We may finally know how cognitive reserve protects against Alzheimer's

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Why does mental effort lead to a more resilient brain that can withstand dementia and decline? We are now discovering the mechanisms behind this cognitive reserve, opening up new ways to boost it

IF I never thought about dementia before, I thought of little else after the condition manifested in my mother. The odd thing was that dementia – Alzheimer's disease, in her case – didn't occur to me until she asked, out of the blue, when we had first met.

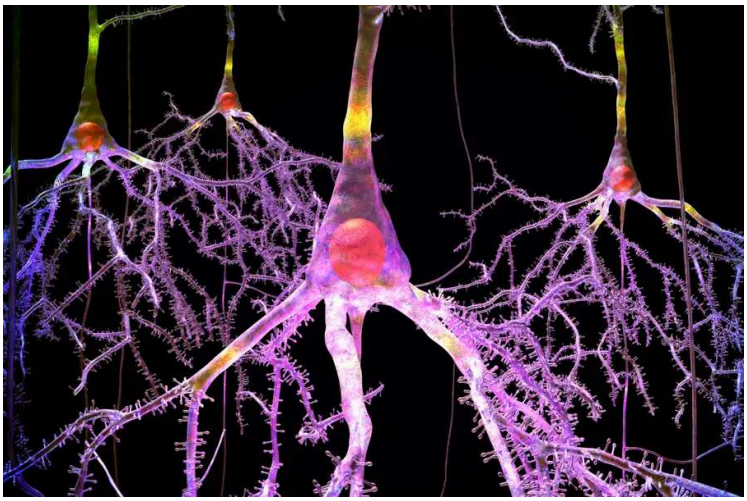
My failure to recognise the extent of her cognitive decline was born partly of denial, but also because she was doubtless compensating for her galloping brain damage, taking cerebral detours around the potholes dug by her condition. After all, she had done this before. Following a stroke four years previously, she had lost the ability to read; after much hard work, she learned the skill again.

So how come this ability to adapt, which seemed to sustain her after her stroke, was unable to withstand the pathology of dementia? This also made me think about my own resilience to cognitive decline and what, if anything, I could do about it.

We have known for almost three decades that some peoples' brains can function normally even when riddled with the plaques and other damage associated with dementia, due to an enigmatic capacity called cognitive reserve. Yet despite growing evidence of its importance, it has been challenging to pin down how this quality operates in the brain. Now, we are finally beginning to understand the mechanisms that underlie cognitive reserve, opening up possible new dementia treatments and fresh ideas about how we can protect our thinking abilities into old age. And it turns out that obsessing about learning another language or doing a daily crossword might be missing the bigger picture.

What is cognitive reserve?

The concept of cognitive reserve arose nearly 30 years ago when Yaakov Stern, a neuropsychologist at Columbia University in New York, and his colleagues found that people with higher education or a more intellectually challenging occupation were less likely to develop Alzheimer's disease. The researchers hypothesised that the extra years of intellectual effort imparted "a reserve that delays the onset of clinical manifestations".



Nerve cells have protusions called dendrites (shown in purple) that collect and transmit information

At first, the concept wasn't taken seriously. "Colleagues made fun of the idea," says Stern. "It seemed so far-fetched that something like education could counter the plaques and tangles of Alzheimer's."

Stern called this capacity “cognitive reserve” to differentiate it from a related concept of “brain reserve” that had been defined a few years previously by Robert Katzman, then at the University of California, San Diego. He studied the brains, post-mortem, of elderly residents of a care home and found that some contained a high degree of plaques associated with Alzheimer’s, even though the cognitive abilities of these individuals had ranked in the top 20 per cent of the nursing home’s residents – as good as, or better than, those without any brain pathology. He concluded that this was due to them having bigger, heavier brains, hence a greater number of neurons and therefore more “brain reserve” to withstand the damage caused by plaques.

Brain reserve is a structural quality measured by brain volume, which gives an indication of the number of neurons and synapses – the connections between neurons through which information flows.

Stern likens cognitive reserve to the software of a computer – a capacity that can be upgraded throughout our lives – whereas brain reserve is the hardware.

Brain reserve was once regarded as having a fixed capacity, but this view has now changed. Not only is there evidence that our brains may be able to make new neurons throughout adulthood, but we now know that many things can influence the functioning of the brain’s hardware. This has led to the recognition of a third pillar that underlies cognitive resilience: brain maintenance, which is the lifestyle or environmental factors that keep the brain in good condition.

It is the combination of cognitive reserve, brain reserve and brain maintenance that enables some individuals to preserve their thinking abilities into old age more successfully than others. “These three aspects are highly interrelated,” says Dorina Cadar at Brighton and Sussex Medical School, UK.

The protective effects of this cognitive resilience have since been confirmed by multiple studies. For example, a 2020 study of the incidence of dementia followed more than 12,000 people aged 50 or over as part of the English Longitudinal Study of Ageing. It found that “many aspects, such as education, type of occupation and lifestyle choices, including leisure and social engagements”, contributed to a higher level of cognitive reserve and hence a reduced risk of dementia, says Cadar.

One of the curious things about cognitive reserve, however, is that we can’t see it in the brain or directly measure it, though Stern has made some progress in identifying what seem to be associated networks. Cognitive reserve is typically measured using proxies such as attainment in cognitive tests. Through this and other proxies, we have discovered a huge amount about the factors that can influence it.

How to increase cognitive reserve

Some of these are down to luck. Our genes, for example, play a strong role in determining our intelligence, and a higher IQ is associated with a higher cognitive reserve. But other factors are more malleable. Higher levels of social engagement in mid or later life, for example, are strongly linked with better cognitive performance in older age and a 30 to 50 per cent lower dementia risk.

Socialising is a mental challenge: you have to remember faces, names and the context of other people, navigate a conversation, ask questions, use humour and observe social cues, says Andrew Sommerlad at University College London. “There’s a lot going on at once,” he says, which stretches the brain, and it also has a stress-lowering effect. In fact, a lack of these kinds of interactions might have predisposed my mother to dementia. She was diagnosed with depression aged 38 and could withdraw from others for months on end.

Stress, obesity and poor diet can all have a harmful impact on our reserve due to the persistent inflammation they trigger, which can disrupt many of the brain’s functions. “It can’t use glucose effectively, nerve activity is upset,” says Craig Ritchie, chief executive and founder of Scottish

Brain Sciences. This also compounds the effects of "inflammaging", the low-level chronic inflammation that inevitably develops as we age.

On the other hand, a good night's sleep can help our cognitive reserve. One study from earlier this year found that a particular phase of our sleep cycle, non-rapid eye movement (NREM), seems to be especially important. This may be because this phase of deep sleep is crucial for the consolidation of memories, as well as for the clearance of toxins that interfere with healthy brain functioning.

Another, perhaps unexpected, factor linked to cognitive reserve is physical activity. A 2020 study of nearly 130,000 US adults, for example, found that cognitive decline was almost twice as common among those who were physically inactive compared with people who were active. This is because the role of exercise in brain health, rather like social engagement, is multifaceted. It supports cardiovascular health and cerebral blood flow – both important for brain health – helps reduce inflammation and elevates the levels of brain-derived neurotrophic factor, a substance that has been shown to increase the size of that all-important memory centre: the hippocampus. Exercise also improves memory by promoting deep sleep.

Unsurprisingly, many more obviously cerebral activities also influence our reserve. Various studies show that speaking more than one language acts as a powerful cognitive stimulant. For example, although bilingual and monolingual people eventually have the same number of Alzheimer's disease cases, "bilinguals tend to be able to stave off these symptoms for longer," says John Grundy at Iowa State University.

But don't rush to learn a new language just yet. What really seems to matter is strong mental engagement and focus on challenging activities, not any specific activity per se. A 2015 study, for example, used functional MRI scanning to compare the brain activity of US participants, aged between 60 and 90, before and after engaging in focused effort over 14 weeks in quilting or digital photography. It found that their brains' neural networks operated more efficiently, adopting more youthful-like patterns compared with those of a control group that didn't take part in these activities. The effect lasted at least a year.

Other studies show that learning and engagement contribute to the preservation of brain volume and prevention of shrinking of memory centres. For instance, a 2023 Swiss study of people aged between their early 60s and late 70s revealed that a six-month music intervention – whether playing it or listening to it – improved memory and increased both neuroplasticity and volume of grey matter, the brain tissue packed with synapses and neuron cell bodies (which are the portion of a cell that contains its nucleus).

Neuroplasticity

Neuroplasticity derives from the brain's innate ability to reorganise itself in order to accomplish tasks in the most streamlined way. As you become more practised at a thing, says Pamela Almeida Meza at University College London, you become more efficient and trim networks. Cognitively demanding tasks strengthen the underlying neural pathways and create alternate pathways that mitigate loss of function due to progressive brain degeneration. We used to think that neuroplasticity was a privilege of youth, she says. "But evidence over the last few years shows there is neurogenesis during adulthood and old age, just not at the same rate."

We need to think of cognitive reserve beyond just education and professional success, says Sommerlad. It is, ultimately, the end point of exercising your brain throughout your life, partly through education (the most studied of all proxies), but other things too: a healthy lifestyle, physical activity, socialising and mentally taxing activities. "There is no silver bullet to building cognitive reserve," says Grundy.

It could be that those with more synapses to start with are protected from dementia. However,

Jeremy Herskowitz at the University of Alabama at Birmingham thinks that our cognitive resilience mechanism is a more dynamic process than this. “It’s actively regenerating,” he says. “If something bad happens, like the accumulation of Alzheimer’s pathology, then your brain remodels itself to continue to work normally. It’s not just that you have a higher starting point. The brain has got its own coping mechanism.”

Some fascinating new research is revealing how this regeneration process works. Dendritic spines come in different forms, including thin ones – hypothesised to be the most plastic type, necessary for learning new things – and mushroom-shaped ones, a more stable form thought to be involved in the retention of long-term memories. Intriguingly, the number of thin spines is reduced in people who have cognitive impairments through Alzheimer’s disease, but maintained in those with normal cognition, despite the pathology of the disease.

Measuring our reserve

Even more surprisingly, it was found that spines are longer in people who are cognitively normal, a discovery that Herskowitz says “is probably one of the most profound moments in my career”. There is now a lot of data to suggest that increased length in thin spines improves resilience to Alzheimer’s disease, he says. What’s more, this research has identified some of the factors that regulate spine density and length in humans, making them a potential candidate for therapeutic intervention.

One of these is neuritin (NRN1), a protein secreted by neurons and found throughout the brain. NRN1 seems to act as a mediator of cognitive resilience to Alzheimer’s disease. Evidence for this comes from the Religious Orders Study of older Catholic brothers, nuns and priests from across the US who agreed to undergo yearly cognitive testing and brain donation after death. When Herskowitz and his colleagues analysed 250 people from this study, they found that higher levels of NRN1 in later life were associated with better cognitive abilities and greater spine density. “It looks like this protein is very supportive of neurons. It’s almost like a vitamin for neurons,” he says. Earlier this year the researchers identified another protein, Twinfilin-2, that influences spine length.

Studies of the brains of nuns have been crucial for our understanding of resilience to dementia

But how exactly do these factors help build cognitive reserve? The idea is that activities that stimulate cognitive processes in the brain increase levels of proteins such as NRN1, which, in turn, helps to create new synapses or preserve existing ones. “I think the mechanism works similarly to your muscles and exercise. So, throughout life, if you continue to read and stay intellectually and socially engaged, you stimulate your mind much like you would stimulate your body doing exercise,” says Herskowitz. The inherent plasticity of your neurons needs to be worked through those kinds of mental stresses, he says. “If you don’t stimulate your brain and stimulate your neurons to think, then you’ll lose those synapses naturally, even without the effects of Alzheimer’s disease.”

It is very early days, but Herskowitz envisages that, one day, NRN1 could be given as a supplement to support brain function, and as an alternative way to forestall the pathological effects of Alzheimer’s disease and dementia to the current approaches, which are mainly focused on eliminating plaques and protein tangles in neurons.

Others agree with this view. “Rather than focusing on eliminating pathology or what led to it – which has been quite unsuccessful, to put it mildly – I think we should be boosting the protective mechanisms implemented by the brain to cope with pathology in the first place: synaptic compensation, repair and regeneration,” says Opazo.

When our reserve declines

This is promising for the future, but it is also important to recognise a sobering reality to cognitive reserve: while a higher reserve correlates with later onset of cognitive impairment, it also tends to lead to a steeper decline once the pathology overwhelms a person, says Stern. This is what seemed to happen to my fiercely intelligent mother, who was in excellent physical health until her stroke, could speak English and French and regularly tackled cryptic crosswords.

As for myself, I will try to add a bit to my reserve each day – through exercise, socialising or writing articles like this. But I am also hoping that our new understanding of how mental effort can build connections between neurons might one day offer new ways to supplement my cognitive bank account.