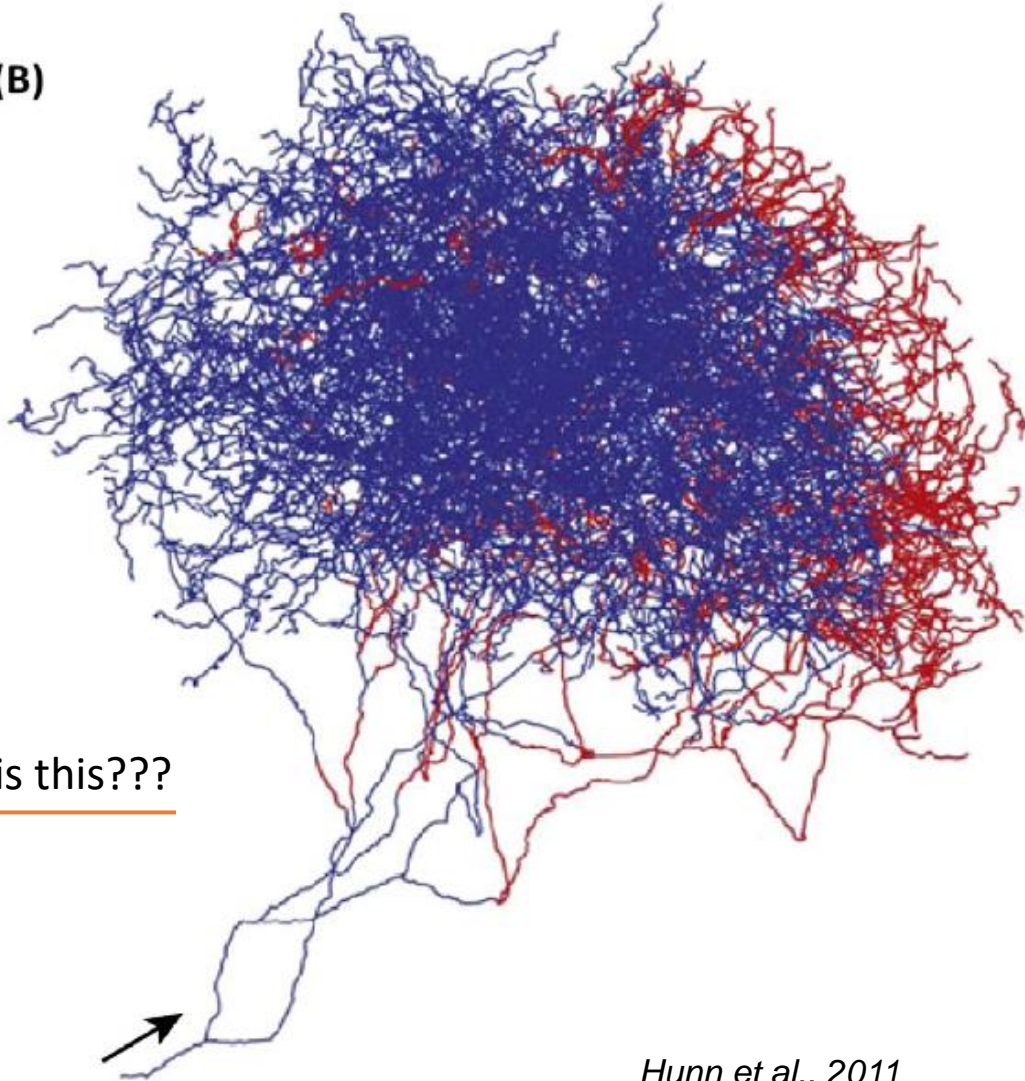


Strengthening brain cells: Determining the failure of brain cell communication in Alzheimer's disease

Dr. Matthew Parsons
Memorial University



(B)



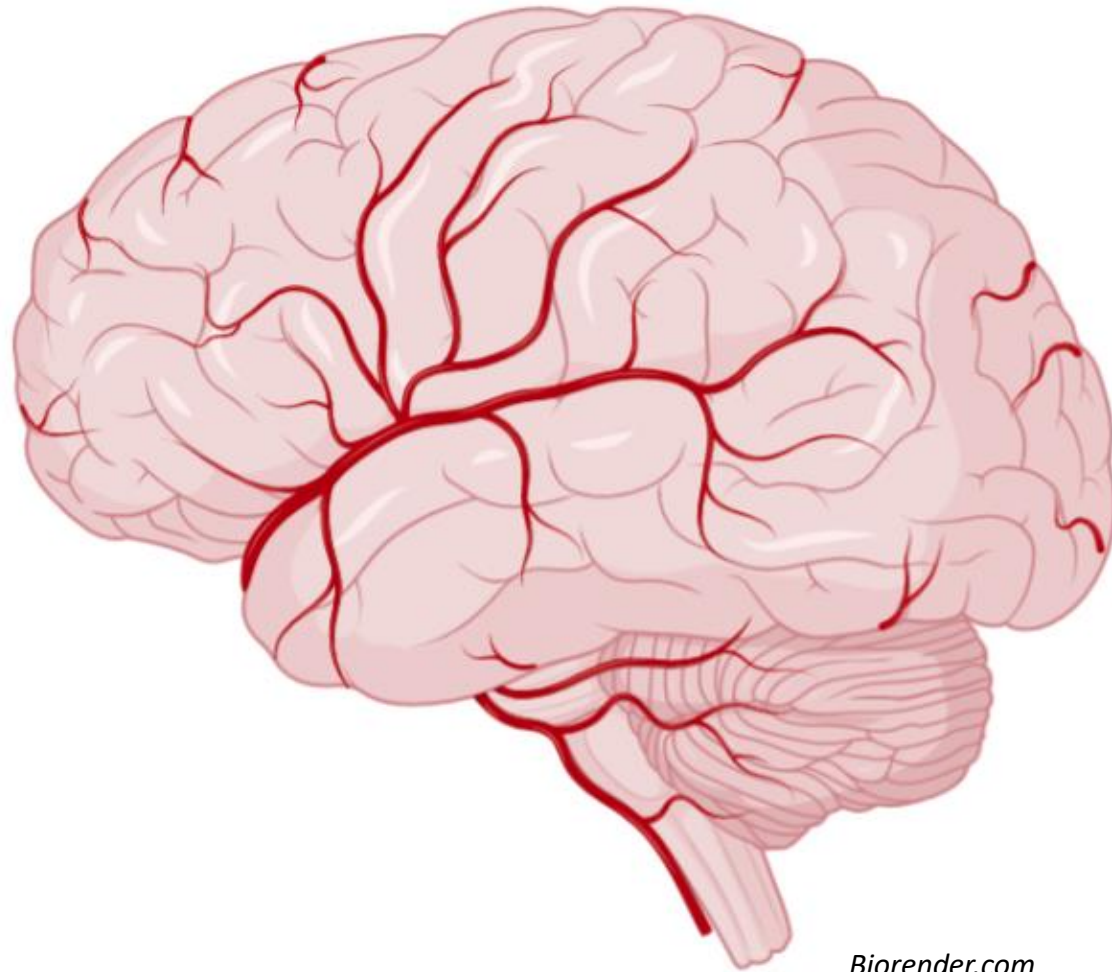
What is this???

- Alzheimer disease is the world's most common **neurodegenerative** disease
- Replacing brain cells is a difficult task
- Before brain cells die, they lose their ability to communicate with each other
- What if we thought of AD as a brain cell communication disease instead? A **synaptic** degenerative disease?

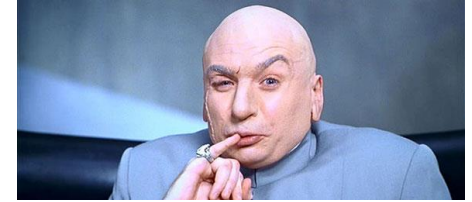
Hunn et al., 2011

TRENDS in Neurosciences

How do brain cells communicate?



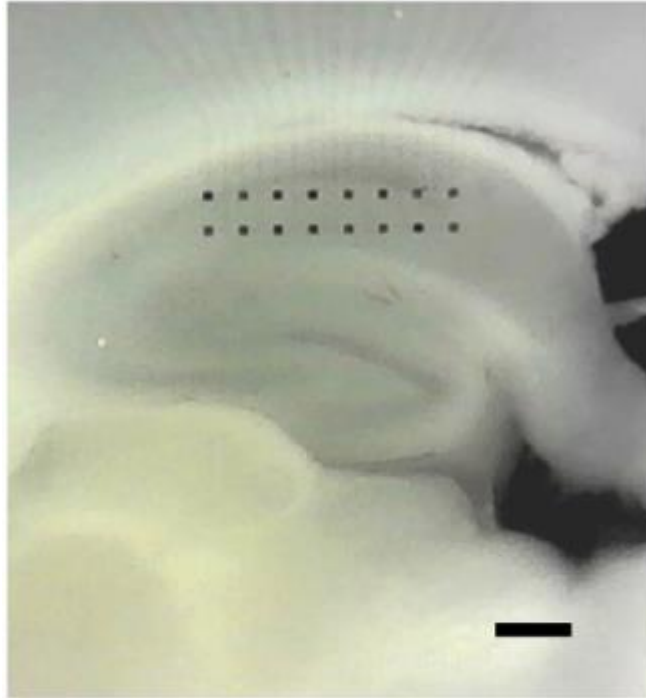
Biorender.com



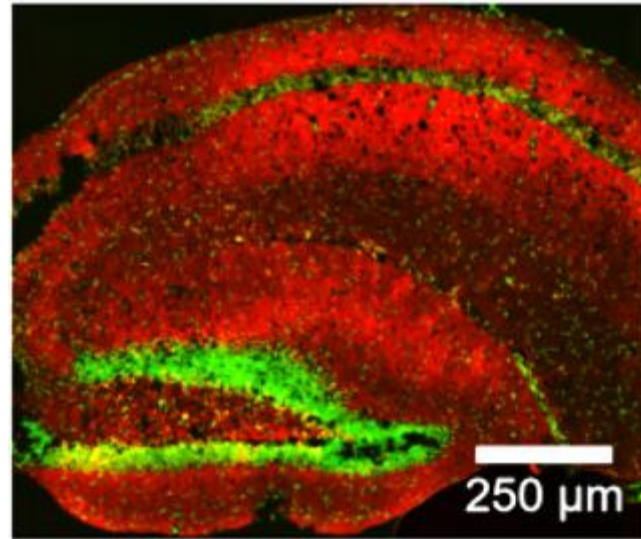
100 billion neurons!

100 trillion connections!

The brain under the microscope: The hippocampus

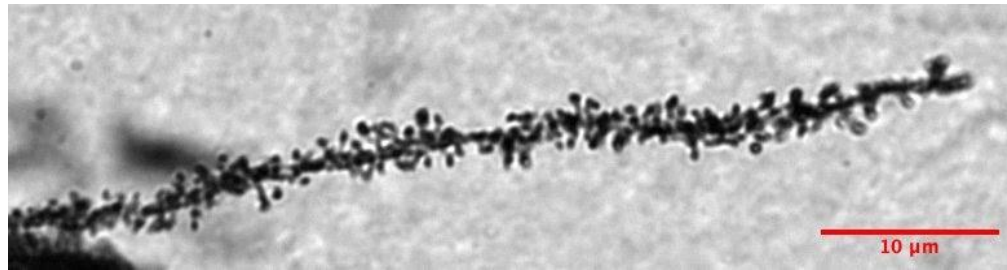


Ravalia et al., 2020



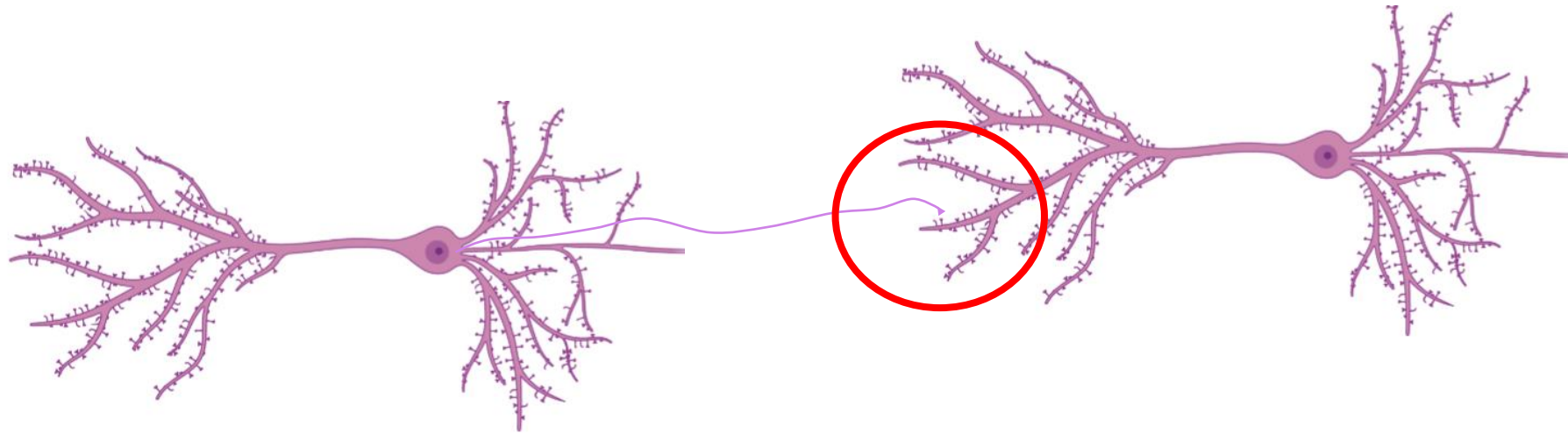
Barnes et al., 2020

The brain under the microscope: A single dendrite



Emily Hurley, PhD candidate

The brain under the microscope: A **synapse**



The brain under the microscope: A **synapse**



The basic requirements for a synapse:

Speaker

Words

Listener



Presynapse
(speaker)

Glutamate
(words)

Postsynapse
(postsynapse)

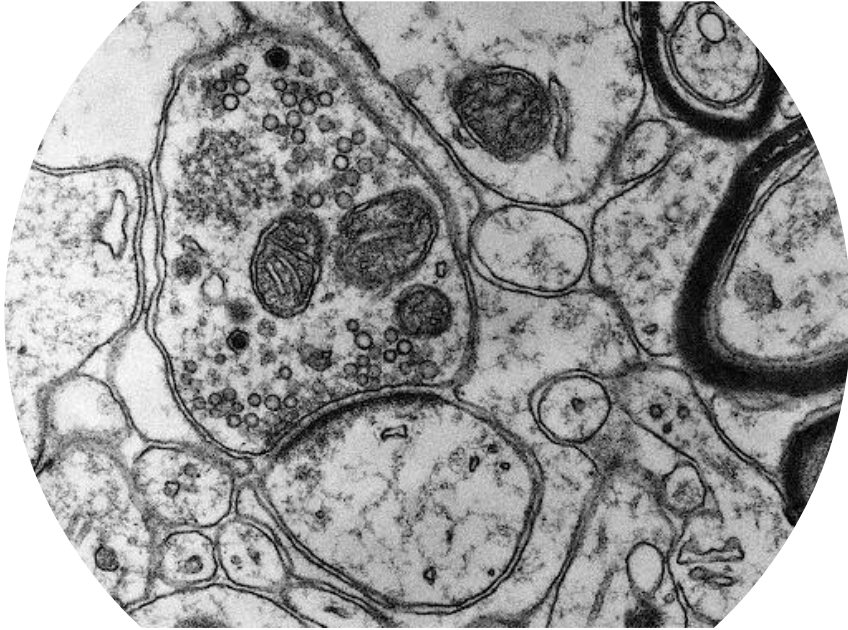
The brain under the microscope: A **synapse**



Where is the speaker?

Where is the listener?

The brain under the microscope: A **synapse**



Neurons are close talkers!

Width of the synaptic cleft: ~ 20 nm

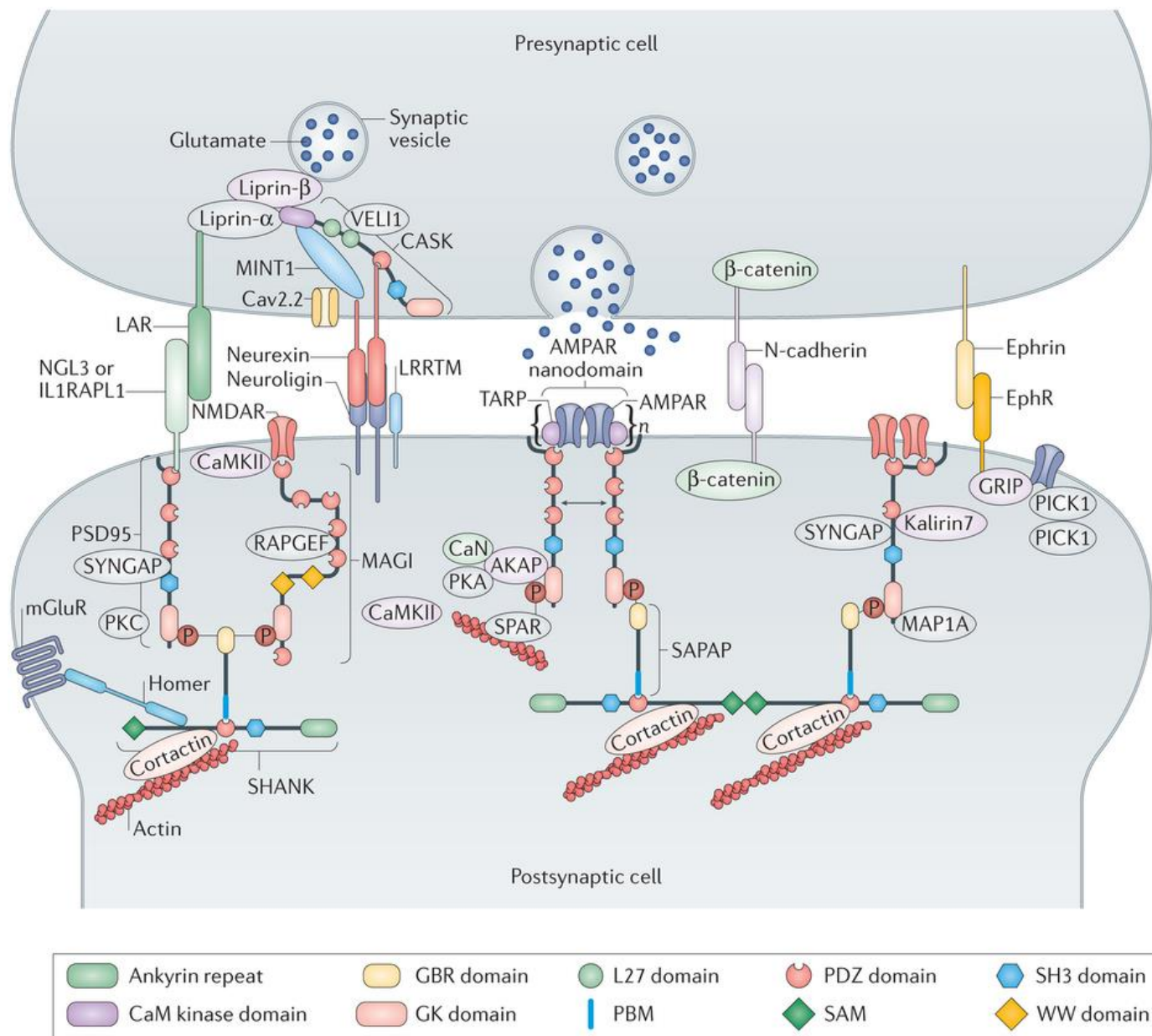
Width of a single human hair: $\sim 75,000$ nm



A single synapse

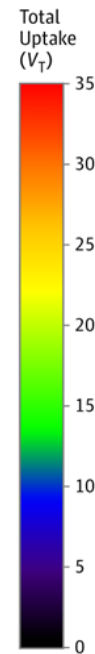
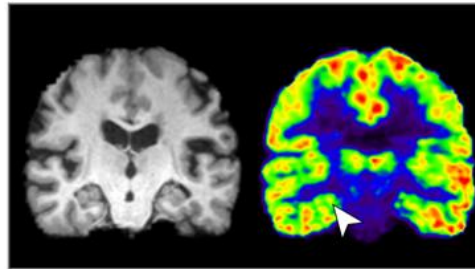
There are 100 trillion of these!

Why so complicated?
Why are all these proteins required?

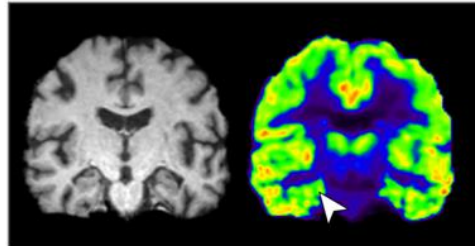


Why do we care about the synapse?

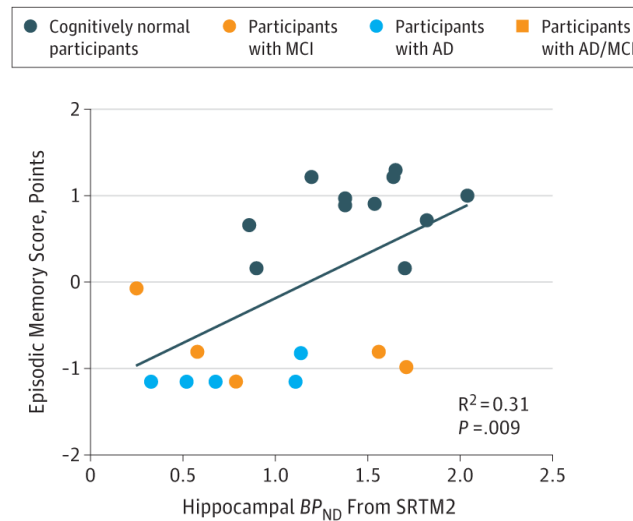
Age-matched control



AD



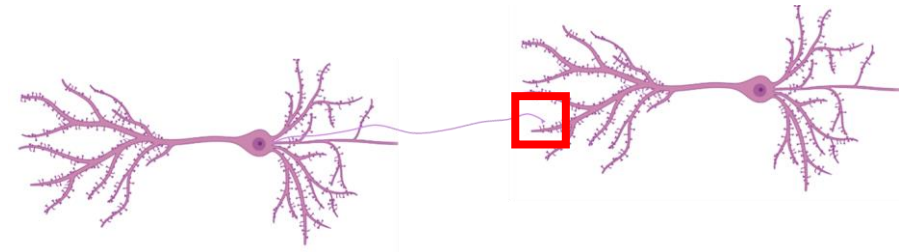
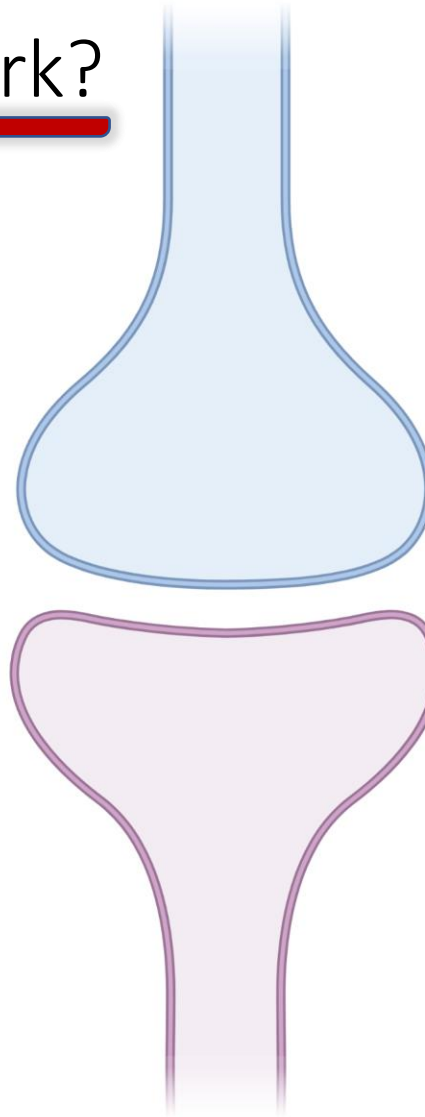
In AD, synapse loss represents the main correlate of cognitive decline!



PET imaging of synaptic vesicle glycoprotein 2A (“hotter” colors means more synapses)

How are synapses lost in AD, and how can we prevent it?

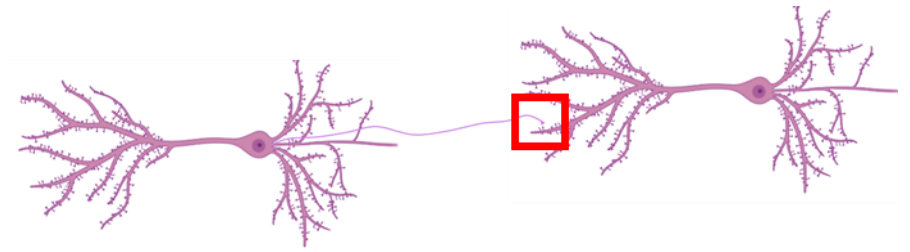
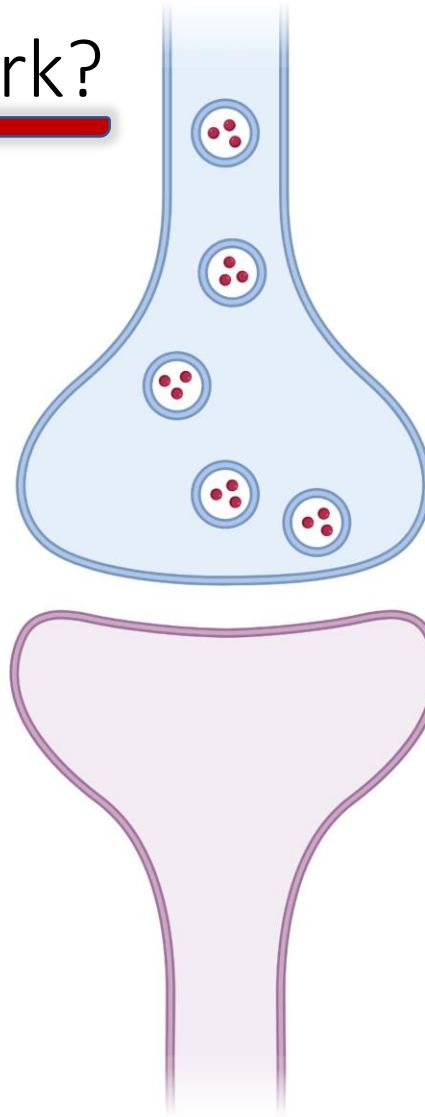
How does a synapse work?



Presynapse
(speaker)

Postsynapse
(listener)

How does a synapse work?

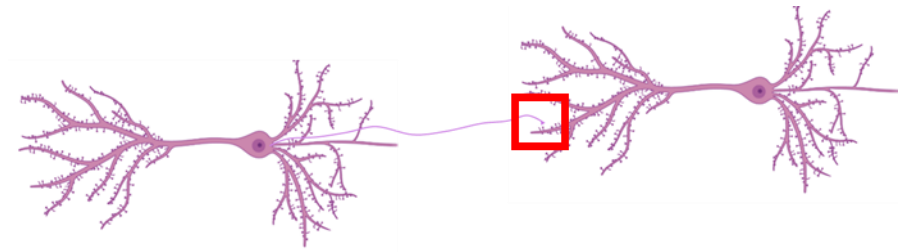
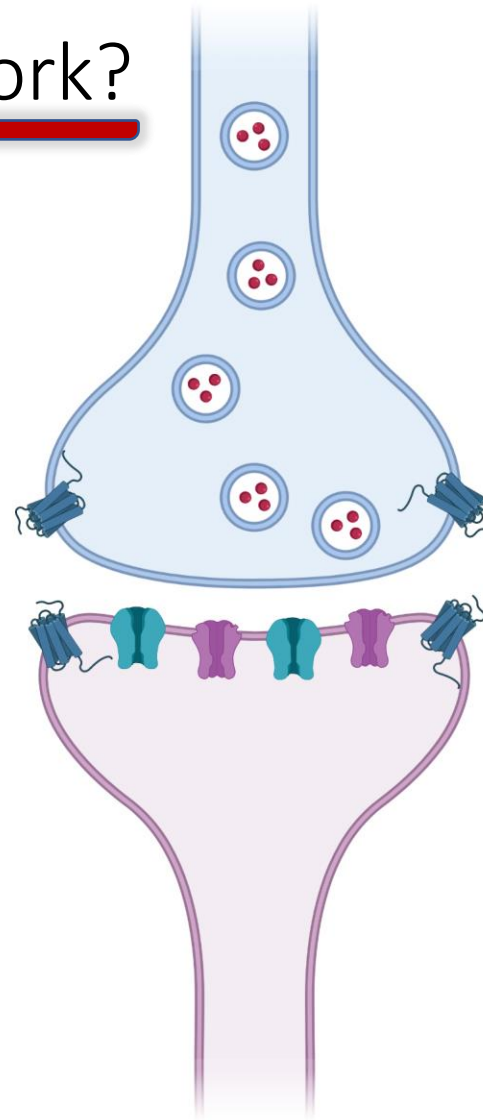


Presynapse
(speaker)

Glutamate
(words)

Postsynapse
(listener)

How does a synapse work?

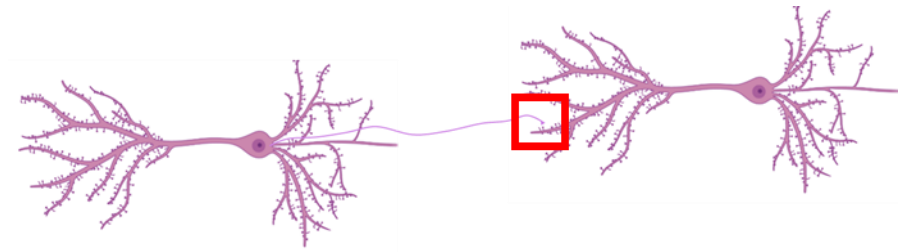
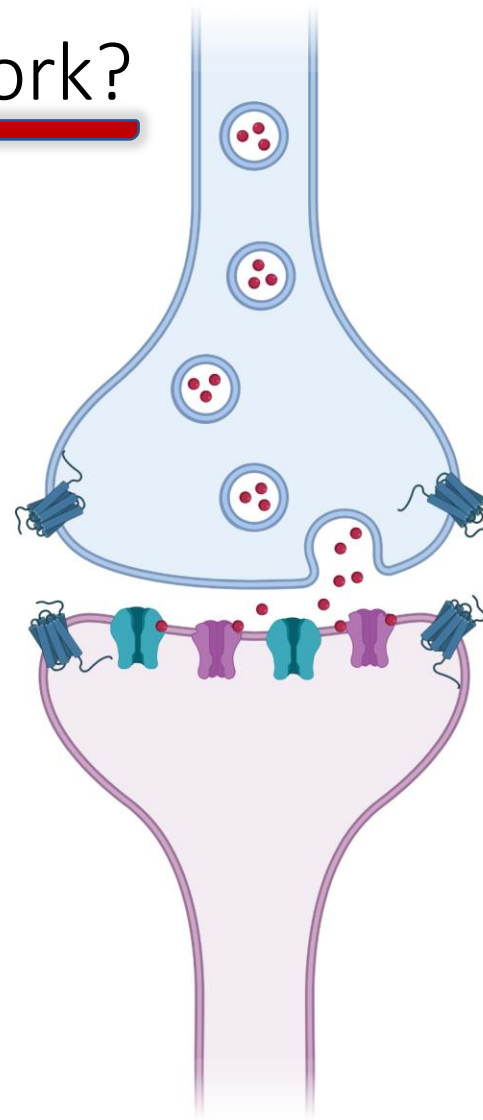


Presynapse
(speaker)

Glutamate
(words)

Postsynapse
(listener)

How does a synapse work?



Presynapse
(speaker)

Glutamate
(words)

Postsynapse
(listener)

How does a synapse work?

The Goldilocks principle applied to glutamate (the words)



Too much

Toxicity, cell death, poor cognition

Just right!

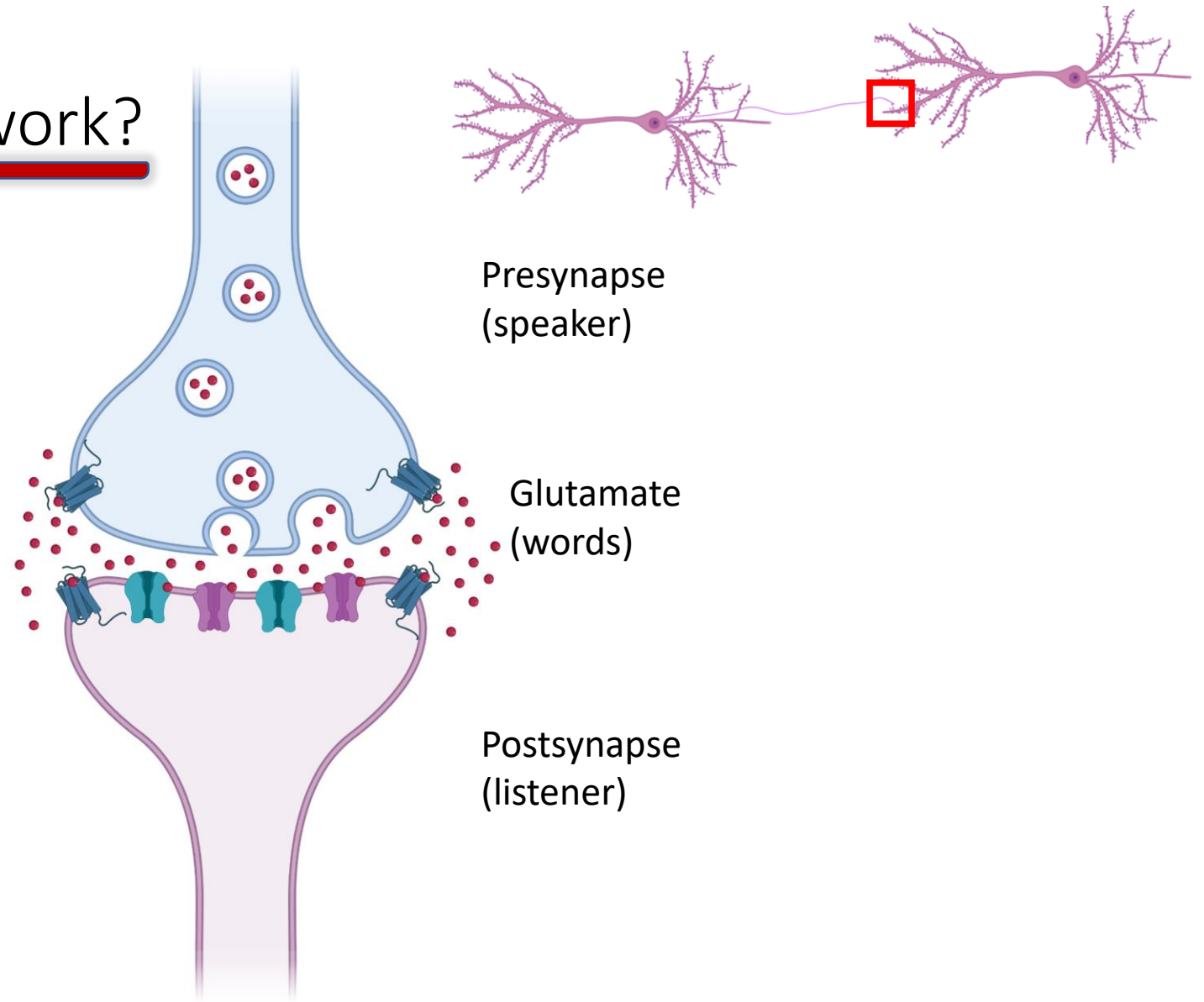
Rapid cell-to-cell communication; fast processing; network stability/flexibility; strong cognition

Too little

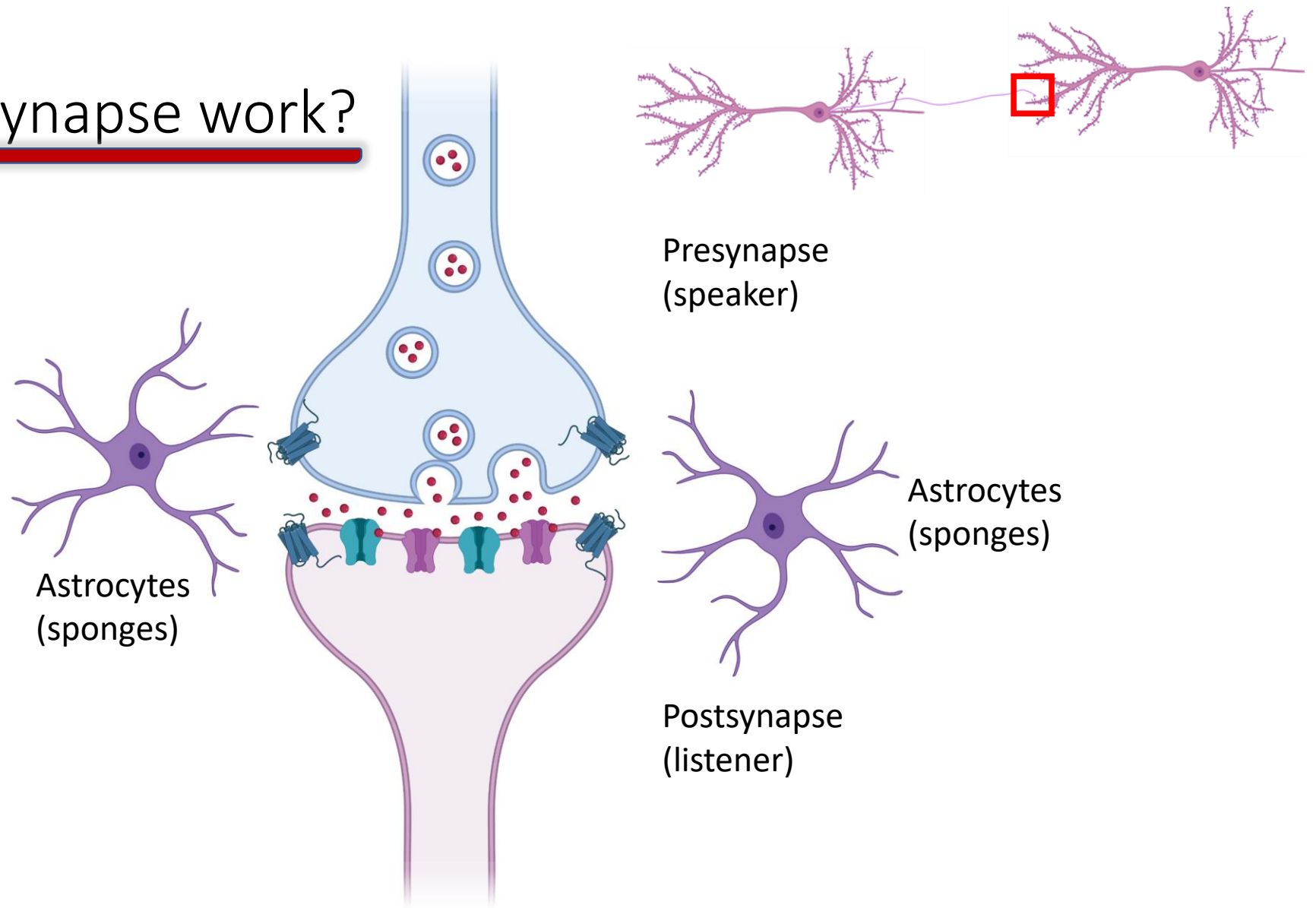
Poor information transfer, slow processing, **synapse elimination**
poor cognition

How does a synapse work?

What happens to glutamate after it is released?

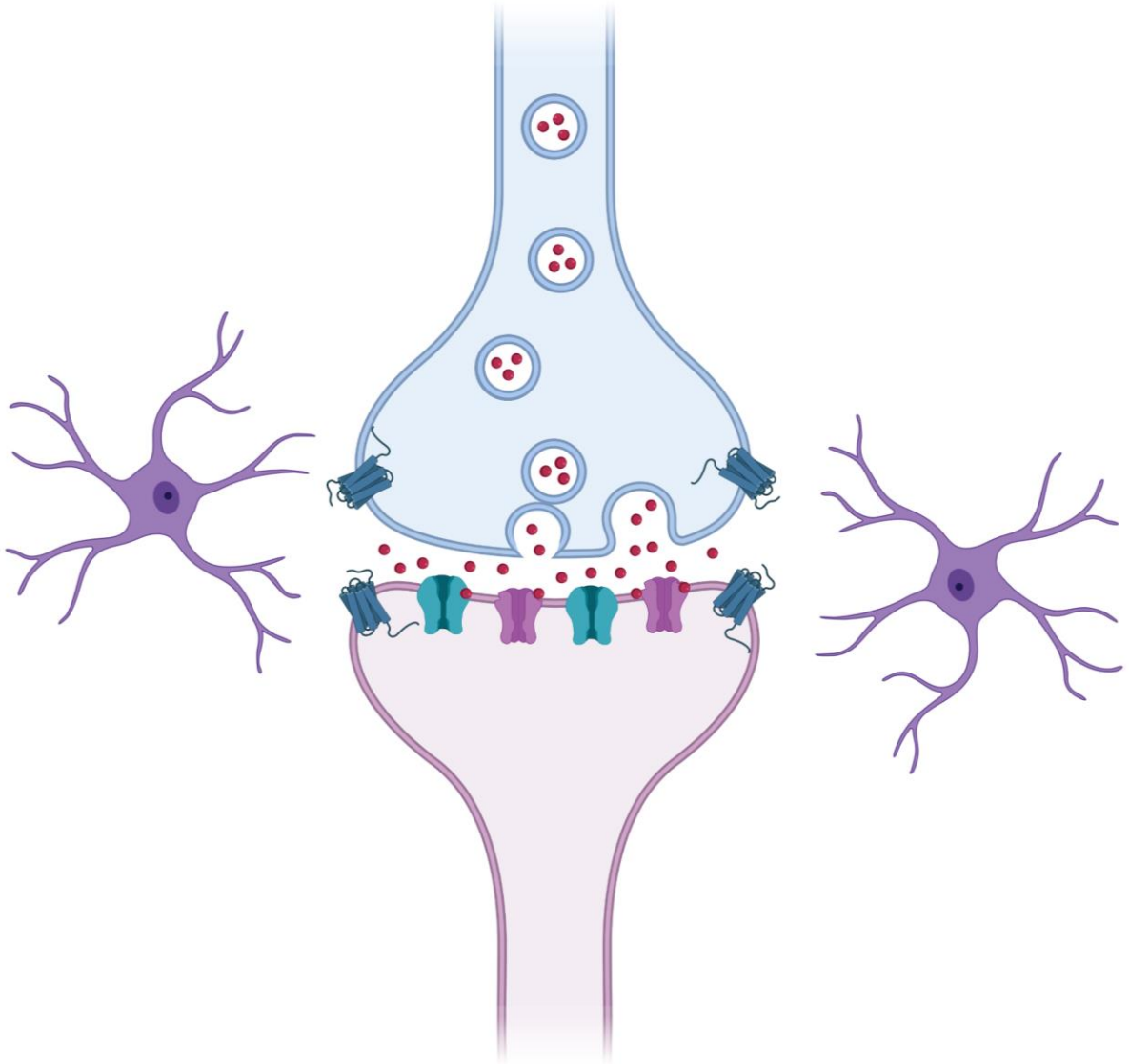


How does a synapse work?

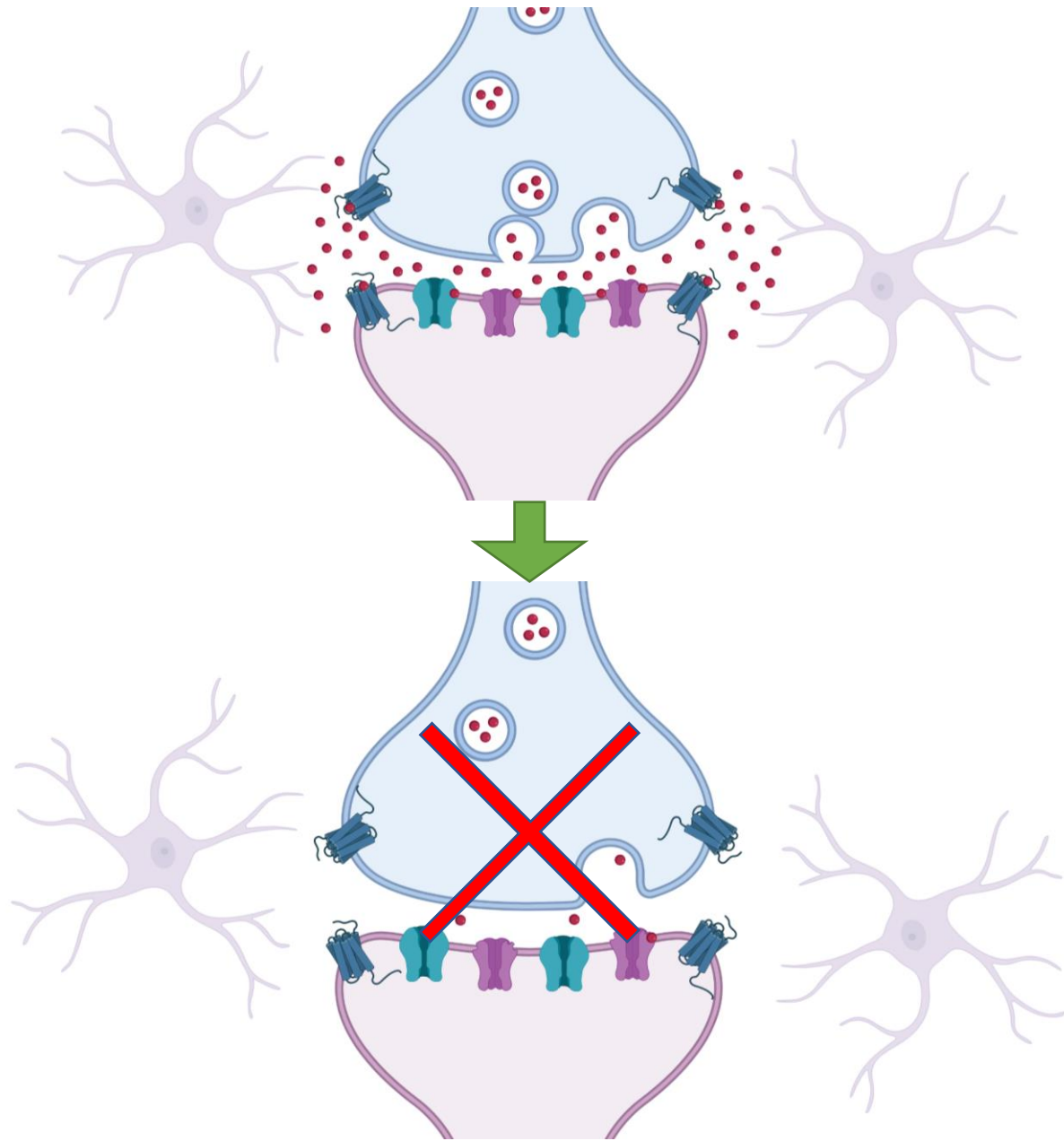


What do we think is happening
to these synapses in AD?

No AD

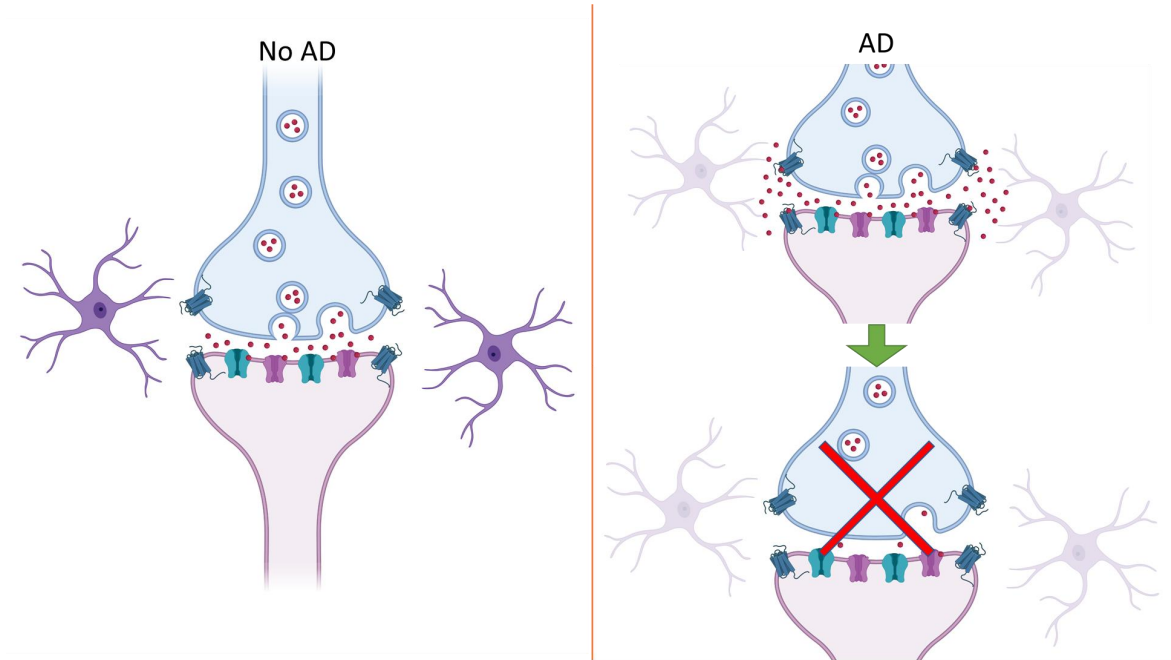


AD



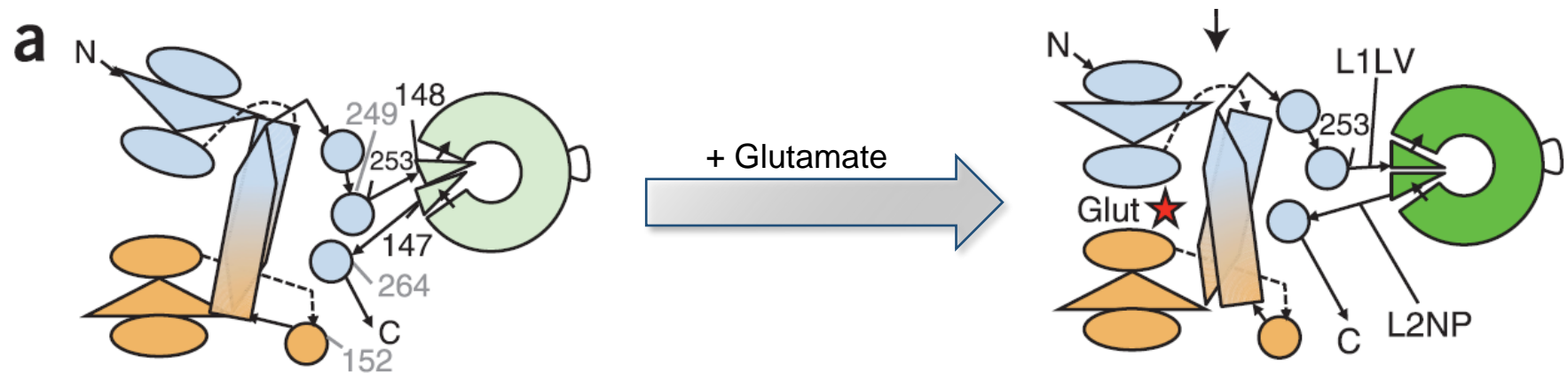
What we think is happening:

- In the AD brain, the sponges fail.
- Leads to the overactivation of receptors on the presynapse (the speaker)
- Makes the speaker think its speaking too loudly
- Responds by lowering its voice (releases less glutamate)
- Becomes a weak synapse that, if sustained, is eventually eliminated
- What evidence do we have to make us think this is happening???



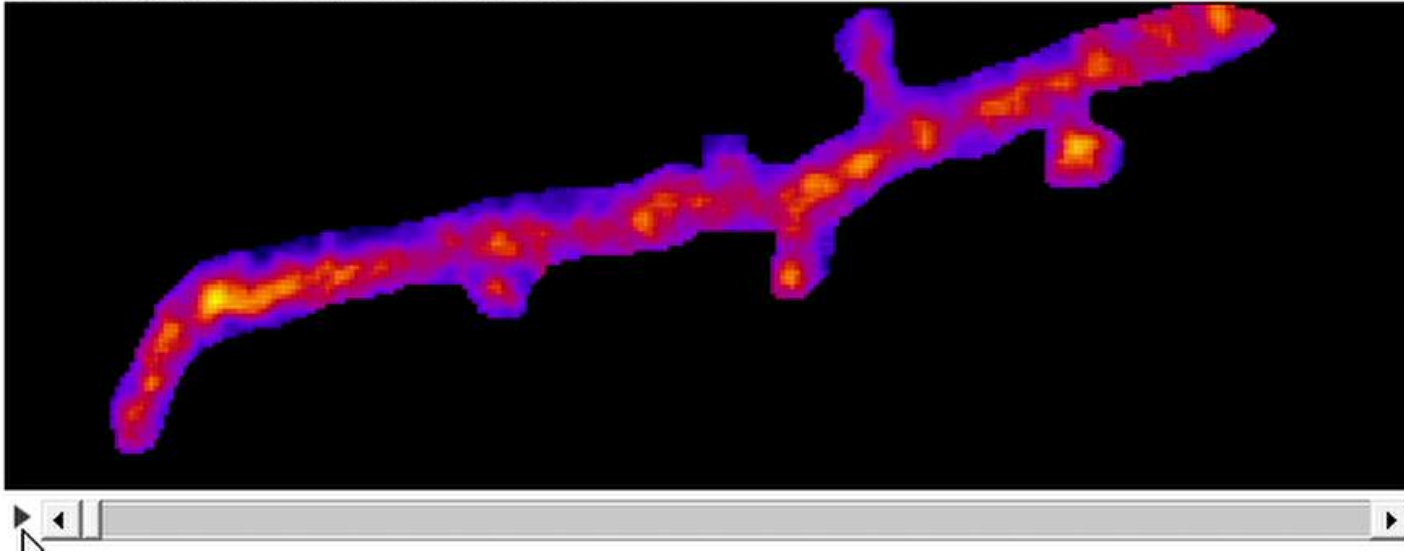
Visualizing glutamate in real-time

- iGluSnFR (pronounced I-glue-sniffer)
- Green protein that lights up when it senses glutamate
- By introducing iGluSnFR into brain cells, we can tell how much glutamate is released and how long it stays around
- We have introduced iGluSnFR to either the speaker (presynapse) or the listener (postsynapse) to see how glutamate is regulated in these areas.



Example video (in real time) of glutamate released onto a single dendrite

1/471 (Proj. 1); 287x100 pixels; 32-bit; 52MB



How do we do this in a human brain?

Hint: we don't...

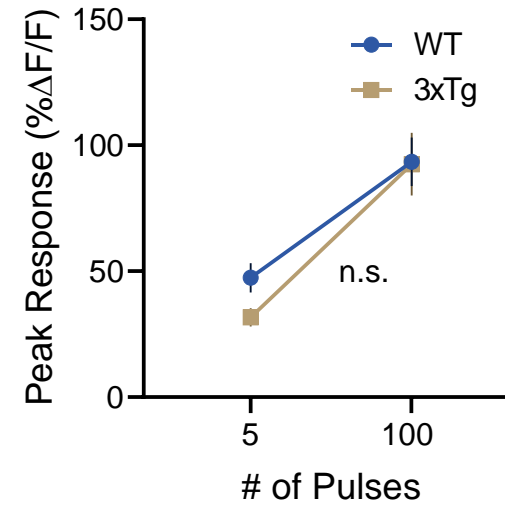
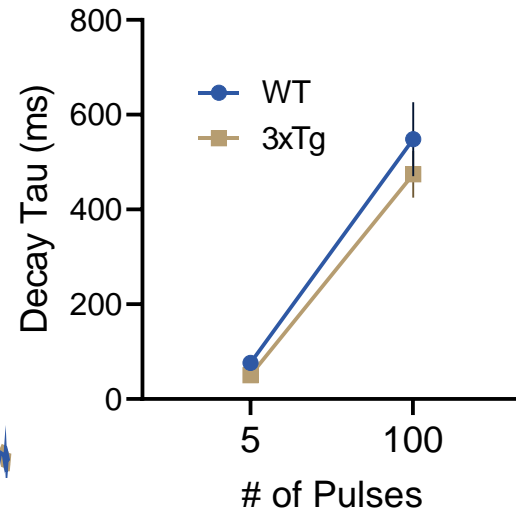
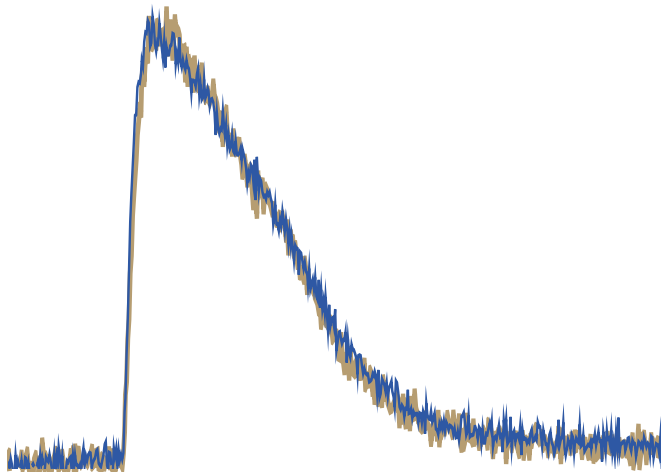
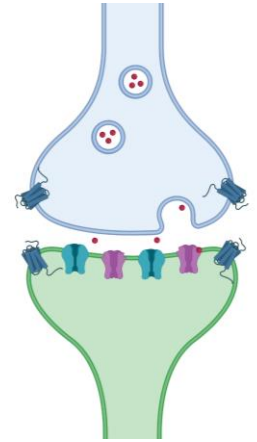
Sense of scale: Stack 75 of these dendrites on top of each other to equal the width of a human hair

The 3xTg mouse model of AD

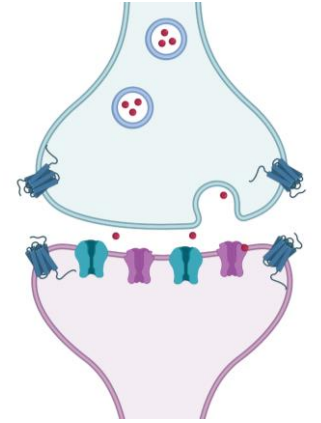
- These mice have three mutations linked to familial forms of AD
- Results in amyloid and tau pathology
- Exhibit synapse weakening over time and eventual synapse elimination
- Exhibit cognitive deficits
- One of the most commonly-used animal models of AD*

Glutamate levels are normal at the postsynapse (listener)

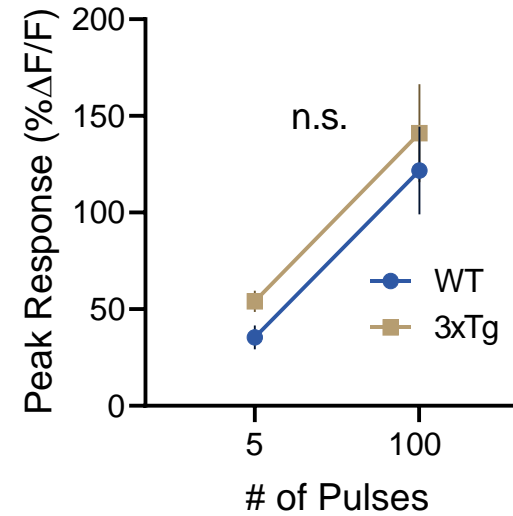
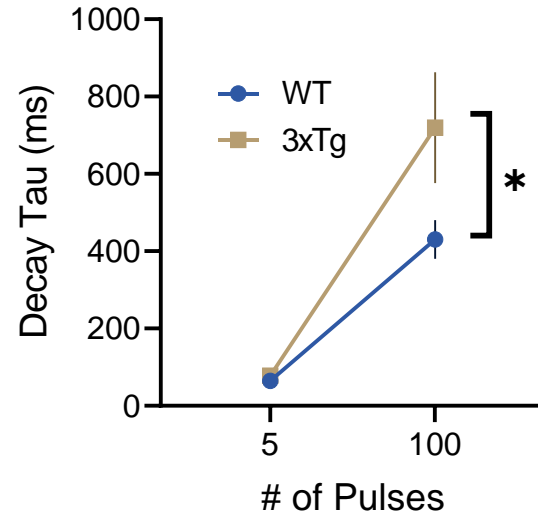
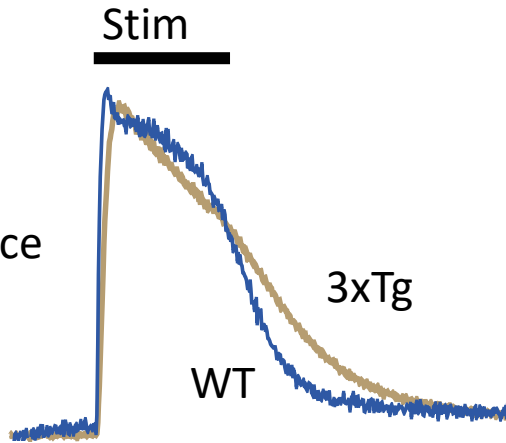
Early disease stage in 3xTg mice



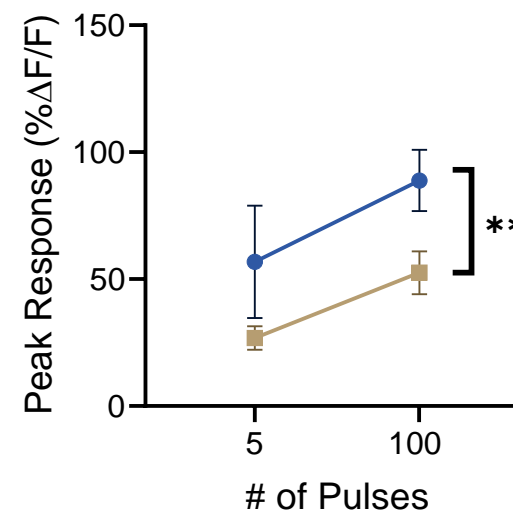
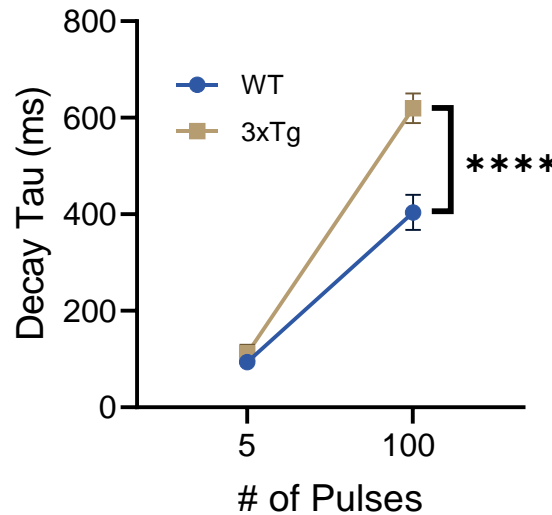
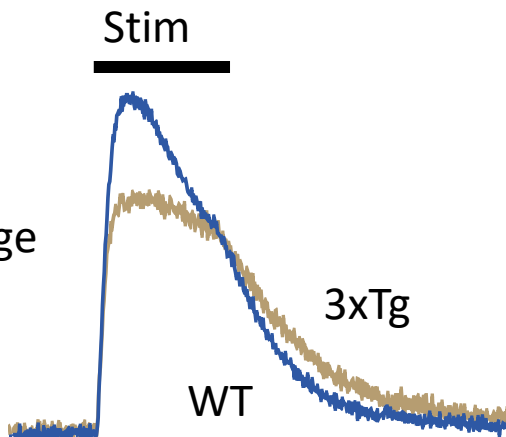
Glutamate levels are prolonged at the presynapse (speaker)



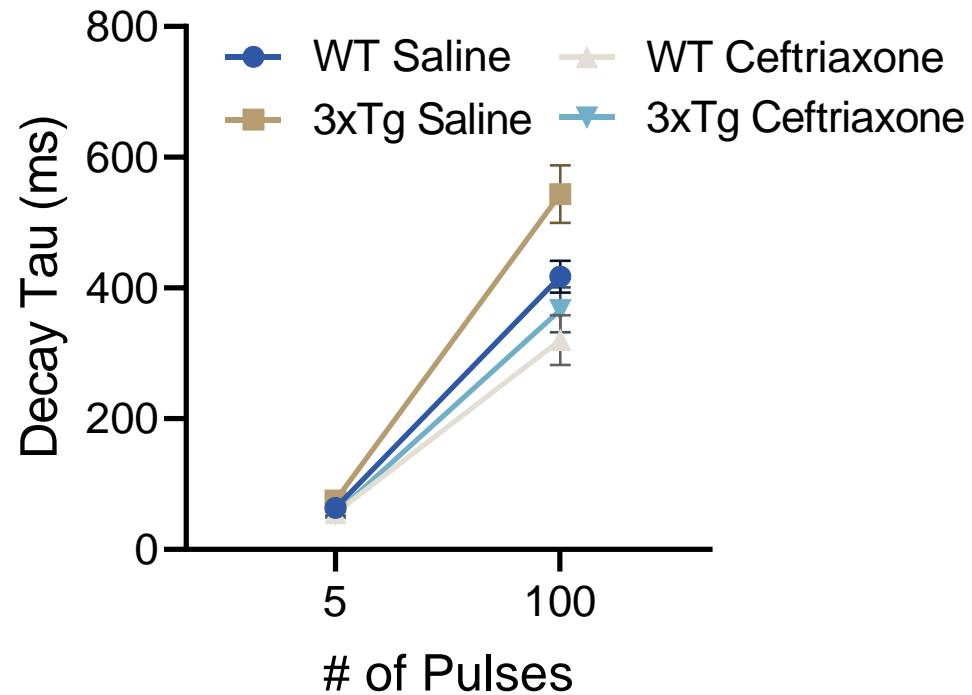
Early disease stage in 3xTg mice



Late disease stage in 3xTg mice



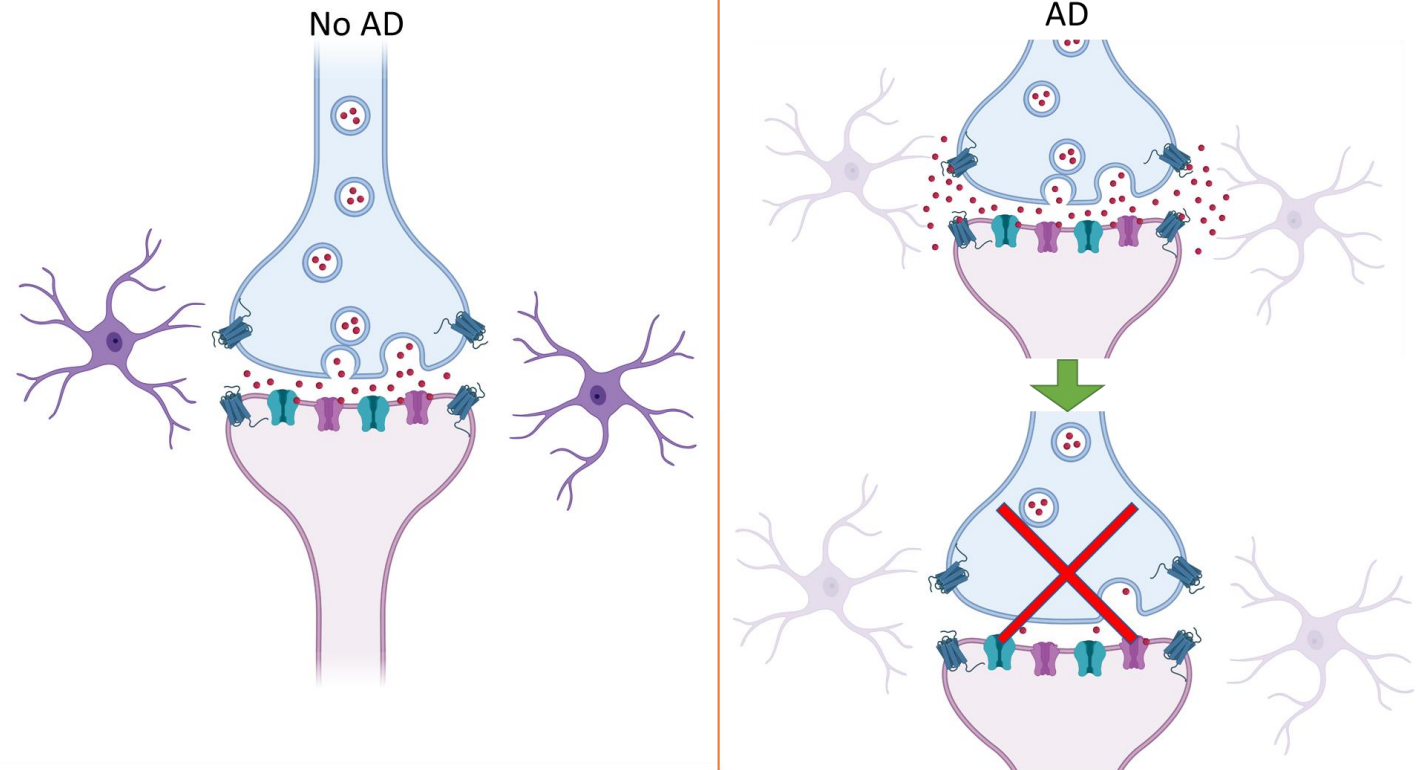
Ceftriaxone restores glutamate levels



Ceftriaxone: A FDA-approved antibiotic that is known to increase GLT-1 (the sponge) in the brain

What we think is happening:

- In the AD brain, the sponges fail.
- Leads to the overactivation of receptors on the presynapse (the speaker)
- Makes the speaker think its speaking too loudly
- Responds by lowering its voice (releases less glutamate)
- Becomes a weak synapse that, if sustained, is eventually eliminated



Is ceftriaxone the cure for AD? Unfortunately, likely not

- High concentrations required
- Ceftriaxone affects more than just the sponge: side effects
- BUT...it does provide us with a better mechanistic understanding of AD that opens up new research paths
- How does the sponge fail in AD and how can we protect them
- What are the exact receptor pools that are overactivated and how can we prevent this?
- Need for early identification! (e.g. PET scanning of SV2A)
- Caveat: of mouse models and the inability to study the same thing in living tissue in the human brain

Summary

- AD is a disease of the synapse
- Preventing synapse weakening and eventual elimination will likely prevent cognitive decline
- Therapeutic strategies that maintain strong synapses are likely be beneficial in AD and other dementias
- **What is needed?**
 - Earlier detection: Who is going to get AD?
 - More detailed understanding of synaptic failure in AD
 - Better bridges between mouse models and humans