Journal & Proceedings of the Royal Society of New South Wales, vol. 157, part 1, 2024, pp. 81–84. ISSN 0035-9173/24/01081-04

Brain cellular ageing

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My specialty is in neurodegenerative diseases, but I'm not telling you anything about that except in a very broad sense. What I am going to concentrate on telling you about is how your brain ages and the cellular consequences of the ageing process on the brain. There are a few myths about brain ageing. Some of them are that (1) there is substantial brain loss, and that's a normal part of ageing, and that (2) all protein deposition in the brain — George has suggested a couple of times today — is abnormal, and (3) because of these changes we can all expect to have significant intellectual decline as we age. At the end of this presentation, I'll show you that these are myths. At the moment, we don't have good evidence for any of them.

You heard about body size in terms of animals and how big a brain can be compared to the animal size. It happens in humans that your brain is related to the size of your body, and it looks as if when we age there's a reduction in brain size. But these are cohort studies. If you've gone through deprivation, then your body size will be impacted. And since brain size is directly related to body size, it doesn't necessarily mean that older people have reduced brain size compared to what they were 10 to 25 years ago.

What determines brain size in a human? Is it bigger cells in the brain (which would mean with age people who have bigger cells might have more trouble with the metabolism of a bigger cell) or is it that there are more cells? It's actually more cells. A long time ago we showed that the size of the brain is related to the number of cells in the brain. Since then, there have been a number of studies that have shown the same thing in humans.

The studies show there isn't a loss of brain cells with age, so the loss of neurons when we measure those things is more likely to be due to a disease trigger rather than just ageing itself or abnormal protein deposition. Even though I said that you don't lose neurons, there is a change in brain structure. You might not lose actual numbers of neurons in the brain, but the connectivity — the white matter — is the place that reduces with age, so you do have a reduction of the structure of the brain with age. This suggests the main thing that might happen with age is that the connectivity of the brain changes.

There are many cells that are necessary for brain connectivity. In the white matter, neurons are not one of them. Neurons have axons that go through the white matter. The white matter is mainly made up of glial cells which do a number of things. There's microglia, which get rid of debris in the brain. There's oligodendrocytes, which insulate the axons so that they can conduct the electricity faster to get to the synapses to have the messages go through. And there's astrocytes, that tile the entire brain that are necessary to deliver the oxygen, glucose,

1 This is an edited transcript of the address [Ed.]

and everything that every cell needs in the brain. There's a number of brain cells that are not neurons that are really important for maintenance of the white matter, and it looks like these are the cells that are going to be most affected during ageing and so are going to affect connectivity.

There's some studies that are now coming out, using quite new technologies (such as genetic transcriptomics), showing mouse brains over time — we have done most of our research on the mouse brain. These studies show that the glia, rather than neurons, have a widespread ageing signature and that the neurons themselves didn't actually change over time with age in the mouse brain. The molecular ageing was particularly accelerated in the white matter, which is where in humans we measure age-related changes most. There's a tenfold increase in age-related signatures in the white matter compared to other brain regions, particularly cortical regions which we've been talking about.

In the white matter, the microglia are most affected, but they're not the only ones: mature oligodendrocytes, the endothelial cells, astrocytes, as well as progenitor cells are all affected. There's particularly a mitochondrial gene downregulation. The mitochondria provide the energy of every cell. Within the white matter, they're the things that are mainly affected.

Now the glia in humans are much larger. The microglia are relatively conserved, but the astrocytes are much larger than in the mouse and much more complex. Astrocytes in the human brain are 15 times larger in volume than in the mouse, and they have 10 times more processes. There are two to three subtypes of astrocytes in humans and primates that we don't see in other animals. They enhance higher-level neuronal functionality, so they're really important, these cells. The compact myelin is substantially increased with the increase in processes of the astrocytes.

There's a direct connection to the connectivity, the electrical conductance through to neurons. They're important cells. Glia are enlarged and are more complicated in humans compared to the animals. Therefore, you might expect an even greater age-related effect on these more complex neurons. The white matter glia do quite a lot of things: you can manipulate neuronal activity both chronically and acutely using bioelectric networks; the bioelectric networks in the brain are maintained by these citium of glia; the astrocyte networks can increase activity — they couple the activity of populations of non-synaptically connected neurons via chemical messages, ATP secretion, and calcium elevation; they affect activity-dependent myelination that maintains our connectivity; and the microglia on the reverse side can suppress neuronal activity through some of the same mechanisms and can limit activity-dependent myelin growth.

There's a yin and yang of how these cells might be affected and how they connect — we think of neurons as having connectivities that are direct. These cells can manipulate multiple non-connected neuronal networks in a different way. That's what happens when we age. There's a group of cells that people don't usually talk about that are quite substantial in humans. We have a lot more myelin than nearly anything. Our myelin is most developing during puberty. Some of the other things that we've been talking about today: myelination may

have a direct effect on these glial cells but I'm going to talk about how this might relate to the loss of the neurons which is related to diseases of the brain, the age-related degenerative diseases.

Age-related proteins that deposit in the brain

There are age-related proteins that deposit in the brain — George was alluding to some of these. The two most common are the A-beta peptide and the Tau protein. The A-beta peptide isn't actually found in neurons, it's not found in any cells. It's found extracellularly, and so it accumulates in the extracellular spaces, rather than affecting any particular neuron or any particular cell. You might be dismayed to know that at least 50% of the population surviving to older age will have an extracellular deposit of these A-beta peptides, but not 50% of the population has a disease of the brain. While Tau's the same, it's a microtubular associated protein that's important for your axon stability and most people — even young people — will have some Tau deposition in their brain. Protein depositions do occur in the brain with ageing, but not all of the people that have protein depositions will have any significant neuronal loss.

Neuronal loss is a prerequisite for a neurodegenerative disease. I've got a map of the normal age-related Tau distribution, and 50% of the population will have some Tau deposition at the age of 50, so I assume everyone in this room some Tau deposition. I don't think it's bad — it's how much you have that's a problem, not how little. By age 80, 70–80% of the population will have some Tau deposition. This is really a normal age-related protein that deposits in some of the neurons in our brain, and we can all look forward to having it. It starts as early as before age 20, so people can have it very early. It doesn't necessarily mean they're going to get a degenerative disease. It's how many you have. You need to have lots of tangles to have dementia.

We can say exactly the same about the extracellular protein, A-beta. 50% of the population by the age of 70 will have some of that in your cortex, so again it's an age-related protein deposition and it's how much you have and how it might affect the neuronal populations associated with dementia.

Is a little bit of abnormal protein deposition enough?

A little bit of the abnormal protein is probably not enough: it's the amount of protein, but also other things that happen. Two detailed studies looked at people who had only mild cognitive impairment (MCI). While some people didn't have any cognitive impairment, they were followed over time. These people are thought in the literature to have a lot of these protein depositions in the brain, but 74% did not have enough protein deposition in the brain to have a neuronal problem, such as Alzheimer's disease. More had cerebrovascular pathologies, and they did have Tau, but as I said, lots of people have Tau. 2.2% had other pathologies (non-Alzheimer's) and 25% had some Alzheimer-type pathologies that Tau and A-beta. The majority didn't have what we would have expected to have as their primary underlying pathology associated with what people think of as dementia in terms of Alzheimer's disease. This suggests — and it's much more prevalent — that just having the

Tau and the A-beta is not sufficient, and in most instances you will have multiple proteins going wrong or having a vascular in problem as well. You have to have multiple things happening in the brain for it to have an effect on neuronal degeneration. It's the severity and the numbers of pathologies.

Now the other thing is that there are distinct glial changes that also happen in these neurodegenerative diseases, which no one really talks about much. In fact, the glial pathologies are more likely to be distinct between the different types of diseases. For example, there are inclusions of alpha protein in oligodendroglia, which is a synaptic protein, and there are the myelinating cells in the brain. We have a protein in an abnormal position in cells that we usually wouldn't see these things. There are astrocytes in patients that have Parkinson's Disease. Now the neurons with the astrocytes are probably not working properly because they have an abnormal protein. The neuron is probably not working properly because its astrocytes are a problem, more so than the neuron itself.

Hence, glia are affected. And then there's completely different types of Tau that happen in different types of the astrocytes in the brain. These are all different types, such as primary tauopathies with astrocytes. The actual neurodegenerative disease is defined by their astrocytic pathology. ARTAG is a very familiar pathology that's seen in chronic traumatic encephalopathy. You'll hear a lot more about astrocyte changes that are to do with longer-term cognitive changes in the brain of people who have had environmental impacts in terms of head injuries or sporting injuries.

Glial cells in the brain are most affected by ageing but neuronal loss defines degenerative diseases

Glia cells are the most affected in the brain with ageing. But neuronal loss and a lot of the cognitive changes are because neurons don't connect, don't fire properly, and the neuronal loss defines degenerative diseases.

To conclude, if we now think about what this might mean, brain ageing mostly affects the white matter, while neurodegeneration mainly affects grey matter structures (in degenerative diseases it's regional). The type of neuron or the function of the neuron is important. Mechanistically that suggests that the connectivity between regions is probably key to disease vulnerability. These are all age-related neurodegenerative diseases, so having a problem with the white matter and the glial connectivity is a predisposing factor. Humans have evolved larger syncytiums of astrocytes and myelinating oligodendrocytes. Mechanistically that suggests that these syncytiums are important cognitively. Something that hasn't been looked at so much: age-related neurodegenerative diseases all have abnormal protein depositions, and the neurons are largely resistant to increased amyloid and Tau protein depositions with ageing. Mechanistically that suggests that there's additional cell or tissue changes needed to have neurodegeneration. There are distinct glial cell pathologies that define most neurodegenerative diseases, which is largely still ignored. Mechanistically this supports important roles for glia in neurodegeneration and suggests that pathological dysfunction of different glia impact differently on these neurodegenerative diseases.