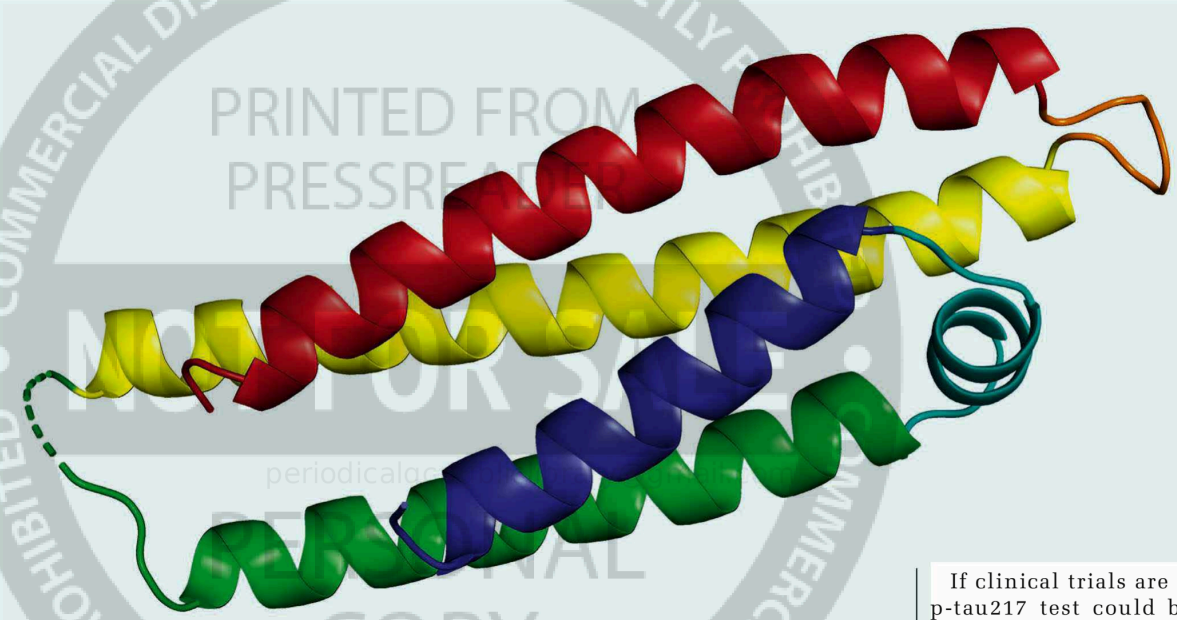


"THE DISEASE'S LONG PRESYMPTOMATIC PERIOD CREATES OPPORTUNITIES FOR EARLY DETECTION AND INTERVENTION"

at the Alzheimer's Association, notes of the new research, "The disease's long presymptomatic and silent period creates opportunities for early detection, early intervention and even prevention of dementia symptoms."

Because that's the key here: intercepting the accelerating deterioration unleashed on the brain if or when the brakes go with the loss of those inhibitory neurones.

PORTENTS OF PROBLEMS

So, if we know there are early signs of dementia, how can we identify them? MRI scans are one option, though they're hardly cheap and need to be repeated annually to monitor change.

Spinal lumbar punctures are another possibility, but they're also expensive and can feel very uncomfortable for patients.

"Blood tests are more promising," says Hornberger. But most of the widely available blood tests struggle to measure the proteins accumulating in the brain, he points out, "mostly because their concentration is so low."

However, in 2024, a large international team of scientists developed a sensitive new test that detects the presence of a specific form of the tau protein, called p-tau217, in the brain. This test not only predicted a second-phase Alzheimer's diagnosis with up to 92-per-cent accuracy (when compared to CT brain scans), but critically, p-tau217 can be also identified during the 'stealth' phase of dementia.

If clinical trials are successful, the p-tau217 test could become widely available within the next decade. The Alzheimer's Society, for example, is currently working on the Blood Biomarker Challenge, an initiative that could bring such dementia blood tests to the National Health Service (NHS) within five years.

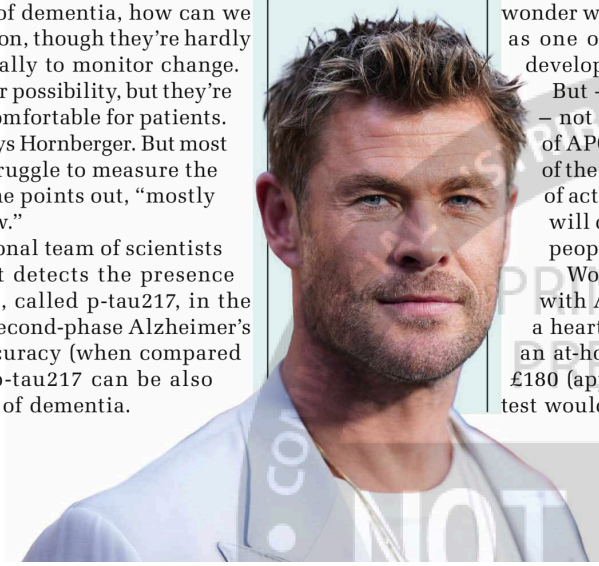
There's no need to wait for a new type of test that could help determine if you're at a higher risk of developing dementia in the future, however.

Some people have a genetic predisposition to Alzheimer's due to a specific version of their apolipoprotein gene, a gene everyone carries in one form or another. The most common variant, APOE3, doesn't appear to influence Alzheimer's risk. Another version, APOE2, is rare, but may offer some protection against the disease.

If you, like a quarter of people, are carrying one copy of the APOE4 gene, however, your risk of dementia is double. And having two copies of APOE4 in your DNA increases your risk up to 10 times. Looking at these statistics alone, it's little wonder why your APOE type is regarded as one of the strongest predictors of developing Alzheimer's.

But – and this is an important but – not everyone carrying two copies of APOE4 (an estimated two per cent of the population, including the likes of actor Chris Hemsworth, pictured) will develop Alzheimer's, and many people without it still do.

Would I – with a mother who died with Alzheimer's – take that test? In a heartbeat – and I'll soon be buying an at-home DNA swab test online for £180 (approximately $220). A negative test would be a relief, but it wouldn't →



→ stop me from being dementia aware. A positive one would galvanise me to look after my brain with greater vigilance and prompt important conversations regarding the what-ifs of dementia care. I never got to have those with my mother.

TAKE ACTION

What should we do if the worst happens? If we take such a test and it shows a genetic predisposition to the disease – or worse, our brains already carry the hallmarks of dementia – what can we do to slow its progress?

Scientists at the Allen Institute are optimistic that early interventions during dementia's stealth phase could delay – or potentially prevent – the disease's progression to its more damaging and destructive second stage.

Further studies are needed to confirm this, however, and even more will be required to identify the most effective interventions. But the first preventive measures to be tested will likely draw on recent learnings about how to reduce your overall dementia risk.

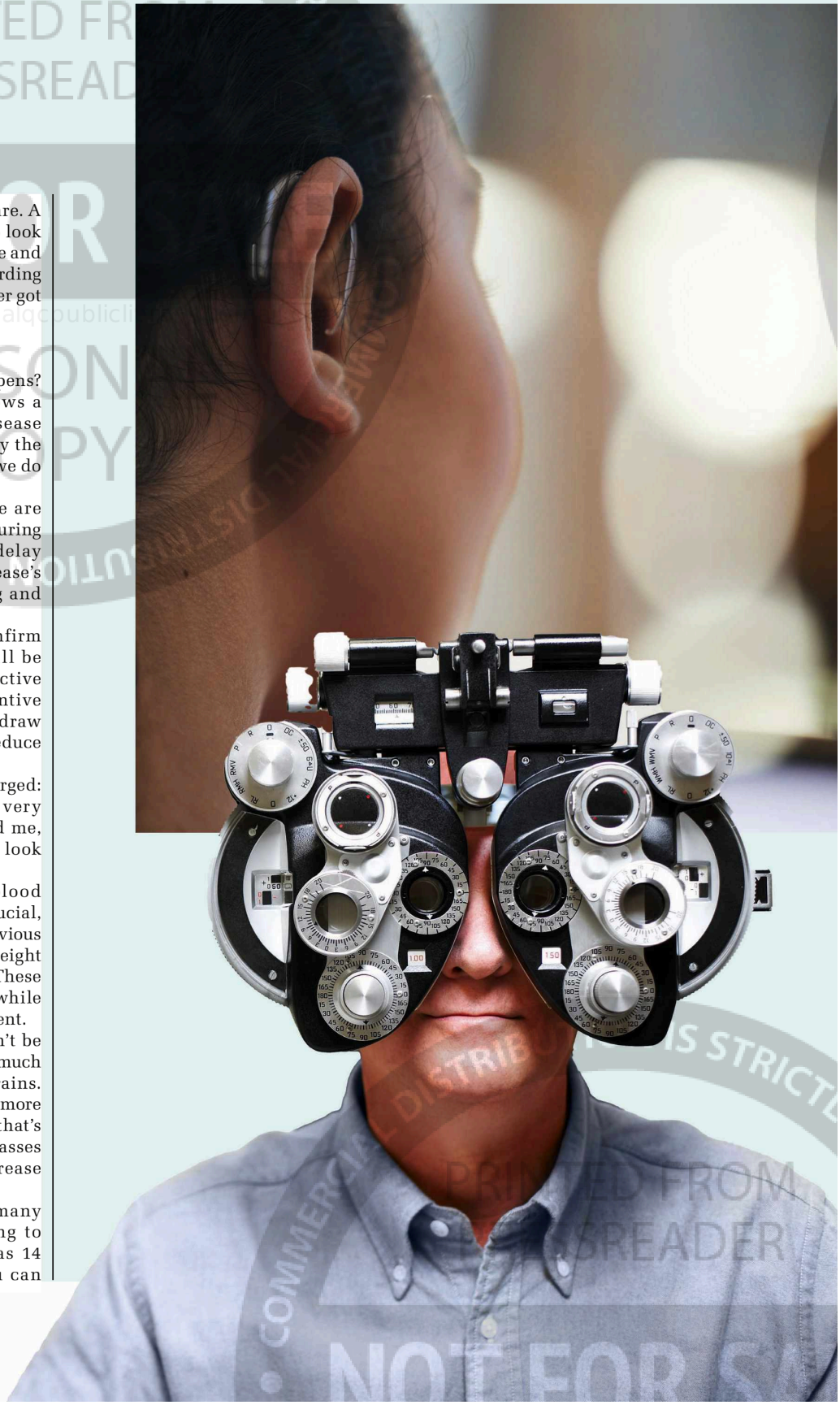
The first crucial lesson that's emerged: your heart and brain health are very closely linked. As one doctor told me, "Look after your heart and you'll look after your head."

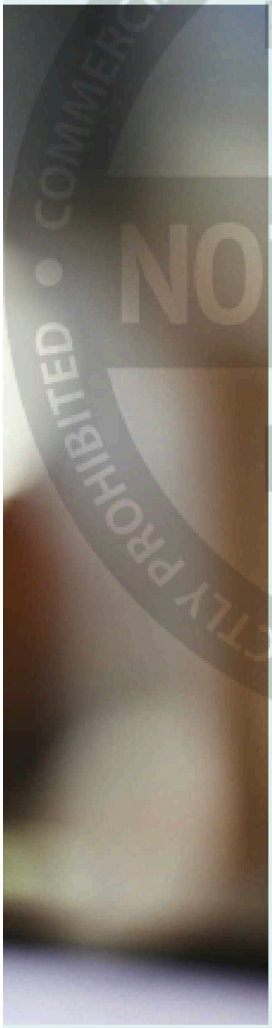
Regularly monitoring your blood pressure and cholesterol levels is crucial, as well as paying attention to more obvious signs: we can tell if we've put on weight or if we're panting while walking. These factors speak to heart health risks while the state of our brain is largely silent.

In the same way, it also shouldn't be news to anyone that not drinking too much is also going to be better for our brains.

One 23-year study found drinking more than 14 units of alcohol a week – that's six pints of beer, or six medium glasses of wine – could significantly increase your dementia risk.

And that's just one change of many you can make. In fact, according to *The Lancet*, there are as many as 14 significant lifestyle changes you can





"NEARLY HALF OF YOUR DEMENTIA RISK IS SOMETHING YOU CAN INFLUENCE"

make today that show a proven and drastic reduction (up to 45 per cent in some cases) to your risk of developing dementia, though some might require more effort than others.

For example, getting more exercise. Research has shown that people who take up regular exercise may be up to 20-per-cent less likely to develop dementia than those who don't. And that's partly because exercising is good for your heart (that mantra again).

Others, though, are surprisingly easy to address. The biggest: wear a hearing aid if you need one. Loss of hearing is one of the most significant independent risk factors for dementia.

Studies have found that even mild hearing loss can double the risk of cognitive impairment. Moderate loss can triple it and people with a severe hearing impairment could be up to five times more likely to develop dementia.

Why? It's thought that difficulty hearing and communicating can lead to social withdrawal and isolation, which are both contributing factors to brain atrophy.

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ABOVE LEFT Hearing loss can increase the risk of developing dementia

LEFT Correcting any visual impairments is helpful in reducing the risk of developing dementia in later life

And while you're getting your hearing checked, get an eye test too. The worse your eyesight is, the higher your dementia risk (again, likely due to being a cause of brain atrophy), but only if you don't get it corrected. Improve your vision with the likes of glasses and you could reduce this risk.

Other key risk factors that are within your control won't be too surprising: carefully managing diabetes if you have it or giving up smoking. The most important takeaway should be that nearly half of your dementia risk is something you can influence.

It's a fact many people fail to grasp. Prof Albert Hofman at the Harvard TH Chan School of Public Health says that one of the biggest problems is the public's "fatalistic attitude" towards dementia as an inevitable disease of the elderly. "We have to change our behaviours to avoid it," he contends.

If we approach dementia in the same way we do heart disease or a stroke – conditions with multiple causes that can be screened and addressed through early interventions – he argues that we can significantly reduce its prevalence.

"There have been enormous successes in the last part of the last century and the early part of this one in preventing heart attack and stroke. The same could apply to dementia," he says.

While he acknowledges we might not eradicate it, Hofman claims that delaying such diseases to the latest possible phase in life would offer people more years of quality living and, as he puts it, "a better death" experience.

Gaining insight into dementia's stealth phase – and learning how to take action before the disease hijacks our minds – could be just the way to do that. **SF**

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by **ANTHEA ROWAN**

Anthea is a journalist and the author of A Silent Tsunami *(Bedford Square Publishers, £20)*

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