Published in *Living Life Loving Life Young & Old* in 2014 by Future Leaders (www.futureleaders.com.au)

2

Brain health

Stephen MacFarlane

Brain development and normal ageing

The human brain is the most complex object in the known universe. Such is its complexity, that even the number of brain cells (neurons) within it remains in dispute, with common estimates ranging from between 86 billion to over 100 billion. Each of these cells forms multiple connections, called synapses, with its neighbouring neurons, with perhaps 125 trillion of these connections existing in the cortex, or surface layer of the brain, alone.

Our brain peaks, in terms of sheer brain cell numbers at least, shortly after birth, with early childhood being characterised by a massive increase in the number of synapses formed by each cell, counterbalanced by a significant decrease, overall, in the total number of brain cells. Throughout childhood and adolescence, of course, the capacity of our brains to learn, reason, adapt, solve problems and to utilise language increases dramatically. The conclusion that can be drawn from this is that the processing power of our brains is not so much determined by the number of brain cells we have, but by the number of connections they form with their neighbours.

The process of neuronal loss continues throughout our adult lives, with some estimates having us lose as many as 10,000 brain cells per day after the age of 40. When weighed against the total number of neurons that we have, these numbers can be put into

some perspective, but it is intuitively unsurprising that, as the years go by, the ability of our brains to function at their optimum is decreased.

There is, therefore, a normal pattern of age-related cognitive decline in certain areas of brain function that can be expected to impact us all, to a greater or lesser extent, as we age. A large part of the task of doctors who diagnose and treat cognitive disorders in the elderly is to dissect out those areas of decline that are normal for any given age, as opposed to a pattern of decline that might indicate brain disease.

What, then, are those areas of brain function in which older persons might be expected to perform less well compared to younger individuals?

Older persons tend to do less well on cognitive tasks that require divided attention, a cognitive domain that allows us to manage input from a number of different sources of information at the same time. An example might be struggling while at a party, socialising with a large group of people who are engaged in multiple strands of conversation, to remain focused on a particular conversation when it is being intruded upon by a number of other distracting conversations. As a result, older persons tend to perform better conversationally while engaged in 'one-on-one' interactions, rather than in group settings.

In much the same way as the speed of a computer is determined by the number of separate calculations it can perform per second, the speed of the brain in processing information is determined to a large extent by the number of synapses that can be engaged in the performance of a task. As brain cell number decreases with age, the 'processing speed' of the brain declines. As a result, reaction time increases with age, and when asked to provide an answer to a question, for example, normal older persons might require longer to produce the answer than their younger counterparts. There is not necessarily, however, a greater likelihood of an incorrect answer. The information still resides

within the brain of an older person, it merely requires increased time to be produced.

So-called 'age-related memory loss' is, therefore, not so much a storage deficit as a retrieval deficit. The information is still there to be remembered, it simply takes longer to be brought to the surface and produced. A useful analogy might be to think of the brain as a large box, containing multiple memories. Normal ageing means that it takes us longer to rummage through that box to produce the memory that is being sought. In pathological causes of memory loss, a storage deficit, rather than one of retrieval, is present. Continuing with our 'brain as a memory box' analogy, in conditions such as Alzheimer's disease the memory fails to become placed in the box at all. A failure of storage occurs such that the memory is not placed within the box for later retrieval.

Dementia

Dementia is a term that refers to a progressive decline in multiple areas of brain function over time that is distinct from that which could be expected due to normal ageing.

There are over 100 different diseases that can produce a dementia syndrome. As such, the term *dementia* is not synonymous with Alzheimer's disease. Alzheimer's is merely the commonest cause of dementia in Western society, accounting for up to 70% of all cases.

A number of other forms of dementia occur commonly. Vascular dementia is caused by reduced blood flow to the brain related to blood vessel disease and the occurrence of multiple strokes, and accounts for perhaps 10–15% of all dementia cases. Dementia with Lewy Bodies occurs at a rate similar to that of vascular dementia, and is characterised by cognitive fluctuations, symptoms that can mimic Parkinson's disease, and the occurrence of visual hallucinations. Frontotemporal dementia accounts for about 5% of all dementia cases, and presents with either behavioural/personality changes or problems with language, while

alcohol-related dementia probably represents another 5% of all cases.

The mathematically astute reader may have noticed at this point that, despite over 100 different causes of dementia existing, the five causes we have listed above would already account for over 100%. The answer to this apparent contradiction lies in the fact that the older we become, the more common it is to find mixed pathology (more than one cause for dementia being present in a given individual).

Many of the causes of dementia are exceedingly rare, accounting for only a tiny proportion of total cases. Some causes are reversible, such as dementias associated with certain infectious diseases, hormonal abnormalities, and vitamin deficiencies.

Fortunately, the risk factors for the common forms of dementia overlap significantly with each other, and with other diseases associated with ageing, such as heart disease, cancer and stroke. This means that we can significantly decrease our risk of multiple age-related diseases by making relatively few adjustments to our lifestyles. The major modifiable risk factors for the common types of dementia include smoking, raised cholesterol, and high blood pressure. A family history can also be important, particularly for dementias that have an early onset, and for some of the genetically determined causes of dementia such as Huntington's disease.

Unfortunately, the biggest single risk factor for the commonest types of dementia is old age itself, to the extent that if we are lucky enough to survive to the age of 90, we have a risk of Alzheimer's disease at this age that approaches 50%. It is largely because, as a population, we are now much more likely to survive into our nineties that we are facing the 'tidal wave of dementia' that we hear about in the media. Alzheimer's Australia reports that there are currently over 300,000 Australians with dementia, with these numbers expected to triple by 2050. The current direct costs of dementia care in Australia total around $5 billion, and will be the single costliest health condition in the country by the

2060s. The total estimated costs of dementia care worldwide were US$604 billion in 2010, and if dementia were a country, it would be the world's 18th largest economy.[1]

Alzheimer's disease

We have already described the symptoms of normal, age-related memory loss. How, then, do the early symptoms of Alzheimer's dementia differ from those of normal ageing?

The first cognitive domains to be affected in Alzheimer's disease are those of short-term memory and orientation to time: a forgetting of recently registered information, such as what we have just eaten for lunch, or how we spent our weekend, combined with a confusion around the relationship recent events have had to each other in relation to time. These might commonly manifest as a tendency to ask the same questions repeatedly, a frequent misplacing of objects, or a forgetting of appointments. These are concerning signs of memory loss that are abnormal, and which merit further evaluation by a doctor.

The currently available medication treatments for Alzheimer's disease, known as cholinesterase inhibitors, are purely symptomatic. As brain cells become damaged by Alzheimer's, they lose their capacity to manufacture, use and recycle various brain chemicals, including acetylcholine, the main neurotransmitter involved in memory. At one level, then, Alzheimer's can be thought of as a condition that results in a deficiency of acetylcholine. Cholinesterase inhibitors block the activity of an enzyme that would normally help remove acetylcholine from synapses during neurotransmission. Blocking the activity of this enzyme helps address the relative deficiency of acetylcholine suffered by cells under attack by Alzheimer's making, in effect, more of this brain chemical available for use by neurons. As such, they essentially help damaged and dying brain cells to function better while they still live, but do nothing to ultimately stop them from dying. Thus, they have benefit for a limited period of time before these

benefits are outweighed by the ongoing loss of brain cell numbers. On average, this period of benefit may be as short as six months. Current treatments thus buy patients time, but merely delay an inevitable decline in the condition. With the alarming projections relating to the future prevalence of Alzheimer's , there is an urgent need to develop treatments that might impact the longer term course of the disease. To consider how this might be done, we need to understand a little about the pathology of the condition.

Alzheimer's disease is thought to be caused by the accumulation of two abnormal proteins within the brain, known as beta-amyloid and tau. The amyloid protein is ubiquitous in nature. Its presence has been demonstrated in virtually all vertebrates, as well as in fungi and bacteria. The embarrassing thing to admit, however, is that we have very little idea what purpose its presence serves, although presumably it might have a vital physiological role in view of its ubiquity. We do know, however, that under certain physiological conditions it can precipitate out and form the insoluble plaques in the brain that are a pathological sine qua non of Alzheimer's disease. Tau is an intraneuronal protein whose normal role is to provide structural rigidity to transport channels within brain cells. When tau undergoes a chemical reaction called hyperphosphorylation, it loses this structural rigidity and collapses in upon itself to form a structure known as a neurofibrillary tangle. The associated loss of the transport channels that normally deliver nutrients and chemical transmitters to the periphery of a neuron leads to a progressive loss of neuronal function that ultimately leads to cell death.

Neuroscientists are split as to which of these two pathologies, plaques or tangles, is the primary cause of Alzheimer's disease. Indeed, a third school of thought holds that the deposition of plaques and tangles is the end result of an unrelated process, rather than the cause of the disease itself. In view of the rising prevalence of Alzheimer's disease, however, a great deal of research effort has been devoted to the development of drugs that hope to impact on

the development of both pathologies. These approaches have utilised dramatically divergent approaches to the problem, and range from the development of agents that aim to inhibit or reverse the hyperphosphorylation of tau, through to various means of removal of amyloid plaques. These approaches have included enzyme inhibitors, active immunisation against amyloid, the use of monoclonal antibodies, and agents that aim to disrupt the toxic interactions of various metals with amyloid species. Unfortunately, after over two decades of drug development, there have been no success stories of note. Many trials of promising drugs have demonstrated no benefit, and the best that can be claimed by the current crop of drugs in development is a slowing of the rate of progression in what remains a disease that is characterised by inexorable cognitive decline.

It is unclear exactly why these trials have failed. Is it because the drugs are targeted incorrectly? Maybe plaques and tangles are indeed the result of Alzheimer's disease, rather than the cause, but another explanation is perhaps more likely. Perhaps we are targeting the disease too late in its progression to give the drugs a reasonable chance of success?

We do know that amyloid begins to deposit in the brains of Alzheimer's disease sufferers at least 10 (and possibly as many as 20) years before the symptoms of Alzheimer's become apparent. The implications of this knowledge are profound.

We observed earlier that as part of normal ageing we lose up to 10,000 brain cells per day. Despite this significant rate of cellular loss we still have brains that are capable of excellent function, in the absence of pathology, into old age. The reason for this relates to the fact that our brains can be conceived of as being massively over-engineered for their purpose. While the old adage that we only use 10% of our brain power is clearly incorrect, it is true that we have a massive redundancy of brain power in relation to that which is actually required to allow us to function at a basic level. In other words, we have a massive 'cognitive reserve'. Perhaps

nature designed us that way so that we could, in fact, afford to lose 10,000 brain cells a day and still have a functional brain at the age of 90?

In relation to the emergence of Alzheimer's disease symptoms, however, there are ominous consequences, as it must follow that, by the time we first develop the symptoms of Alzheimer's and present to our doctors for a diagnosis the brain has, by definition, already exhausted the massive functional reserves it has at its disposal, and is no longer able to compensate for this loss of processing power. The conclusion we must draw is that an enormous amount of damage has already been done by the time the first symptoms of Alzheimer's become apparent, and that as a result it might be hugely optimistic to expect that a drug targeting the pathology of the disease could reasonably produce a cure in the face of up to 20 years of accumulated damage.

Drug treatments for Alzheimer's disease are now, therefore, faced with the challenge of identifying patients who are not yet patients (that is, those who are asymptomatic, yet have the pathology within their brains) in order to target them with potential disease-modifying treatments much earlier, in the hope of preventing or delaying the onset of symptoms rather than of 'curing' what can be conceived of as a very advanced disease by the time people first become symptomatic. Certain types of nuclear medicine brain scans are increasingly being used to identify such currently healthy 'amyloid carriers' in order to target them in treatment studies hoping to prevent progression to symptomatic illness.

Prevention of Alzheimer's disease

If prospects of a cure for symptomatic illness are indeed unrealistic, is there anything that can be done to minimise our own risk of developing symptoms of Alzheimer's disease? The development of a cure is certainly not the only thing that has the potential to impact on the rates of Alzheimer's disease into the future. Given that the biggest single risk factor is old age, and that the prevalence

increases exponentially with each decade of advancing age, it can readily be demonstrated mathematically that the total number of cases in the community could be almost halved if we, as a society, are able to achieve a goal as modest as a five-year delay in the onset of symptoms.[2]

The risk factors for Alzheimer's disease are well known. While older age is the single largest risk factor, this, along with family history, is unmodifiable. The possession of certain gene combinations, specifically the presence of two copies of a gene known as ApoE4, which is involved in cholesterol metabolism, can also increase risk, but is unmodifiable. The other major medical risk factors that are known include high blood pressure, raised cholesterol, and smoking, all of which are amenable to modification. These are all major risk factors not only for Alzheimer's disease, but for vascular dementia, heart attacks and stroke, all of which are, in themselves, major treatable causes of illness and disability that increase with age.

The cholesterol link is intriguing. Amyloid protein is formed by the cleavage of a precursor protein (rather unimaginatively named 'amyloid precursor protein', or APP) that is incorporated into cell membranes. The site at which APP is cleaved determines the molecular length of the amyloid that is produced, with only certain fragment lengths being predisposed to precipitate out into the amyloid plaques associated with Alzheimer's disease. The site of cleavage relates directly to the amount of cholesterol that is stored within the cell membrane, which is itself related to the cholesterol levels in our blood. A lower blood cholesterol results in a thinner cell membrane and a lower likelihood that the abnormal, plaque-promoting form of amyloid will be produced. There is some evidence that taking cholesterol-lowering medications known as statins can, in itself, lower the subsequent risk of developing Alzheimer's disease and other forms of dementia.[3] While there have been some concerns raised in the media that these drugs can themselves be associated with cognitive side-effects, it

would appear that such problems are rare, reversible on stopping the drugs, and are unrelated to dementia.

It is hypothesised that the amyloid proteins in the brain cause their damage to cells by the interaction of various metals that bind to amyloid (among them copper, zinc, lead, iron and aluminium) with the oxygen in our bloodstream to produce oxidative by-products called free radicals. These free radicals, chief among which is hydrogen peroxide (commonly used as hair bleach), damage neuronal membranes, leading to a progressive disruption of cell function that leads ultimately to brain cell death. In the test tube, at least, hydrogen peroxide production in Alzheimer's disease-affected brains can be vastly reduced by the addition of various antioxidant compounds, all of which are relatively cheap and readily available without prescription. These antioxidants include such things as Vitamin C, Vitamin E, Vitamin B12, folic acid, selenium, curcumin (a component of curry powder) and co-enzyme Q10. Unfortunately, the clinical trials that would be needed to demonstrate the potential effectiveness of antioxidant cocktails as a preventative treatment for Alzheimer's disease will never be done, largely for reasons relating to prohibitive costs, so taking antioxidants in a preventative way remains a leap of faith at present, despite being supported to an extent by basic science.

We discussed earlier the fact that there is a massive redundancy of unused processing power, or cognitive reserve, within our normal healthy brains. It is well-known that those with higher IQs are at a lower risk of being diagnosed with Alzheimer's. This is not because they are any less likely to accrue amyloid and tau within their brains, but because of the increased cognitive reserve that the possession of a higher IQ implies. Those with greater cognitive reserve are better able to compensate for the ravages that any pathology might commit, and thus to remain symptom-free for longer, to the extent that they are perhaps more likely to die of something else before they lose sufficient neuronal power to develop symptoms of memory loss.

While that's fine for those who are endowed by nature with high intelligence, what does this knowledge suggest for the rest of us mere mortals?

Perhaps the answer might lie in brain training. We observed earlier that, despite an overall decrease in brain cell numbers over the lifespan, the processing power of the brain lies not so much in the absolute numbers of neurons that we have, but in the parallel processing power with which they are endowed by virtue of their multiple synaptic connections with their neighbours. While we cannot guard against an overall decrease in brain cell numbers as a result of age-related attrition, we can continue to influence the degree to which new synapses are formed, throughout the lifespan. We can do this through by ensuring that our brains continue to be stimulated into our older years. Such stimulation effectively forces the development of new synaptic connections between neurons, regardless of brain cell numbers. Anything that challenges our brains, forcing adaptation or new learning, can be sufficient to promote the development of new synapses in this way.

Most people receive cognitive stimulation through their work. The daily adaptive challenge that our employment poses keeps us cognitively active and enforces ongoing synaptic development. Thus, retirement is a particularly dangerous time for the ageing brain. While we associate retirement with the opportunity to relax and enjoy the fruits of our labours, there is a very real risk that the loss of cognitive stimulation that might accompany this life change can pose real dangers to our cognition in later years. Perhaps the worst thing that we can do upon retirement is to resign ourselves to 30 years of daytime television! There is some good evidence that cognitive stimulation into old age can help delay a diagnosis of dementia.[4]

Cognitive stimulation does not require one to invest in any of the variety of commercially available brain-training packages that are available. Nor does it have to be onerous or unpleasant. It can involve activities as simple as indulging in a favoured hobby,

volunteer work, learning art, a language or a musical instrument, or even reading a book such as this. The time to stimulate your brain in these ways is now, while we remain healthy. Unfortunately, by the time we develop those symptoms of cognitive decline that accompany a diagnosis of dementia, the opportunity has passed, and our ability to compensate for neuronal damage has, by definition, been exceeded.

There seems to be a significant benefit to be gained from regular physical exercise as a preventive treatment for dementia, also, with a risk reduction in the order of one third being reported.[5] The precise mechanism of this risk reduction is unclear, but may well relate to the benefits of exercise on blood flow to the brain.

While there are clearly things that we should be striving to accomplish in order to preserve brain health into old age there are, equally, things that should be avoided if we are to best preserve cognitive function into old age.

Alcohol is thought to have been consumed by man for at least 10,000 years. The acute effects of alcohol intoxication can be understood to a great extent by their impact on the frontal lobes of the brain. The frontal lobes are the most recently evolved parts of our brains, and their development in many ways is what separates us from the lower species. The frontal lobes are responsible for what are known as the executive (or higher) functions of the brain, and include such cognitive domains as planning and organisation, logical reasoning, abstract thought, control of impulsive behaviours and of emotions, the production of speech and language, fine motor coordination, initiative, motivation, drive, problem solving, attention and concentration, and insight (the ability for each individual to act as an objective judge of his own behaviour). Alcohol acts acutely to inhibit these frontal lobe functions, which can readily be recalled by the simple expedient of holding a mental image of an intoxicated person in mind.

The chronic cognitive effects of alcohol mimic to a large extent those of acute intoxication. While to some extent the cognitive effects of long-term alcohol abuse can be reversible after periods of prolonged abstinence,[6] this is a long-term process that often leaves residual deficits detectable after many years. Alcohol can also cause a long-term irreversible dementia known as Wernicke-Korsakoff syndrome, which alcohol precipitates via interference with the metabolism of thiamine (vitamin B1).

While alcohol does not appear to kill brain cells directly, it does appear to reduce their ability to form new synapses, which we have indicated is an important facet of preserving brain function into old age. How much alcohol, then, is it safe to drink? Currently, the National Health and Medical Research Council recommends a daily limit of no more than two standard drinks per day, with an added recommendation that to avoid alcohol-related injury no more than four standard drinks should be composed in one sitting.

Conclusion

The fear of developing Alzheimer's disease and other dementias is cited by many older persons as being greater than their fear of cancer.

While the prospects of a cure for dementia remain some decades away at this time, our knowledge of the common forms of the disease is growing rapidly. In parallel with this, our awareness of those modifiable factors that promote the maintenance of brain health is ever increasing. For most of us, addressing these risk factors from middle age onwards is the best protection we might have from those common age-related diseases that rob our brains of their vitality.

Endnotes

1. Summary of dementia statistics in Australia. Retrieved from http://www.fightdementia.org.au/understanding-dementia/statistics.aspx

2. V Vickland et al., *Modelling the impact of interventions to delay the onset of dementia in Australia: A report for Alzheimer's Australia*, Alzheimer's Australia, Brisbane, Australia, 2012.
3. KJ Swiger et al., 'Statins and cognition: A systematic review and meta-analysis of short- and long-term cognitve effects', *Mayo Clinic Proceedings*, vol. 88, no. 11, 2013, pp.1213–1221.
4. RS Wilson et al., 'Cognitive activity and the cognitive morbidity of Alzheimer disease', *Neurology* , vol. 75, no. 11, 2010, pp. 990–996.
5. EB Larsen et al. 'Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older', *Annals of Internal Medicine*, vol. 144, 2006, pp. 73–81.
6. HF Moselhy et al., 'Frontal lobe changes in alcoholism: a review of the literature', *Alcohol and Alcoholism*, vol. 36, no. 5, 2001, pp.357–368.