Brain Pathology

Alzheimer's Disease (AD) is a specific neurodegenerative disease and is the most common cause of dementia in old people. Clinically, it is characterized by loss of memory, inability to learn new things, loss of language function, a deranged perception of space, inability to do calculations, indifference, depression, delusions, and other manifestations. These deficits affect patients' social functioning and make it difficult or impossible for them to carry on with daily living. Memory impairment is an early component of Alzheimer's, the disease is inexorably progressive as it spreads from one region of the brain to another and is fatal within 5 to 10 years. Alzheimer's patients usually die of complications of chronic illness. **Alzheimer's is the most common cause of death in the UK**. Sometimes Alzheimer's involves people in their 40s and 50s (or occasionally younger), but is mainly a disease of old age. Based on clinical evaluations, 13% of persons over 65 years and 45% of those over 85 have AD.

Mild cognitive impairment (MCI) is a clinical state characterized by memory and other cognitive impairments that do not affect social functioning or daily living. Some MCI patients progress to Alzheimer's but others remain stable or revert to normal, indicating that MCI has diverse causes.

Alzheimer's is driven by two processes: *extracellular deposition of beta amyloid and intracellular accumulation of tau protein.* Both these compounds are insoluble. β-amyloid (Aβ) fibrils are the main component of neuritic senile plaques and hyperphosphorylated tau is the component of neurofibrillary tangles. Aβ deposition is specific for Alzheimer's and is thought to be primary. Tau accumulation is also seen in other degenerative diseases and is thought to be secondary. Neuronal death results in associated cerebral atrophy. These pathological changes are most prominent in the hippocampus, entorhinal cortex (memory and navigation), and association areas of the neocortex (sensory perception, cognition, generation of motor commands, spatial reasoning and language) and are believed to be responsible for the clinical features. (see images)

β-amyloid is a 36 to 43 amino acid peptide, which is part of a larger protein, the Amyloid Precursor Protein (APP). APP is a transmembrane protein, made by neurons and other brain cells, it spans the entirety of the biological membrane to which it is permanently attached. (Many transmembrane proteins function as gateways to permit the transport of specific substances across the biological membrane.) It is also found in other tissues and is especially abundant in platelets. Its function is unknown. The Aβ amyloid residue includes part of the transmembrane domain of APP and is derived from cleavage of APP by the enzymes β- and γ-secretase. (Secretases act on APP to cleave the protein into three fragments. Sequential cleavage by β-secretase and γ-secretase produces the amyloid-β peptide fragment that aggregates into clumps called "plaques"). Aβ monomers and are further degraded by other enzymes. Defective clearance of Aβ from aberrant cleavage of APP and other mechanisms results in its accumulation. Aβ monomers polymerize initially into soluble oligomers and then into larger insoluble fragments such as Aβ, which precipitate as amyloid fibrils. Aβ is toxic to neurons. (A plaque's size and density renders it insoluble, and consequently unable to move. Whereas the oligomers, which give rise to Alzheimer's disease, are small enough to spread easily around the brain - killing neurons and interacting harmfully with other molecules - but how they are formed was until recently a mystery.) In brain slice preparations, Aβ causes loss of long term potentiation, (a persistent damaging of synapses) and kills neurons. Moreover, it shows selective neurotoxicity for the hippocampus and entorhinal cortex (areas that are severely affected in Alzheimer's) while sparing cerebellar neurons. This damage is mediated by free radicals, which are generated when soluble Aβ is complexed with Zn^{2+}, Cu^{2+}, and Fe^{3+}. There is a high correlation between the amount of soluble Aβ and the severity of the neurological dysfunction in Alzheimer's. The beta amyloid hypothesis has been the basis of several unsuccessful drug treatment development for Alzheimer's

Neurofibrillary degeneration is characterized by the deposition in the neuronal body and processes of insoluble polymers of over-phosphorylated microtubule (tubular protein polymer) associated protein tau. Tau aggregates as pairs of filaments that are twisted around one another (paired helical filaments). Neurofibrillary tangles (NFTs) are aggregates of the hyperphosphorylated tau protein that is most commonly

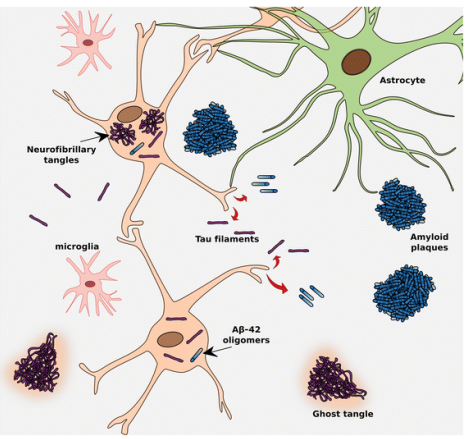
known as a primary marker of Alzheimer's disease. Tangles consist of tau, a protein normally involved in maintaining the internal structure of the nerve cell. While tau is normally modified by phosphorylation, or the attachment of phosphate molecules, excessive phosphorylation appears to contribute to tangle formation and prevents the protein from carrying out its normal functions. These deposits interfere with cellular functions by displacing organelles (tiny cellular structure that performs specific functions within the cell.) By distorting the spacing of microtubules, they impair the axonal transport thus affecting the nutrition of axon terminals and dendrites. Abnormal tau first appears in the entorhinal cortex, then in the hippocampus, and at later stages in association cortex. Recent observations in genetically modified mice suggest that the spread of the pathology to anatomically linked areas occurs by passage of abnormal tau across synapses.

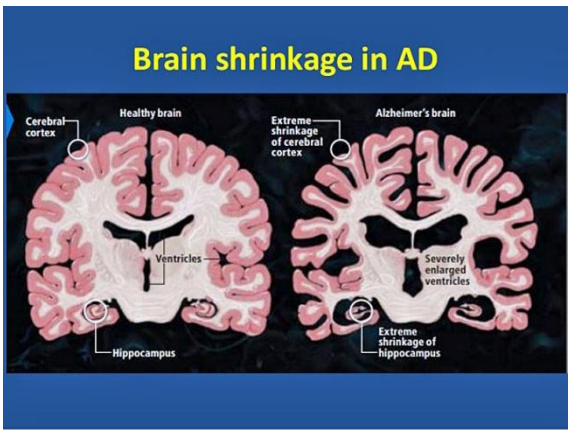
Alzheimer's disease is characterised by loss of neurons and synapses (structures that permits a neuron to pass an electrical or chemical signal to another neuron or to the target cell) in the cerebral cortex and certain subcortical structures below the cortex. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus (part of the limbic lobe).

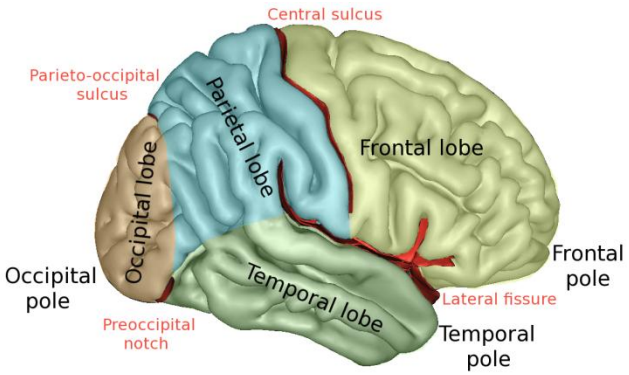
Alzheimer's disease has been hypothesized to be a protein misfolding disease caused by accumulation of abnormally folded Aβ and tau proteins in the brain. Several neurodegenerative diseases are classified as proteopathies (proteopathy - refers to a class of diseases in which certain proteins become structurally abnormal, and thereby disrupt the function of cells, tissues and organs of the body) as they are associated with the aggregation of misfolded proteins. The classic neuropathological signs of Alzheimer's disease are amyloid plaques and neurofibrillary tangles.
Oxidative stress, or damage to cellular structures by toxic oxygen molecules called free radicals, is also regarded as a pathology characteristic of Alzheimer's. Individuals with Alzheimer's typically experience brain inflammation

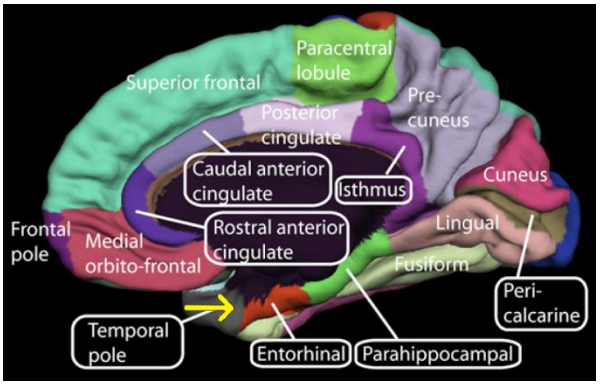
Brain images of individuals with Alzheimer's show increased hippocampal and overall brain atrophy, but absolute levels of shrinkage have not been quantified and standardized. Growing evidence suggests that with advancing age, dementia that "looks like" Alzheimer's is increasingly likely due to a combination of Alzheimer's pathology and other pathologies known as "mixed dementia."

Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons. Many diseases – including multiple sclerosis, Parkinson's, Alzheimer's, and Huntington's – occur as a result of neurodegenerative processes. Such diseases are incurable, resulting in progressive degeneration and/or death of neuron cells. As research progresses, many similarities appear that relate these diseases to one another on a sub-cellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate many diseases simultaneously. There are many parallels between different neurodegenerative disorders including atypical protein assemblies as well as induced cell death.






Central sulcus
Parieto-occipital sulcus
Parietal lobe
Frontal lobe
Occipital lobe
Occipital pole
Frontal pole
Temporal lobe
Lateral fissure
Preoccipital notch
Temporal pole


Paracentral lobule
Superior frontal
Pre-cuneus
Posterior cingulate
Caudal anterior cingulate
Isthmus
Cuneus
Frontal pole
Medial orbito-frontal
Rostral anterior cingulate
Lingual
Fusiform
Peri-calcarine
Temporal pole
Entorhinal
Parahippocampal