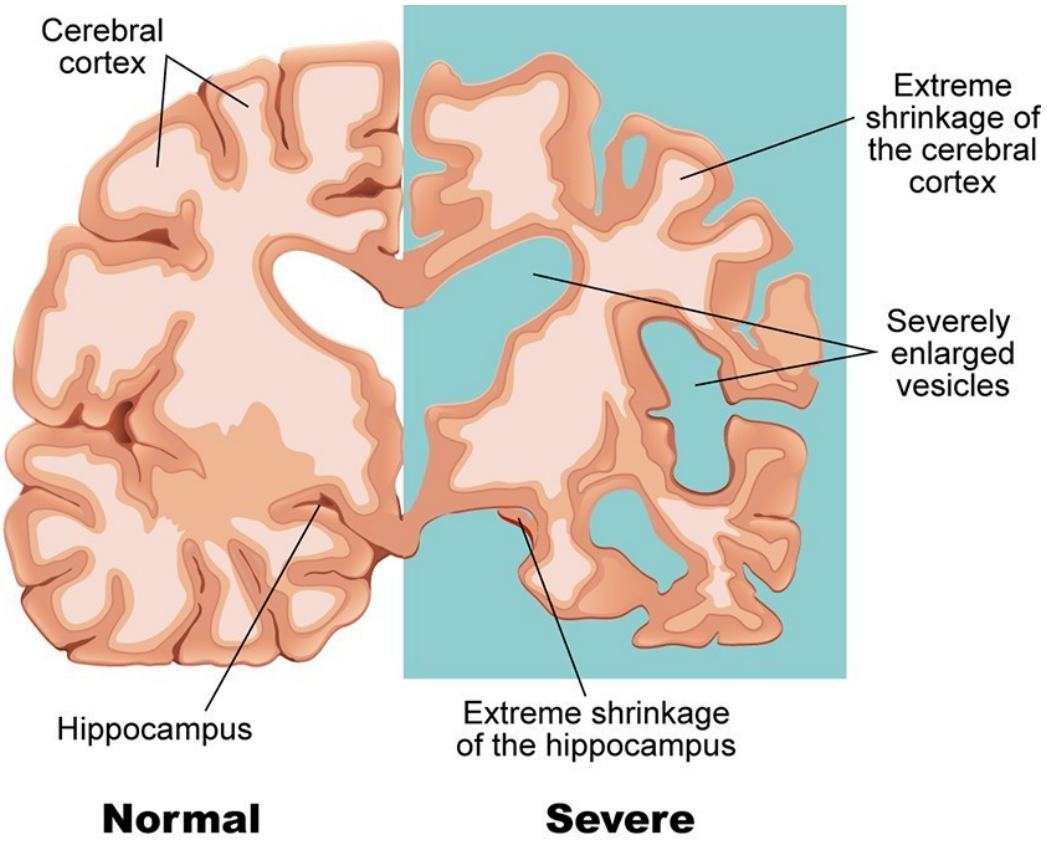
Dementia

Dementia is a neurodegenerative disorder that is considered a progressive disease that is associated with impaired cortical function. It is an all-encompassing term. Note the diagram of the brain below that demonstrates the effect of dementia on the cerebral cortex that demonstrates severe cortical shrinking:



Dementia is not a stand-alone disease, but rather, a group of symptoms caused by an underlying condition. Most dementias worsen over time and are irreversible, but some types can be reversed with treatment. While the incidence of dementia increases with age, it is not a normal part of aging. The most common causes of progressive dementia are:

1. Alzheimer's disease (50-70%): is discussed in detail in the next section.
2. Vascular dementia (25-30%): blood supply to the brain impairs normal function of neurons; symptoms may appear suddenly after a stroke (post-stroke dementia) or gradually due to vascular wear and tear that occurs with aging or any conditions that damage or narrow blood vessels over time (high blood pressure, hyperlipidemia, and diabetes) Incidence of vascular dementia increases with age and cardiovascular risk factors.
3. Lewy body dementia (15-20%): Refers to abnormal protein clumps found in neurons. The earliest and most prominent feature is a sleep behavior disorder where patients physically and sometimes violently act out their dreams (sleep walking, screaming,

laughing, kicking, punching). It is a REM sleep disorder with failure to inhibit movement during sleep. There can also be visual hallucinations; memory loss may not be noticeable until later stages. Dementia caused by advanced Parkinson's disease dementia belongs in this group and will be discussed later in more detail.

4. Frontotemporal dementia: is another common type of progressive dementia. It is characterized by neuronal cell death in the frontal and temporal lobes of the brain. The areas associated with this relates to behaviors and language. Common signs and symptoms include changes in behaviors (social inappropriateness, impulsivity, apathy, emotional indifference) and language deficits This type has a strong genetic component and tends to occur earlier between the ages of 40-50 years.

More than one type of the dementias mentioned above may co-exist in one patient (mixed dementia).

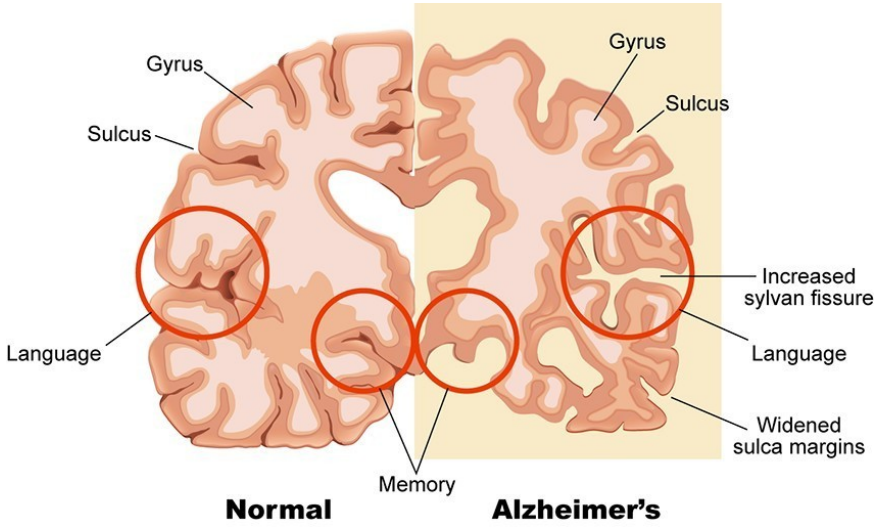
Less common causes of dementia include Huntington's disease, Creutzfeldt-Jakob disease and traumatic brain injuries.

Dementias may also develop from metabolic and endocrine processes such as thyroid disorders and vitamin deficiencies (B1, B6, B12) or infections like Lyme disease and neurosyphilis. For these types of dementias, symptoms can be reversed.

Alzheimer's Disease

Alzheimer's disease is the most common neurogenerative disease in the world. Ten percent of individuals over the age of 65 have Alzheimer's disease. Alzheimer's, like dementia, is a progressive disorder associated with impaired cognitive function and impaired cortical skills. The speed by which it develops varies among individuals and can occur over many years (4, 8 or 20 years). It is associated with neuronal loss (dying or atrophy of the neurons). This results in a smaller brain.

In the brain of a patient with Alzheimer's disease as compared with the normal brain in the diagram below, there is cortical atrophy and overall reduction in brain size and weight which causes an overall reduction in cortical mass. There is also enlargement of the ventricles and reduction in size of the hippocampus.



The signs and symptoms associated with Alzheimer's disease is based on the changes in the brain. A reduced hippocampus size is associated the decreased short-term memory, but the individual's long-term memory may be intact. Because Alzheimer's disease is a progressive, it spreads from the hippocampus to more cortical regions of the brain. At that point, the long-term memory can become altered.

The Cause of Alzheimer's Disease

The cause of Alzheimer's disease is unknown. There are some underlying genetic and environmental causes, though, that interact to cause the disease.

There are several hypotheses that explain the development of Alzheimer's disease.

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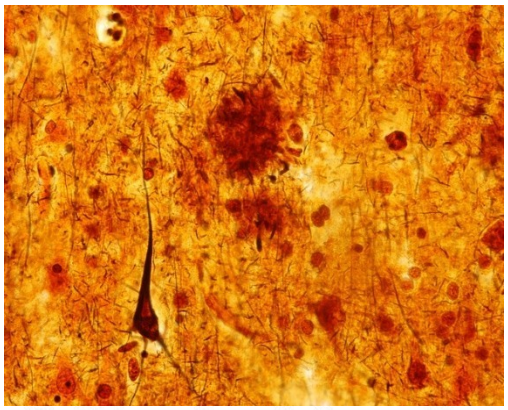
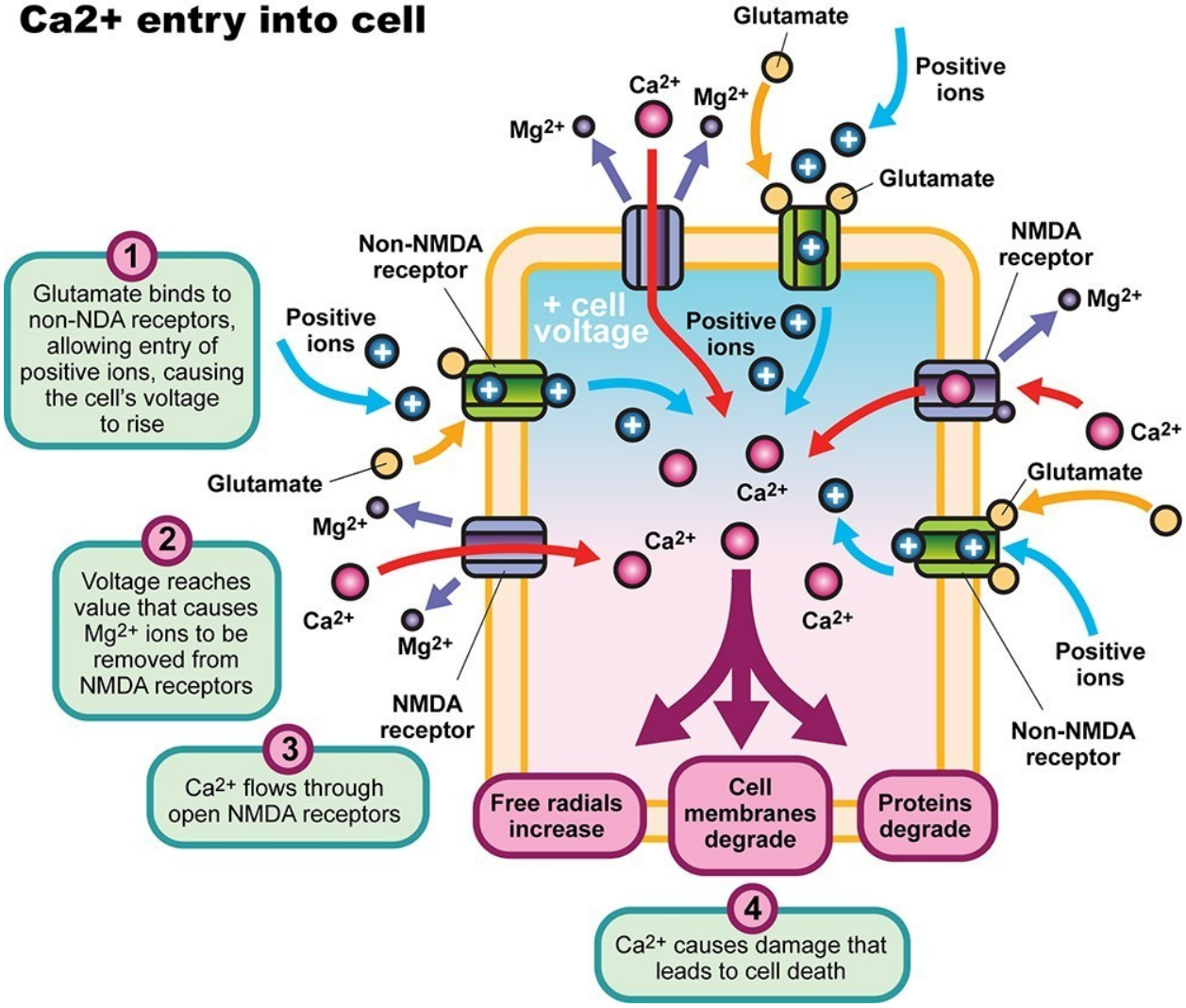
- Amyloid Hypothesis
- Cholinergic Hypothesis
- Glutamate Excitotoxicity

In the healthy brain, the Tau protein helps to lengthen and support the microtubule structure. Microtubules play a crucial role in the transport of nutrients and information molecules throughout the neuron. When Tau dissociates, the microtubule assembly becomes compromised thereby disrupting the neuron's transport system leading to malfunctions in biochemical communication between neurons.

Neurofibrillary tangles are involved in this process. Remember that healthy brain neurons will send signals from the cell body down the axons to the synapse so that it can release neurotransmitters. In addition to sending action potentials, neurons also send proteins, nutrients and other important molecules. The microtubules are responsible for carrying these. In Alzheimer's disease, the microtubules become misfolded and tangled which alters their function. These are called neurofibrillary tangles.



Ca2+ entry into cell



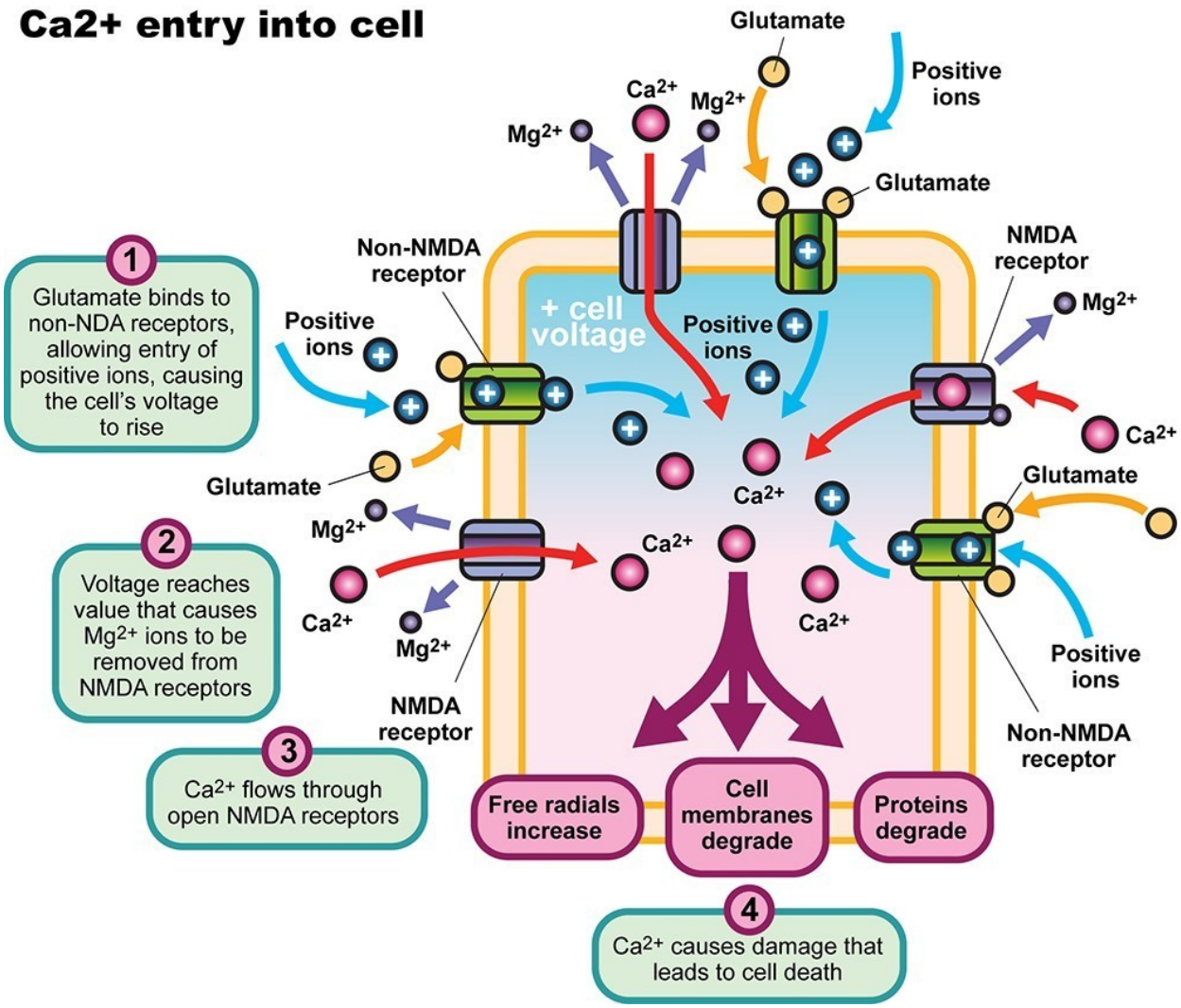
Amyloid hypothesis

This hypothesis involves the formation of senile plaques (amyloid plaques). Beta-amyloid is a metabolic waste disorder found in the fluid between the brain cells. It induces neuroinflammation and disrupts communication between the neurons. On the plasma

membrane, there are numerous proteins. Some proteins ensure appropriate neurotransmitter function at the synapse. Other proteins, like the neurofibrillary tangles also misfold, malfunction and then get released into the extracellular fluid and come together to form an even larger misfolded protein (Beta-amyloid clump). This is a senile plaque. The diagram to the right depicts neurofibrillary tangles.

Cholinergic hypothesis

This hypothesis involves reduced levels of acetylcholine (ACH). ACH, is a cholinergic, excitatory neurotransmitter in the central nervous system. It is important in forming new neuronal function and synapses that involve memory. It is unclear why ACH is reduced in Alzheimer's disease. But it provides us an opportunity manage the signs and symptoms pharmacologically. If there is reduced ACH, it needs to be increased. One of the ways to increase ACH is by reducing the amount of enzyme that breaks down ACH. The enzyme is called acetylcholine esterase (ACH esterase). If a patient can receive an ACH esterase inhibitor, it will stop the enzyme from destroying ACH and improve ACH levels in the system. Note that there is no cure for Alzheimer's disease and the neurodegenerative process cannot be stopped, but if ACH can be increased for as long as possible, then some symptoms can be controlled.



Glutamate exotoxicity

Another theory on what causes Alzheimer's disease involves glutamate excitotoxicity. Glutamate is another excitatory neurotransmitter of the CNS. It works on the neuron. If we have a neuron and we want that neuron to fire off an action potential, starting at the cell body and send it to the neurotransmitters, we need to excite it. Glutamate can be given. Glutamate comes down to the cell body to bind with glutamate receptors. Once this occurs, the action potential is sent. Remember that neurons are negative on the inside of the cells. Positive ions located on the outside rush into the cell in a domino effect. Glutamate stimulates this by binding to receptors to open the calcium channels that allows calcium to rush inside the cell. When the positive ion Calcium enters the cell, it will lead to depolarization and production of an action potential. In Alzheimer's disease, the patient may have too much glutamate being released which results in a toxic effect. If too much glutamate binds with the neuron, then too much calcium is going into the cell. Too much calcium entering a cell usually results in cell death. This is one thought on how cells begin to die off in Alzheimer's disease. The diagram