Dementia

There are various forms and mechanisms for dementia, but all are related to neuropathology of the brain. Typically, dementia is characterized by memory deficits, but other deficits in brain function are also found in cases of dementia. At the root of dementia is a dysfunction of neurons or neural connections in the brain (neuropathology). There are different types of dementia, which may be caused by various types of neuropathologies. Ultimately, dementia is the result of neuronal dysfunction and/or neuronal cell death within the learning and memory networks of the brain.

Neuropathologies of Dementia

Neuropathologies associated with dementia result in dysfunction and/or death of neurons in the brain, particularly those within the learning and memory networks/circuits of the brain. Described below are the different types of neuropathologies associated with dementia.

• Vascular dysfunction

• Neurotransmitter imbalance

• Extracellular protein build-up

• Intracellular protein build-up

Vascular dysfunction: disruptions/dysfunctions of the vascular system of the brain.

Though not a pathology of the neurons or their connections themselves, vascular dysfunctions of the brain have a major impact on neuronal functioning. Without a sufficient blood supply, neurons are not able to function.

Typically vascular dysfunction refers to vascular lesions or a lack of adequate cerebral blood supply. Vascular lesions or a decline in cerebral blood flow results in neurons not receiving the blood, and therefore nutrients, they need to survive. Neurons begin to dysfunction and ultimately die. Neuronal dysfunction or death within learning and memory circuits of the brain result in a loss of memory and/or loss of ability to consolidate memory.

Types of Dementia associated with vascular neuorpathologies:

Vascular dementia: learning and memory loss resulting from neuronal dysfunction *due to* vascular dysfunctions within the brain. Vascular dementia may coexist with other forms of dementia, commonly Alzheimer's disease.

Neurotransmitter imbalance

Cholinergic neurons that use *Acetylcholine (Ach)* as the neurotransmitter are the predominant type of neuron in the memory networks, particularly the declarative memory networks. A decreased synthesis of Ach will reduce the functioning and communication of these cholinergic neurons within the memory networks.

The cause of the decreased synthesis in Ach is not known, but may be related to extracellular plaque build-up outside the cholinergic neurons (see below).

Types of Dementia associated with neurotransmitter inbalances:

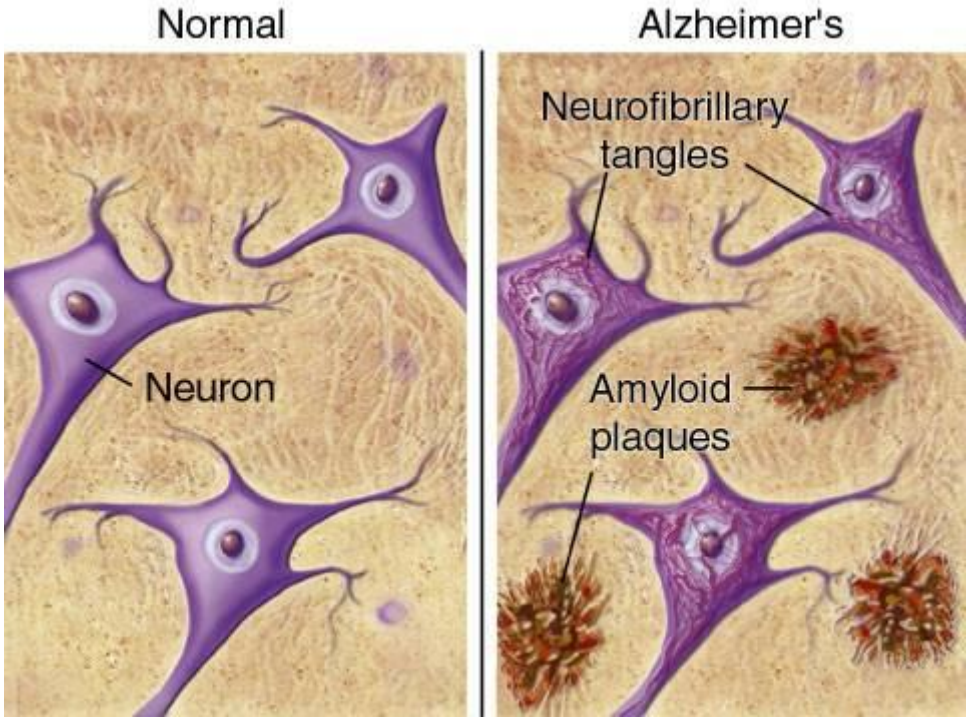
Alzheimer's disease

Dementia with Lewy bodies.

Extracellular protein build-up

Amyloid beta (Aβ) is a peptide (small protein) formed from *amyloid precursor protein (APP)*. The function of APP is unknown, but it is found in various cells throughout the body, including neuronal cells. APP is involved in forming Aβ outside of cells. Normally, APP is broken down to keep a balance in the amount of Aβ formed outside the cell.

In cases of dementia it has been found that APP breakdown in neurons is abnormal, resulting in excessive production of "sticky" Aβ. When this occurs, the increased Aβ production results in a build-up of sticky *Aβ plaques* outside the neurons.



As the Aβ plaques build-up, they begin encroaching on the space of the surrounding neurons, putting pressure on them and beginning to physically damage the neurons. As the neurons become damaged, their function and communication is interrupted, and eventually they cannot function at all and die.

The dead neurons then stick to the Aβ plaques, enlarging them. Growing plaques continue to encroach on surrounding neurons, killing them and growing larger and larger, killing more neurons, so on and so forth.

Types of Dementia associated with extracellular (Aβ) protein build-up/plaque formation:

Alzheimer's disease

The cause of the abnormal breakdown of APP into sticky Aβ is mostly unknown, however in some cases of the rare early onset Alzheimer's disease, a chromosomal abnormality for APP has been discovered. This chromosomal abnormality increases the likelihood that APP will be broken down abnormally into sticky Aβ, resulting in plaque build-up. Chromosomal abnormalities of APP may be linked to the more common late onset Alzheimer's disease as well, but this is not currently known.

Intracellular protein build-up

Intracellular protein build-up is similar to extracellular protein build-up in that there is an abnormal build-up of proteins or plaque formation. The difference is that the build-up/plaque formation occurs *within* the neuron. Three (3) different cellular proteins that abnormally form plaques have been implicated in dementia. These three proteins will be looked at individually below.

TDP-43

TAR DNA-binding protein 43, or TDP-43 is a protein found in the nuclei of neurons.

TDP-43 functions to aid DNA and RNA transcription and synthesis in the neuron. These processes are essential to the ongoing functioning of the neurons.

It has been found in some cases of dementia that there is an abnormal build-up of TDP-43 (plaque formation) within the nuclei of neurons. TDP-43 plaque formation causes tangles of proteins within the nucleus of the neuron. These protein tangles:

-disrupt DNA and RNA transcription/synthesis, resulting in cellular dysfunction

-physically disrupt other cellular processes within the nucleus.

Without a properly functioning nucleus, the neuron cell will die. With TDP-43 plaques, this typically occurs within neurons of the frontal and temporal lobes of the brain. TDP-43 plaques have been associated with other conditions besides dementia, such as Amyotrophic Lateral Sclerosis (ALS), more commonly known as Lou Gehrig's disease.

Types of Dementia associated with TDP-43 plaques:

Frontotemporal Dementia

Alpha-synuclein

Alpha-synuclein is a protein found in the presynaptic axon terminals of neurons.

Alpha-synuclein is uploaded during synaptic rearrangement (though it's function is not understood). Recall that synaptic rearrangement is part of the small changes that occur in synaptic communication as part of memory consolidation due to long-term potentiation (LTP).

Identification of abnormal plaques within neurons, known as *Lewy bodies,* has occurred in some cases of dementia. Lewy bodies were discovered to be an abnormal build-up of alpha-synuclein within the neuron. These Lewy bodies result in disrupted synaptic rearrangement and communication (thus affecting LTP).

The reason for the formation of Lewy bodies is unknown, but it's affect are similar to other types of abnormal protein plaque formation- dysfunction of neuronal cellular processes.

Types of dementia associated with Lewy bodies:

Dementia with Lewy bodies

Tau protein

Tau is another protein found in neurons and functions to stabilize microtubules.

Microtubules are the transporting mechanism for the neuron, delivering various proteins and cellular components to various parts of the cell (For example mitochrondria- the power providers of cells are transported to and from the axon terminal and nuclei to provide energy for various cellular processes).

Abnormal structure of tau proteins (as found in cases of dementia) results in the protein becoming twisted and bunched up. This, in turn, tangles up the microtubules, preventing proper transportation of elements within the neuron. Without the proper transportation of necessary cellular elements, the neuron will begin to dysfunction and ultimately die.

The cause of the abnormal structure of tau proteins is still unknown.

Types of dementia associated with abnormal tau proteins:

Alzheimer's disease

Frontotemporal Dementia