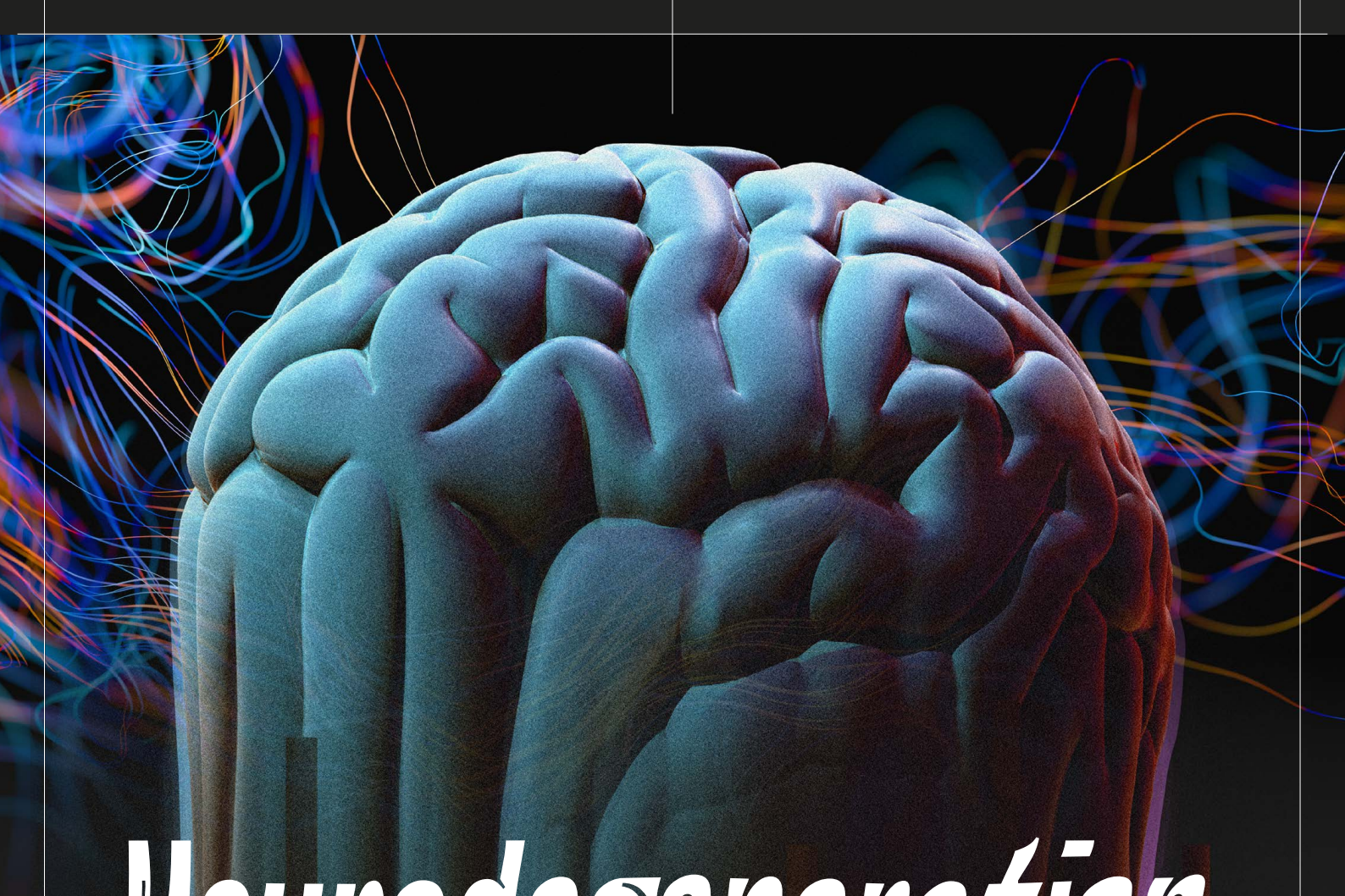


Neurodegeneration

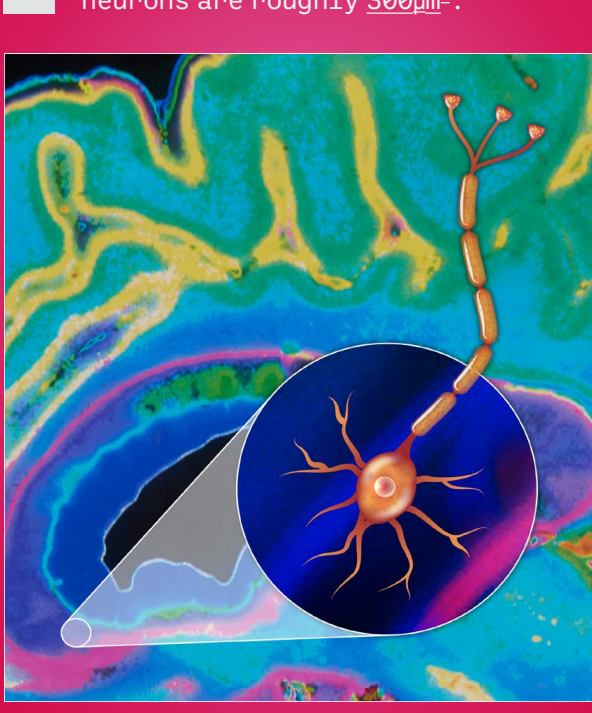
A Closer Look

The burden of neurodegeneration is one that weighs heavily on the world's aging population. To understand why conditions like Alzheimer's disease are so difficult to treat, we must first understand how they affect the brain. In this infographic, we take a deep dive into the degenerating brain, examining the changes that occur at every level.

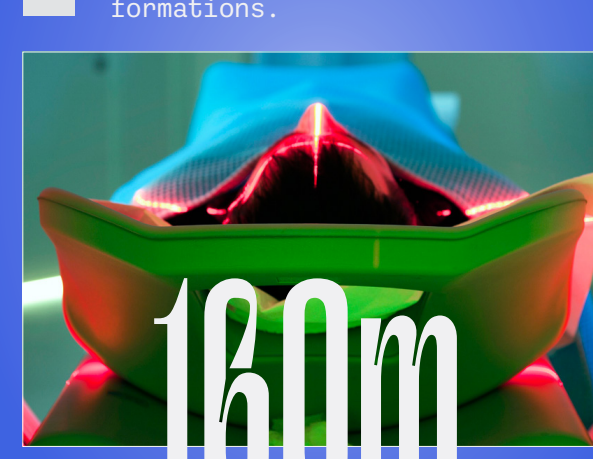
Brain Structure

Neurodegenerative disease involves the death of neurons and related nerve cells.

→ Neurons in the central nervous system (CNS) are microscopic. CA2 hippocampal neurons are roughly 300µm².



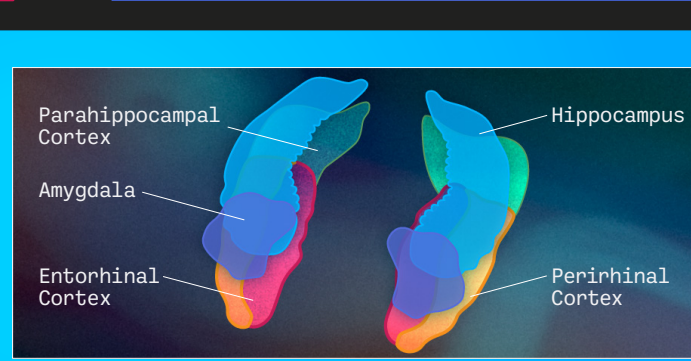
→ But neuronal death is so widespread in the later stages of neurodegeneration that structural changes can be easily seen using imaging techniques. In one study as many as 160 million cells were lost in patients' hippocampal formations.



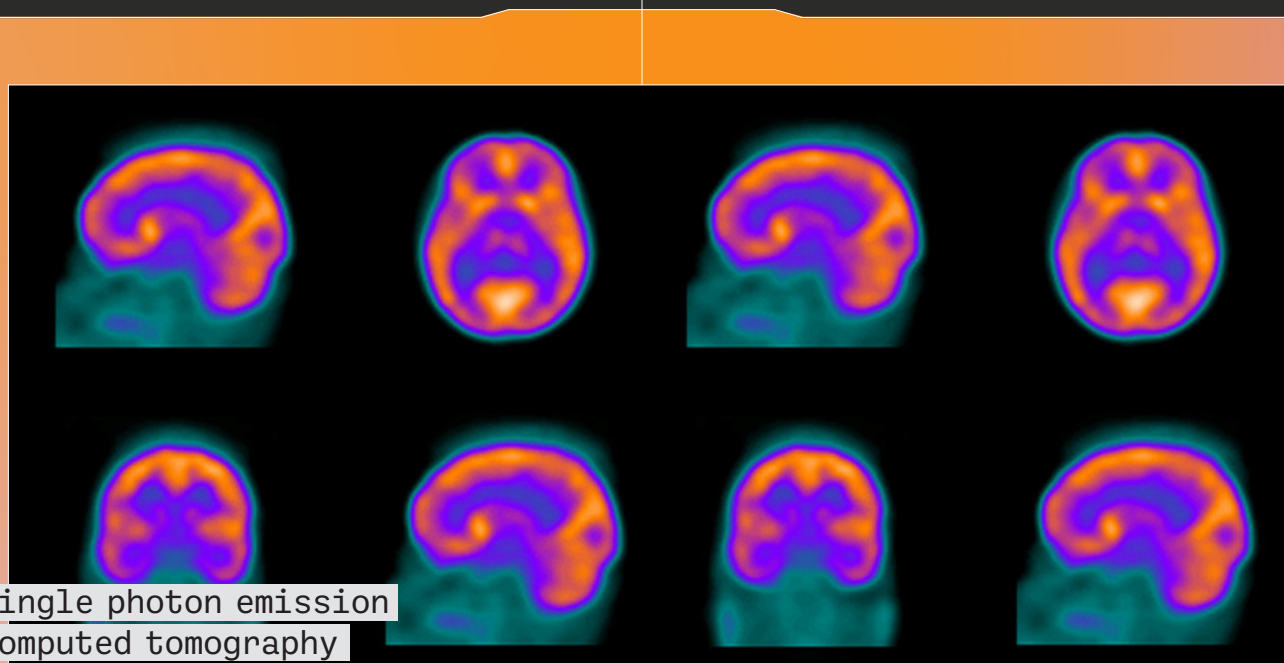
160m

cells lost

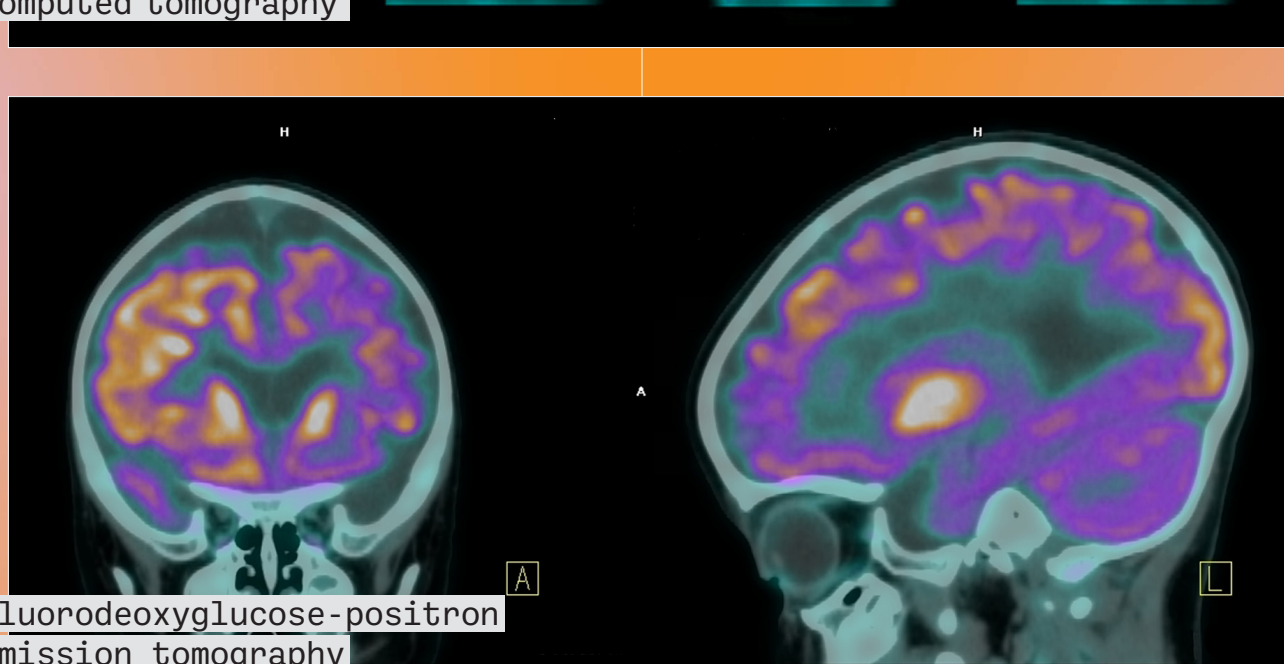
→ This loss of neurons can be measured using imaging techniques such as magnetic resonance imaging (MRI). This is a well-established process that looks at areas of the brain that are heavily affected by neurodegenerative disease, such as the medial temporal lobe.



Neuronal death also results in other global changes, such as lesions that represent clumps of dead cells and reduced cerebral blood flow that can be picked up using techniques such as:



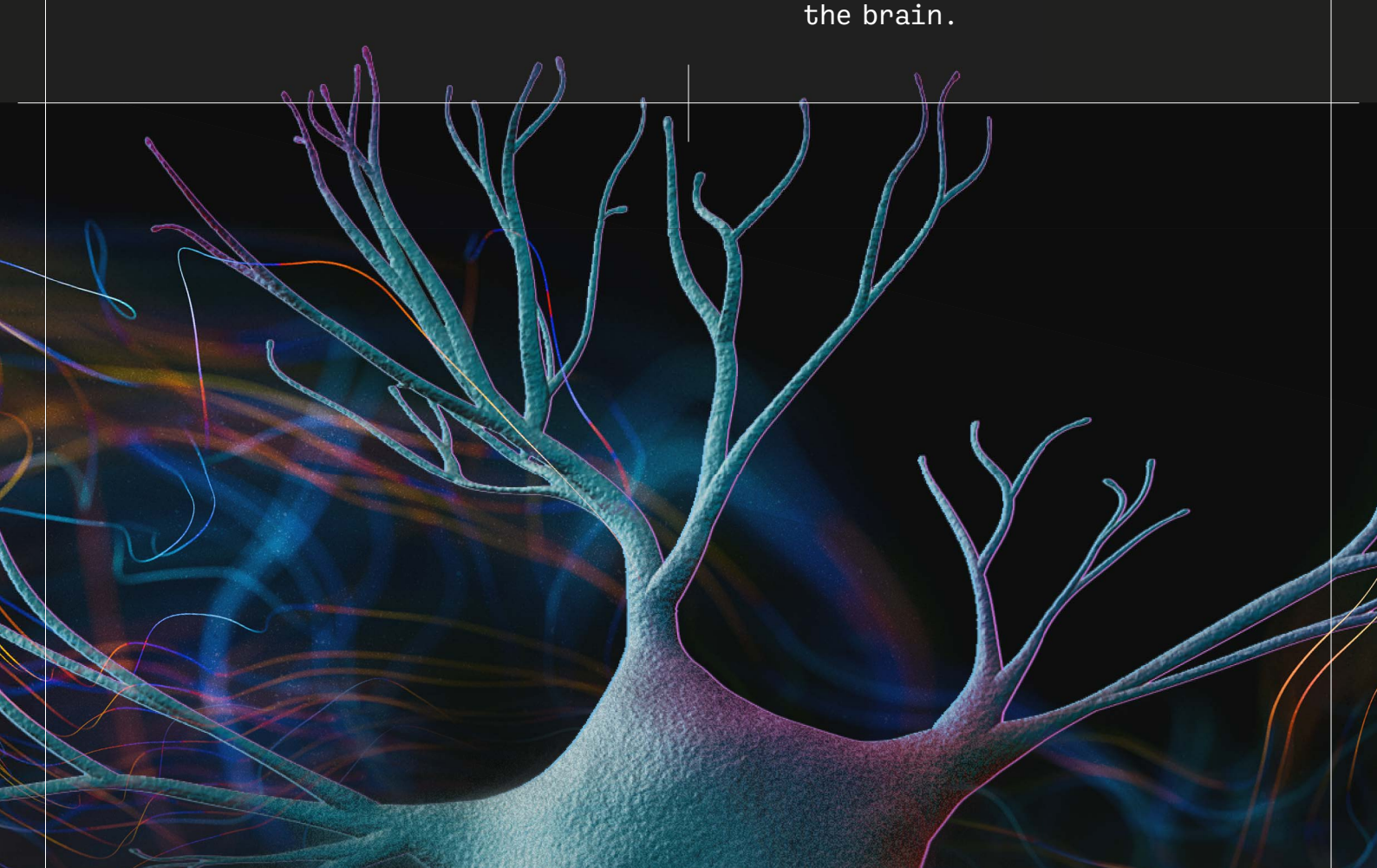
Single photon emission computed tomography



Fluorodeoxyglucose-positron emission tomography

Cellular Changes

Looking more closely at distinct subsets of neurons and glia can reveal a world of detail into how neurodegeneration affects the brain.

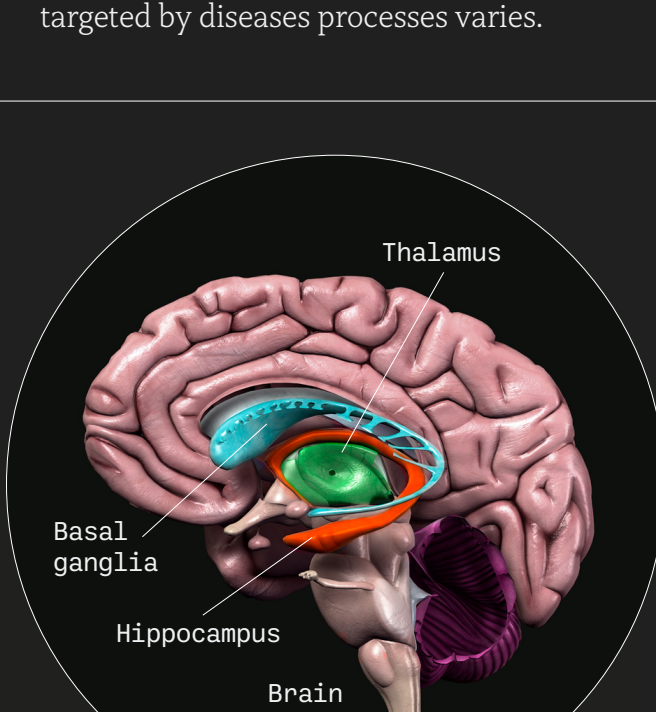


Neurons

A recurring hallmark of neurodegeneration is the spread of protein abnormalities across neuronal populations. These diseases are called proteinopathies.

location location location

Whilst the loss of neurons is common to all neurodegenerative diseases, the type of neuron targeted by diseases processes varies.



Brain stem: Affected by amyotrophic lateral sclerosis and spinocerebellar ataxia

Basal ganglia: Affected by Parkinson's disease, Huntington's disease, Alzheimer's disease and frontotemporal dementia

Thalamus: Affected by Parkinson's disease, Alzheimer's disease and frontotemporal dementia

Hippocampus: Affected by Alzheimer's disease

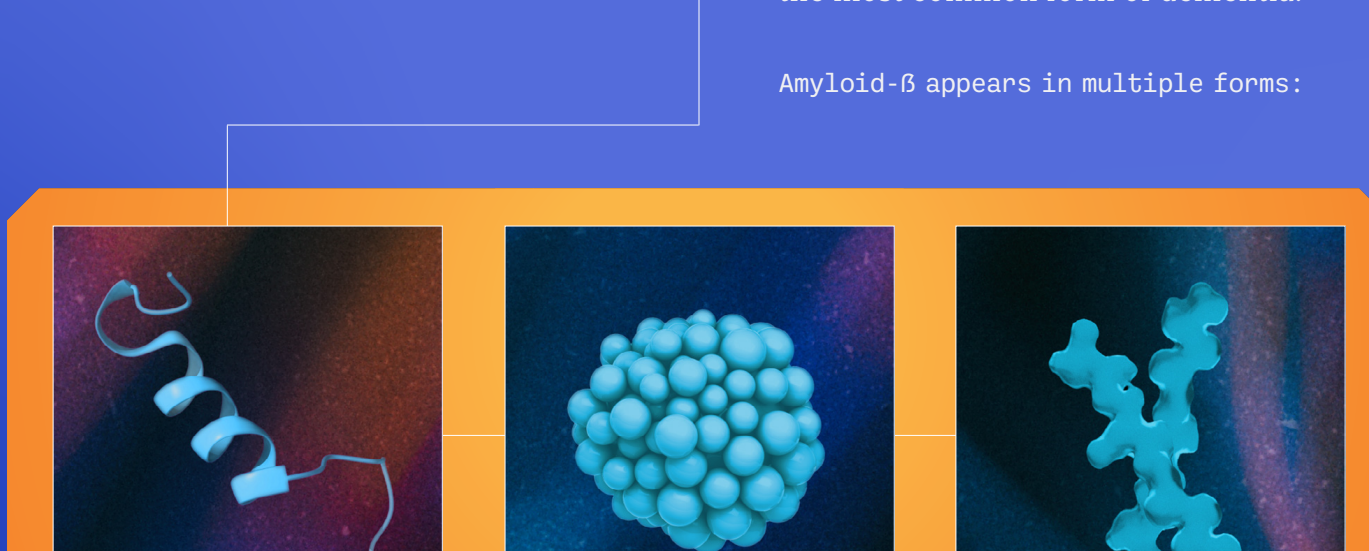
The structures of these protein inclusions are often messy and jumbled. They are composed of neuronal proteins that usually also fulfil roles in healthy neurons, rather than being alien proteins that only appear in disease states.

Common Pathological Proteins

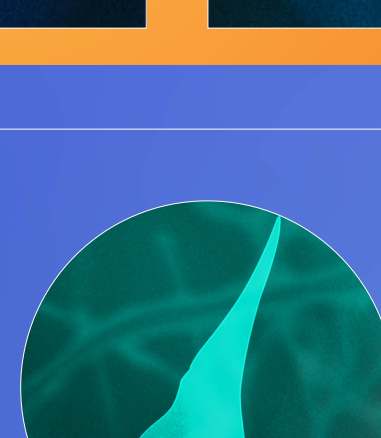
Amyloid-ß

Misshapen inclusions of this protein are one of the key hallmarks of Alzheimer's disease, the most common form of dementia.

Amyloid-ß appears in multiple forms:



It was previously thought that amyloid fibrils, which deposit themselves as plaques between neurons, were the driving force behind Alzheimer's pathology. But new evidence has pushed researchers towards focusing on soluble amyloid oligomers and other pathological proteins.

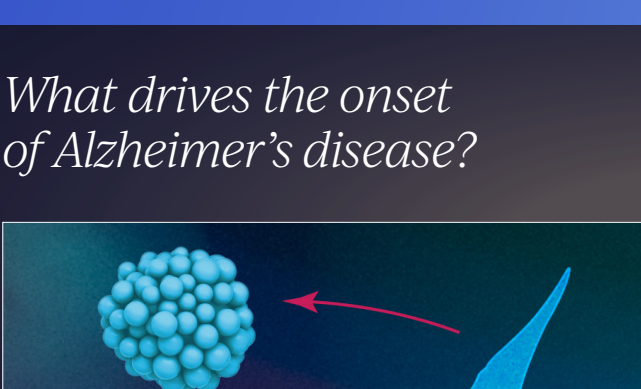


Dementia

Tau

Neurofibrillary tangles of the protein tau, which normally plays a structural role in axons, have recently been shown to be far more predictive of Alzheimer's disease burden than amyloid-ß when imaged using positive emission tomography (PET).

What drives the onset of Alzheimer's disease?



↓ The prevailing view remains that amyloid-ß protein start a cascade

↓ That then induces tau protein changes

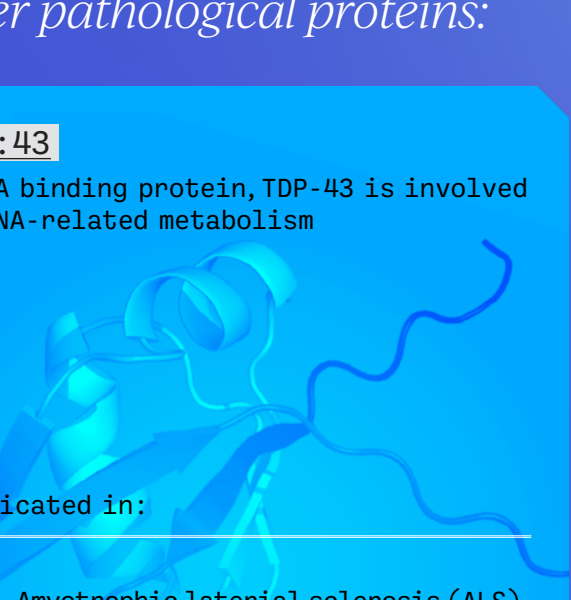
→ Which then feedback to amyloid pathology

It is likely that to cure Alzheimer's disease, the burden of these two proteins will have to be considered together, not separately.

Other pathological proteins:

TDP:43

A DNA binding protein, TDP-43 is involved in RNA-related metabolism



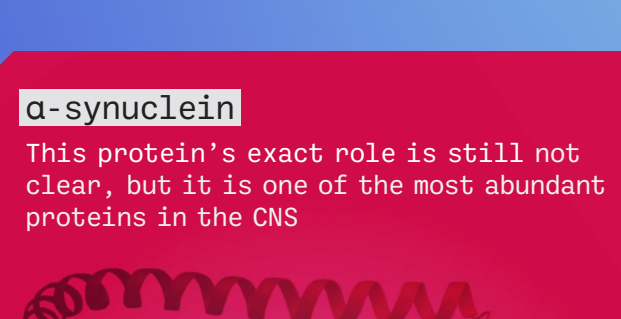
Implicated in:

→ Amyotrophic laterial sclerosis (ALS)

→ Frontotemporal dementia (FTD)

α-synuclein

This protein's exact role is still not clear, but it is one of the most abundant proteins in the CNS



Implicated in:

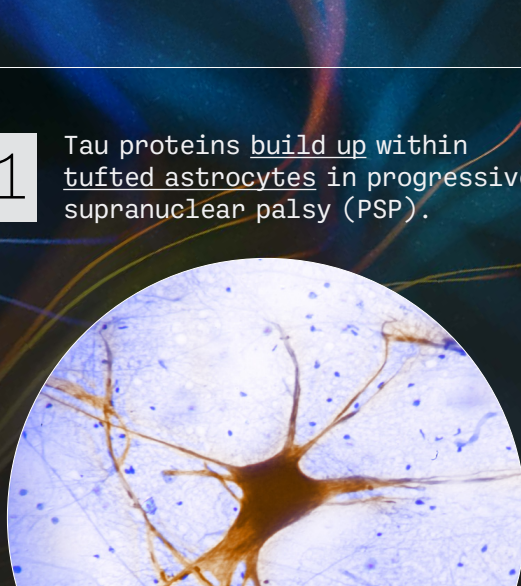
→ Parkinson's disease

→ Dementia with Lewy bodies

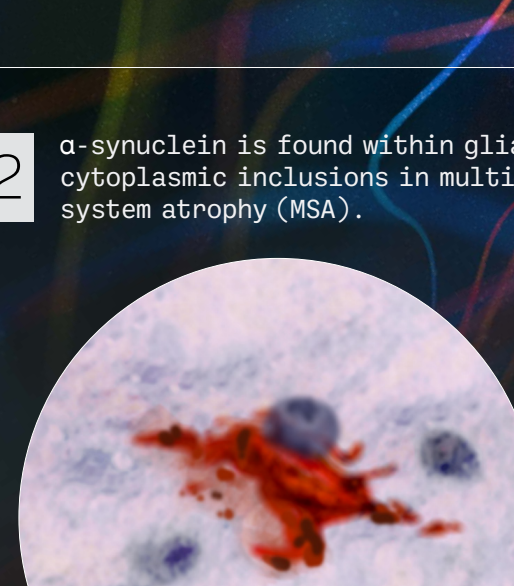
Glia

Glial cells are also widely affected by neurodegeneration.

1 Tau proteins build up within tufted astrocytes in progressive supranuclear palsy (PSP).



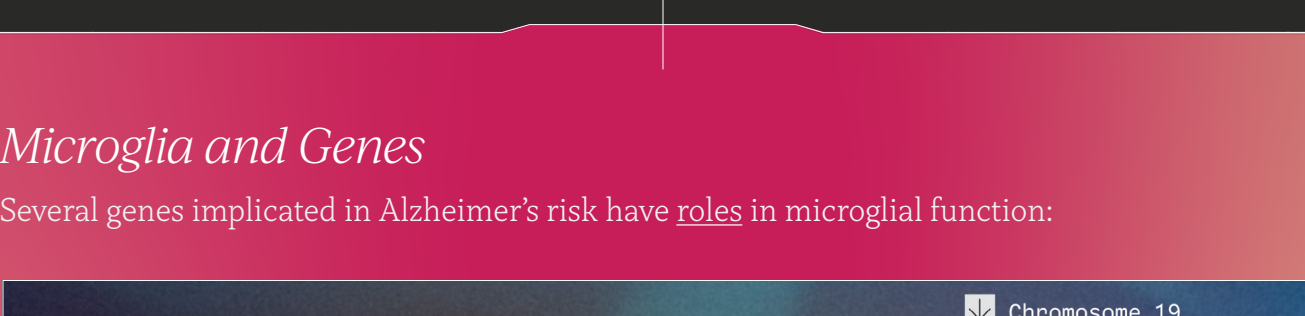
2 α-synuclein is found within glial cytoplasmic inclusions in multiple system atrophy (MSA).



But of increasing interest is the role that glial cells play in responding to neurodegeneration.

Microglia and Genes

Several genes implicated in Alzheimer's risk have roles in microglial function:



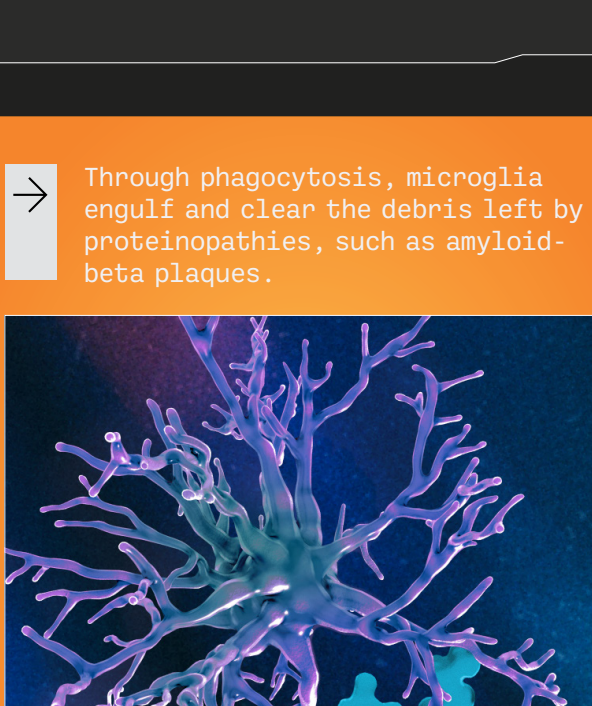
APOE: Moves amyloid-ß protein to receptors for clearance

TREM2: Plays roles in chemotaxis and phagocytosis

INPP5D: Produces the protein SHIP1, which modulates microglial endocytosis and phagocytosis

Microglia, the brain's resident immune cells, are a common finding at the sites of neurodegenerative damage. It's now widely thought that microglia protect against Alzheimer's disease pathology, but can also accidentally aggravate disease as well.

→ Through phagocytosis, microglia engulf and clear the debris left by proteinopathies, such as amyloid-beta plaques.



A landmark genomics study of nearly 75,000 individuals found risk genes for Alzheimer's disease were involved in the immune system.

75k

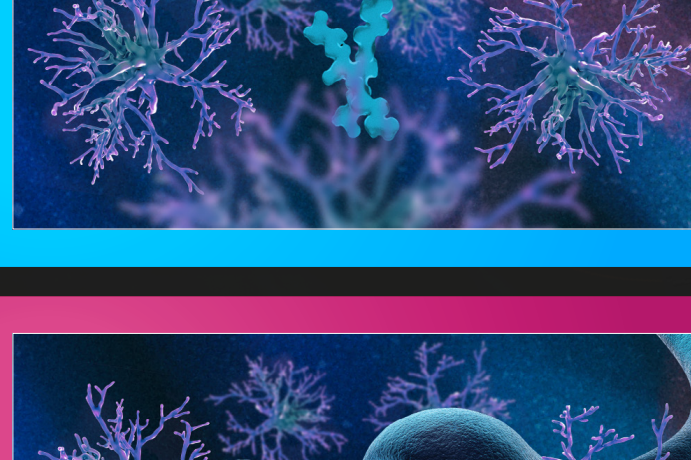
individuals

→ There is also evidence that microglia assemble around amyloid-ß plaques, packing and sequestering them to stop spread and protect the brain.

→ However, there may be a flip side to this protective function.

In a healthy brain, microglia regularly devour synapses as part of a "pruning" process that involves the immune complement system.

Overzealous synapse-eating by microglia may lead to pathological synapse loss, which is closely linked to neurodegenerative disease progress.



At a global and cellular level, neurodegenerative diseases remain a complex challenge. Through better understanding of how neurodegeneration begins, the key molecular players involved and the biological changes they produce, we can come closer to effective therapies for these conditions.