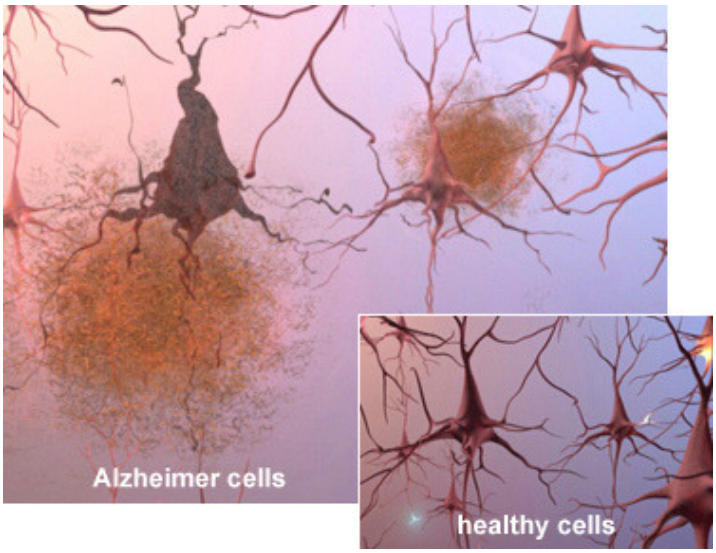
Alzheimer’s Disease

Dementia is an umbrella term used to describe a group of cognitive, behavioural and psychological symptoms that affect a persons ability to function and live independently. Alzheimer's disease (AD) accounts for 50-75% of dementia cases. AD is an age related progressive neurodegenerative disease of the brain that is characterized by the deterioration of memory and other cognitive skills that eventually leads to dementia.

The greatest risk factor for developing AD is advancing age: for every 10 years after the age of 65, the risk doubles. The second greater risk factor is family history (genetics). Alzheimer's presents in two forms: early onset AD (EOAD) and late onset AD (LOAD). EOAD develops before the age of 65 and accounts for less than 6% of all cases. It is primarily caused by inherited mutations in genes encoding for amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2). LOAD accounts for more than 90% of AD cases and occurs later in life (>65 years), with multiple risk factors contributing to disease development. One of these risk factors is the presence of certain APOE genotypes. APOE codes for apolipoprotein E (ApoE) which is a major cholesterol carrier in the brain that supports injury repair and lipid transport. Existing as three polymorphic alleles (ε2, ε3 and ε4), the presence of the APOE ε4 (epsilon 4) genotype greatly increases the risk of developing AD. Carriers of two copies of the APOE ε4 allele have a ten fold greater risk of developing AD than non carriers.

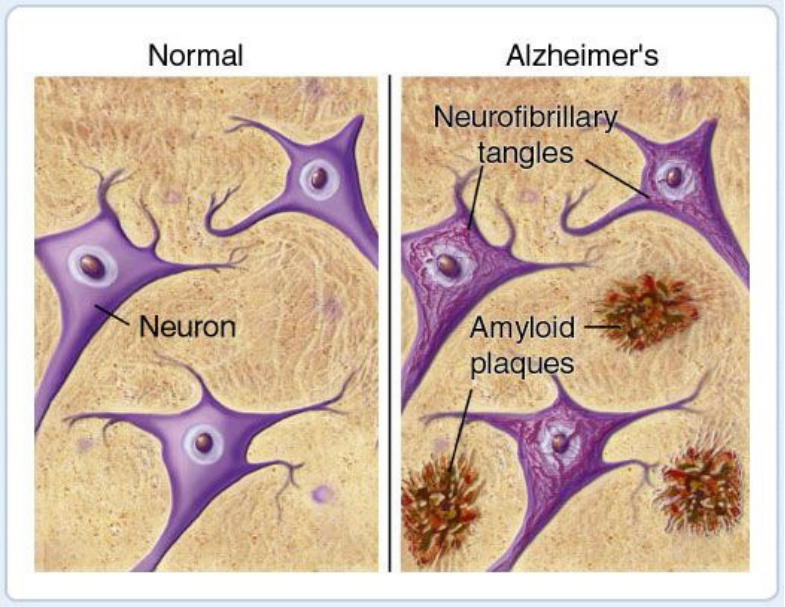
ApoE also regulates the aggregation and clearance of amyloid beta (Aβ) proteins. Aβ proteins are formed by the cleavage of APP: common membrane proteins that are concentrated at neuron synapses. When APP is cleaved by alpha (α) - secretase, soluble APPα is produced and utilised for neuronal plasticity and survival. However, when APP is sequentially cleaved by beta - secretase and then gamma - secretase, two main forms of Aβ peptides are generated: Aβ40 and Aβ42. Aβ40 is more abundant however Aβ42 is more toxic as its hydrophobic nature makes it prone to forming fibrils that gradually aggregate to form plaques. The imbalance between Aβ protein production and its' clearance leads to an overexpression of Aβ that over time decreases the dendritic spine density of neurons in the brain. As such, the overexpression of Aβ is currently believed to be the key trigger of AD pathogenesis as summed up by the currently leading Amyloid Cascade theory.



The hypothesis posits that the overproduction of Aβ leads to a downstream cascade of neuro-toxic events that includes the activation of an inflammatory response. Initially inflammation contributes to synaptic function and maintenance, however over time chronic inflammation perpetuates the cycle of further Aβ production leading to Aβ-induced phosphorylation of tau. Tau are microtubule-binding proteins that keep microtubules in a structurally assembled state to enable the passage of neurotransmitters and nutrients within neurons. Phosphorylation of tau enables its functionality, however in AD, tau becomes hyperphosphorylated 3-fold more than normal brain tau causing tau proteins to detach from microtubules and gradually aggregate as paired helical filaments that form neurofibrillary tangles (NFT's).

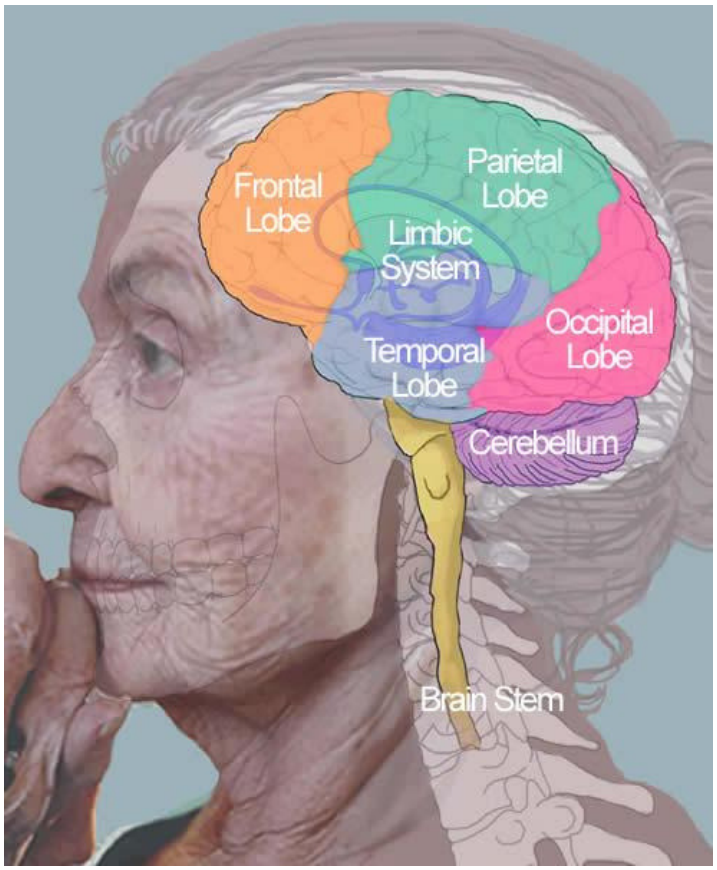
"AD is characterized pathologically by cortical atrophy, neuronal cell death, neuroinflammation, synapse loss, and the accumulation of two definitive pathological lesions: neurofibrillary tangles and senile plaques" (Koffie, Hyman and Spires-Jones, 2011). Composed of hyperphosphorylated tau proteins, NFT's aggregate within neurons, whilst Aβ plaques composed of Aβ peptides aggregate between neurons. NFT's and amyloid plaques follow distinct topographic patterns during disease progression. NFT's are primarily found in the limbic and associated cortices, becoming most densely located in the pyramidal neurons of the medial temporal lobe, whilst amyloid plaques are far less abundant, occupying only 5% to 10% of the total cortical mantle. Interestingly, it is the density and distribution of NFTs that correlate with the severity of AD symptoms. As NFT's spread through the brain, clinical symptoms increase as their cortical correlates deteriorate. Although neuronal atrophy is a core part of the disease process, it is the loss of synaptic connections that correlates with cognitive decline as information is "stored in the brain by multiple synaptic mechanisms... such synaptic plasticity is thought to be fundamental to learning and memory in the brain" (Yu and Lu, 2012).

As Alzheimer's advances, neuropathological changes progress through the brain in a bilaterally symmetrical fashion. By advanced AD, the brain shows dramatic weight loss and atrophy that is more pronounced in the frontal, parietal and temporal lobes, leaving the primary motor and sensory cortices relatively spared. These structural changes in the brain manifest clinically as progressively worsening symptoms with the eventual outcome of clinical dementia.



AD progresses along a disease continuum, beginning with a preclinical phase before progressing through the early, mid then final stages of the disease. Alzheimer's pathology is believed to start decades prior to the onset of clinical symptoms. Neuropathological changes initially start in the entorhinal cortex and the hippocampus of the medial temporal lobe. Gradual deterioration of the hippocampus leads to memory loss, the 'typical' first symptom of AD. In the early stages of AD, most recent events and memories are forgotten whilst autobiographical and other long term memory remain relatively intact. Initial short term memory loss presents daily in many ways such as becoming lost to or from a familiar place, difficulty following conversation, forgetting appointments and events, getting days mixed up and misplacing items. Unable to action previously seamless tasks due to an increasingly unreliable memory, patients experience growing confusion and disorientation. As pathology spreads to the limbic system, emotional outbursts of anger, blaming and suspicion emerge. Damage to the amygdala followed by the frontal cortices leads to various neuropsychiatric symptoms such as agitation, anxiety, delusions, hallucinations, paranoia and wandering. Behavioural symptoms such as apathy, depression and disinhibition are very common and gradually increase during disease progression. More than 70% of patients experience apathy which correlates to dysfunction of the frontal anterior region of the brain.

In the mid to late stages of the disease, cognitive symptoms worsen as neurofibrillary degeneration and pathological changes progress through the medial temporal lobe, parietal lobe and frontal lobe. Deterioration of the medial temporal lobe correlates to long term memory loss, typically beginning with losses to episodic memory. Over time, episodic memory eventually deteriorates to a point where patients can no longer recall past personal events, like the death of a relative or where they were wed. Damage to the visual system of the temporal lobe compromises facial and object recognition resulting in an inability to recognise family or friends, use familiar items like scissors, or differentiate between a fork and a brush. With atrophy to the parietal lobe, losses to semantic memory affects language, memory, the ability to calculate, draw, read and write. Verbal fluency and vocabulary declines as patients struggle to describe colours, find words and name items. An inability to perform activities in a sequence compromises many aspects of daily living from counting and cooking to getting dressed.



As the disease progresses, pathology spreads through the frontal lobe impairing the ability to organise and plan. Various symptoms present such as being unable to follow or respond to conversation, sustain attention or think consecutively. Patients may ask the same question repeatedly, experience distorted or false memories and display very noticable behavioural changes with an eventual inability to control emotions. In the late stages of AD, speech deteriorates to a point where it can become inarticulate and devoid of content or no longer speech at all, but rather repetitive speech sounds. Errors in judgement become pronounced in areas such as interpreting colour, contrast, objects, place, time and navigating three dimensional space and stairs. Linked to damage to the frontal areas and parietal lobe dysfunction, gait apraxia is a persistent feature of AD which increases in the later stages of the disease, resulting in falls, fractures and an eventual reliability on walkers and wheel chairs for mobility. As long term memory further deteriorates, settings that were once familiar become unfamiliar leaving patients disoriented and sometimes asking repeatedly to 'go home' as they seek the familiar. As the basal ganglia and cerebellum are relatively spared from atrophy in the early stages of AD, procedural memory remains mostly intact enabling patients the ability to walk and participate in life learned skills such as knitting. By the end stages of AD dementia, procedural memory is the last to deteriorate resulting in eventual immobility and even swallowing difficulties. By the end stages of AD, patients are bed bound, incontinent and non verbal, requiring full time assistance with all aspects of daily personal care. From diagnosis to death, the average duration of the disease is 8 - 12 years.

Alzheimer's is a multifactorial disease with many genetic and non genetic factors contributing to pathological changes. Co-existing co-morbidities also contribute to overall cognitive and functional decline. Although the ‘typical’ symptoms of AD are shared, each person’s lived experience of AD is unique.

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