

# Alcohol Dependence Neurexin 3

Elif Kurt



# What is Alcohol Dependence?



# What is Alcohol Dependence?



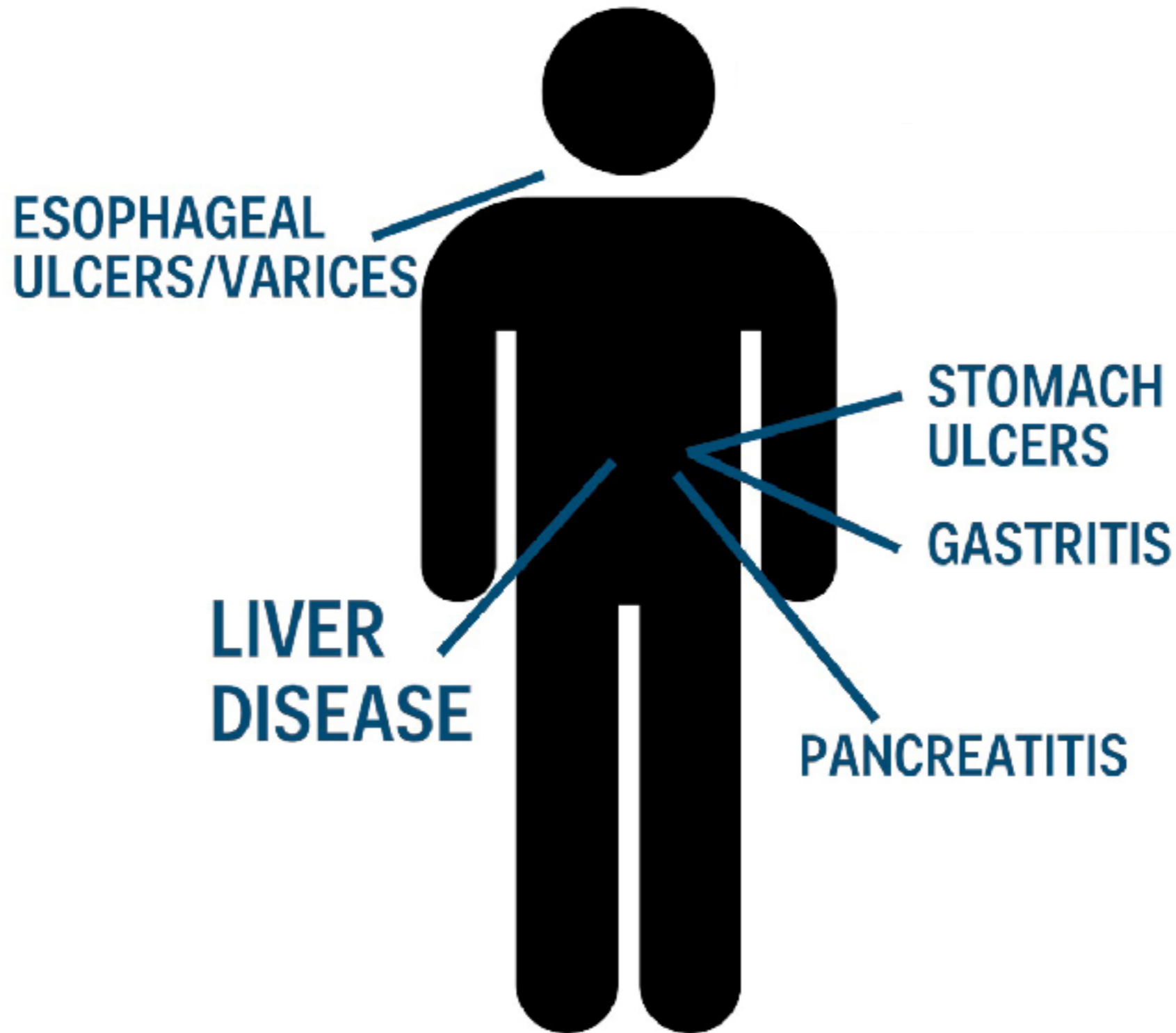
A serious form of drinking problem that describes a strong, almost uncontrollable, desire to drink

What are the signs of Alcohol Dependence?

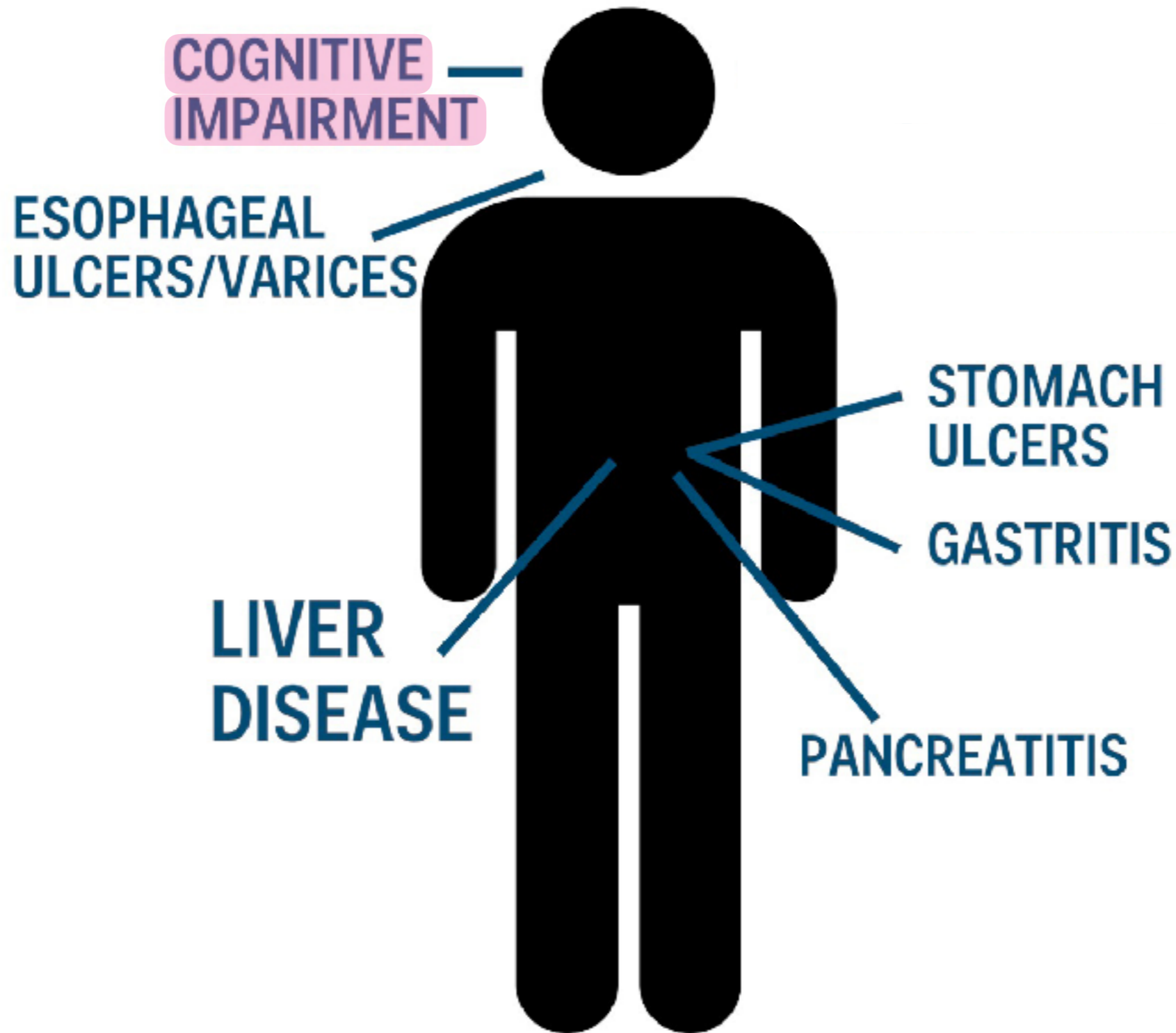
# What are the signs of Alcohol Dependence?



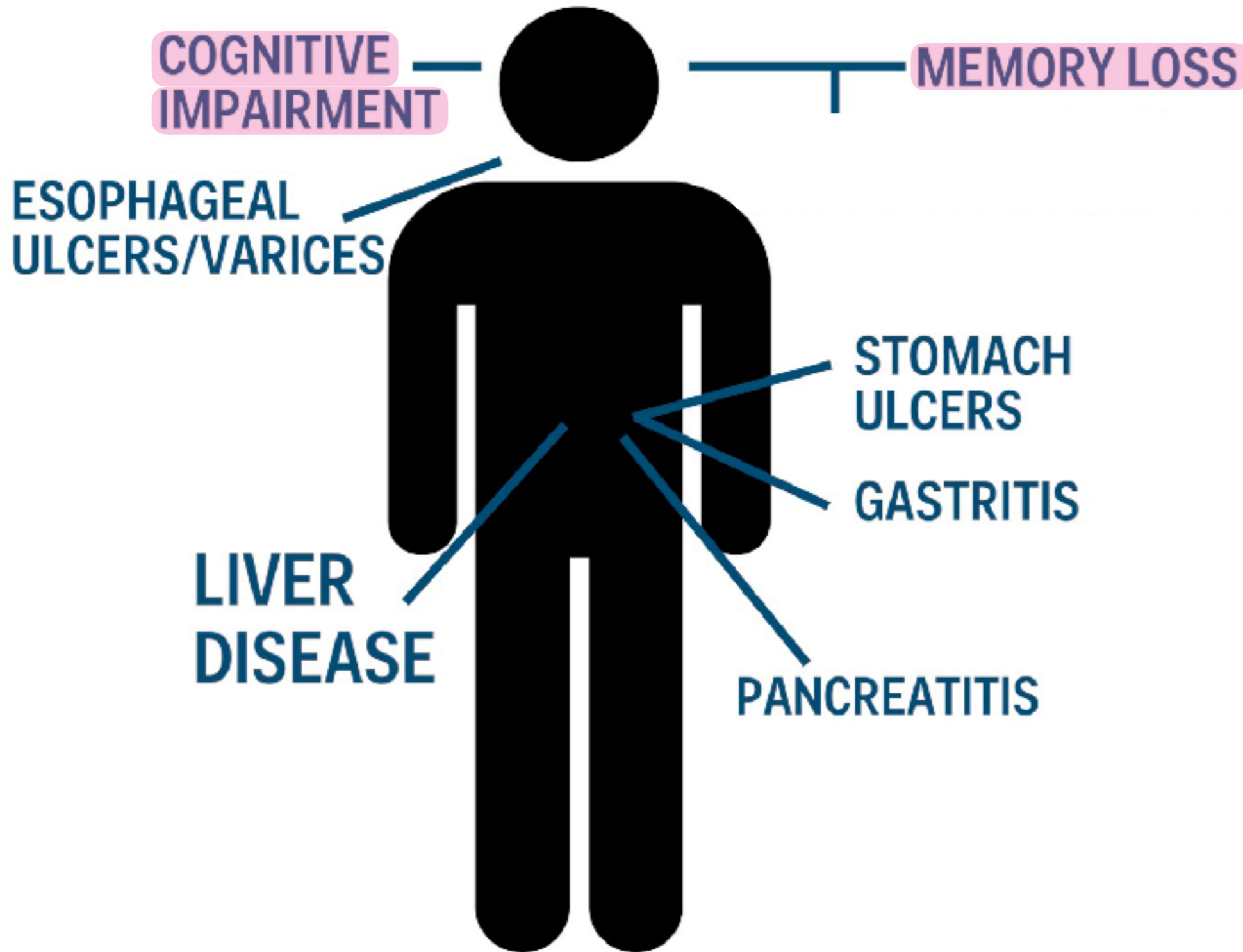
# Alcohol's Affect on the Body



# Alcohol's Affect on the Body

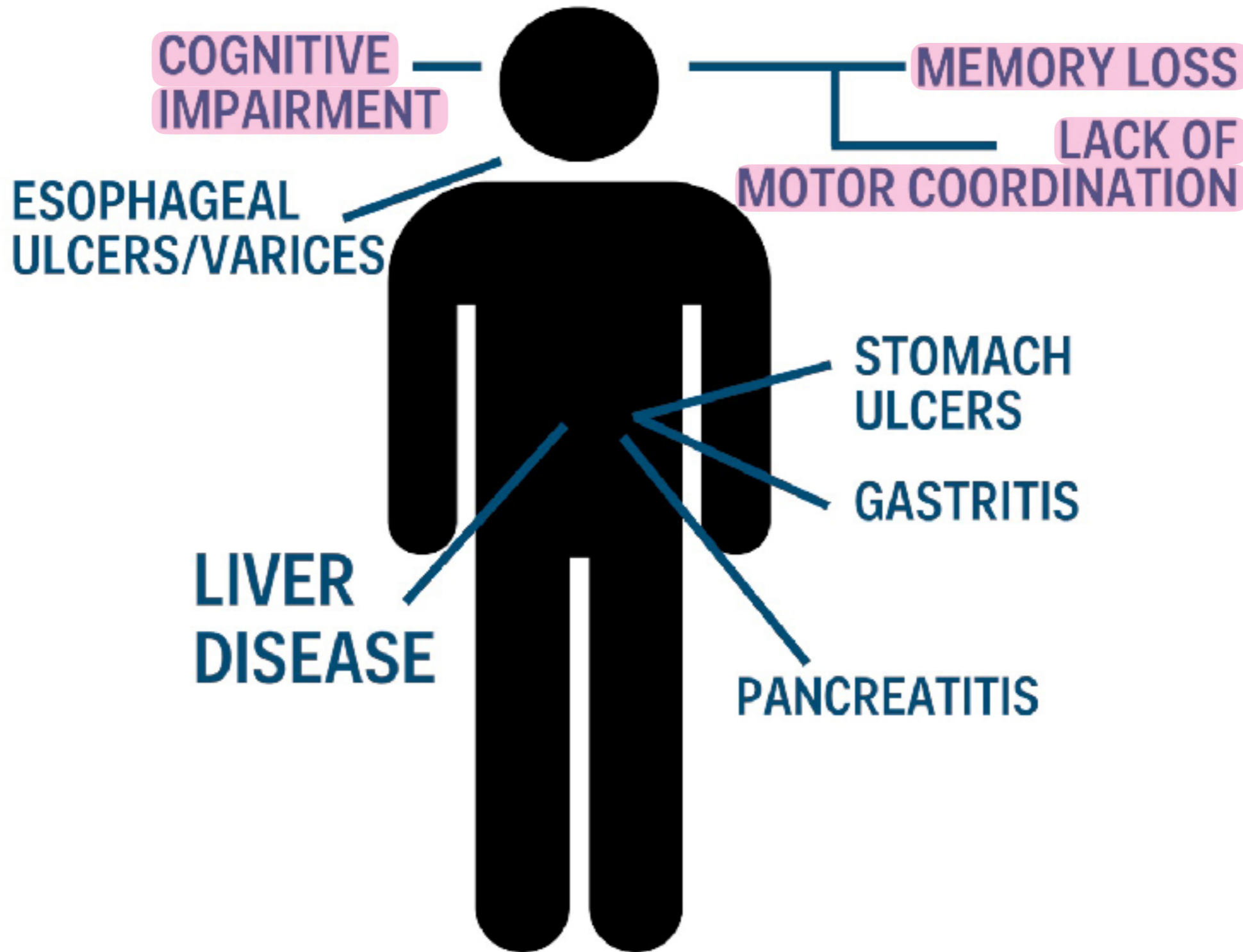


# Alcohol's Affect on the Body

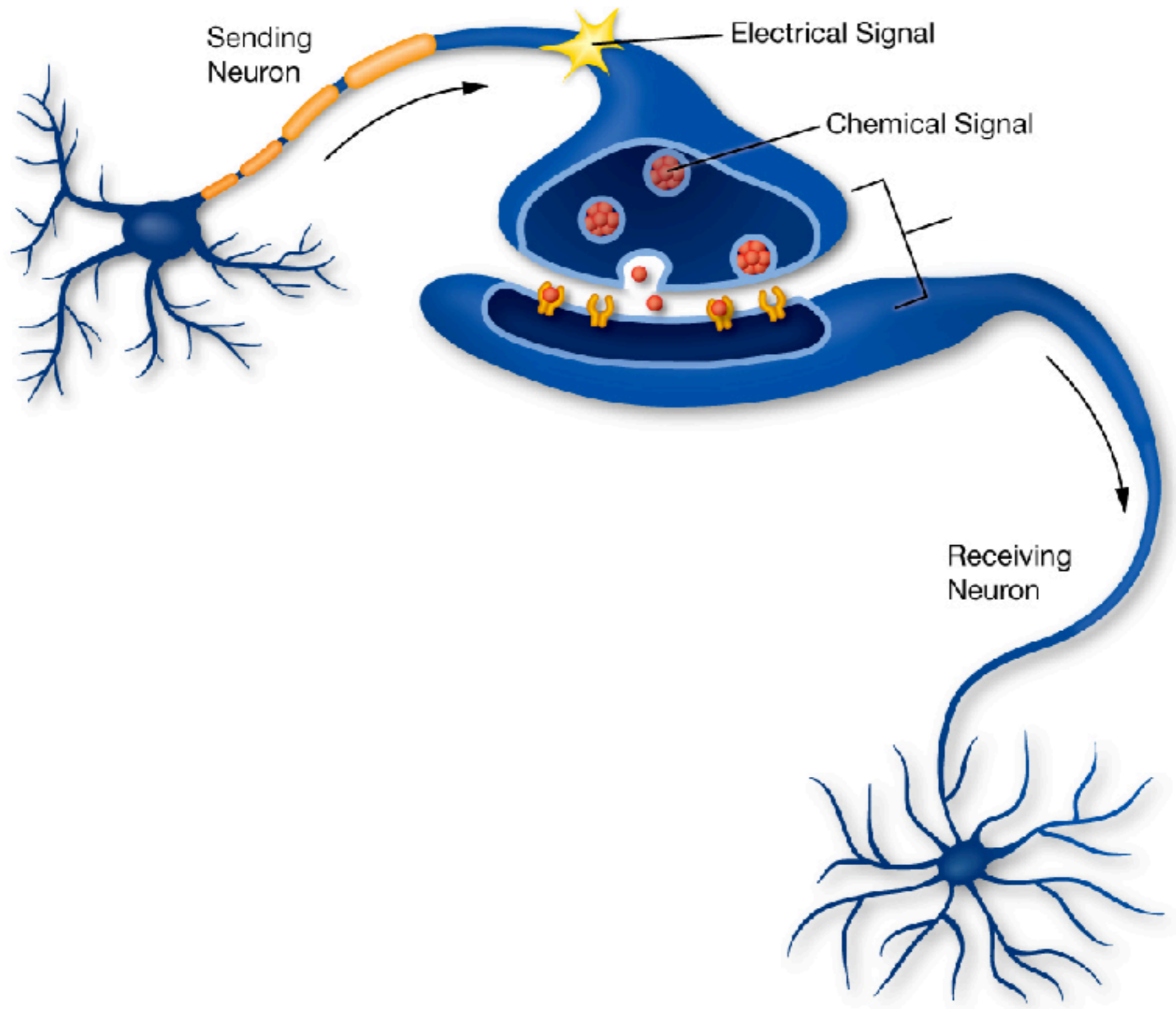




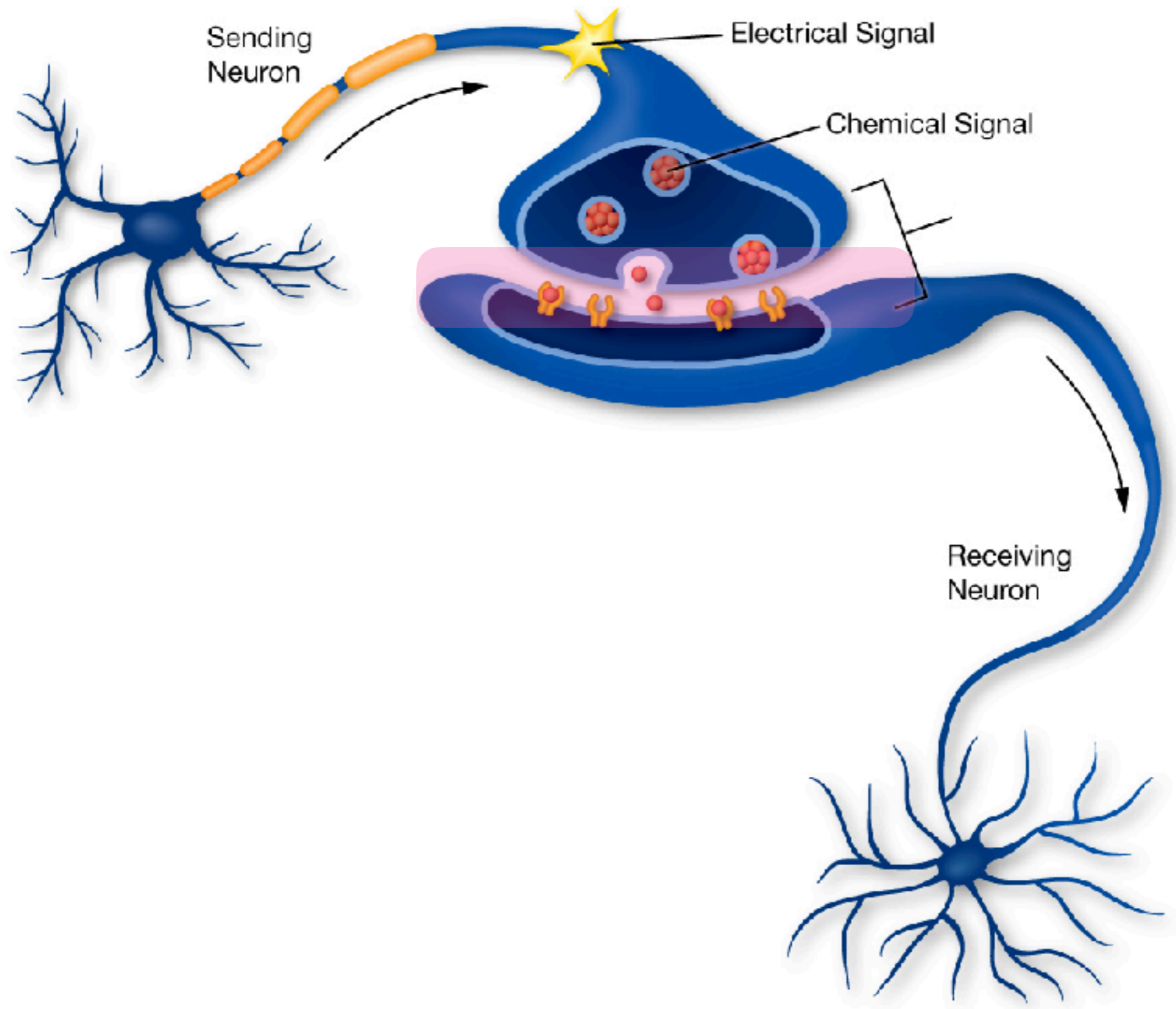
# Alcohol's Affect on the Body



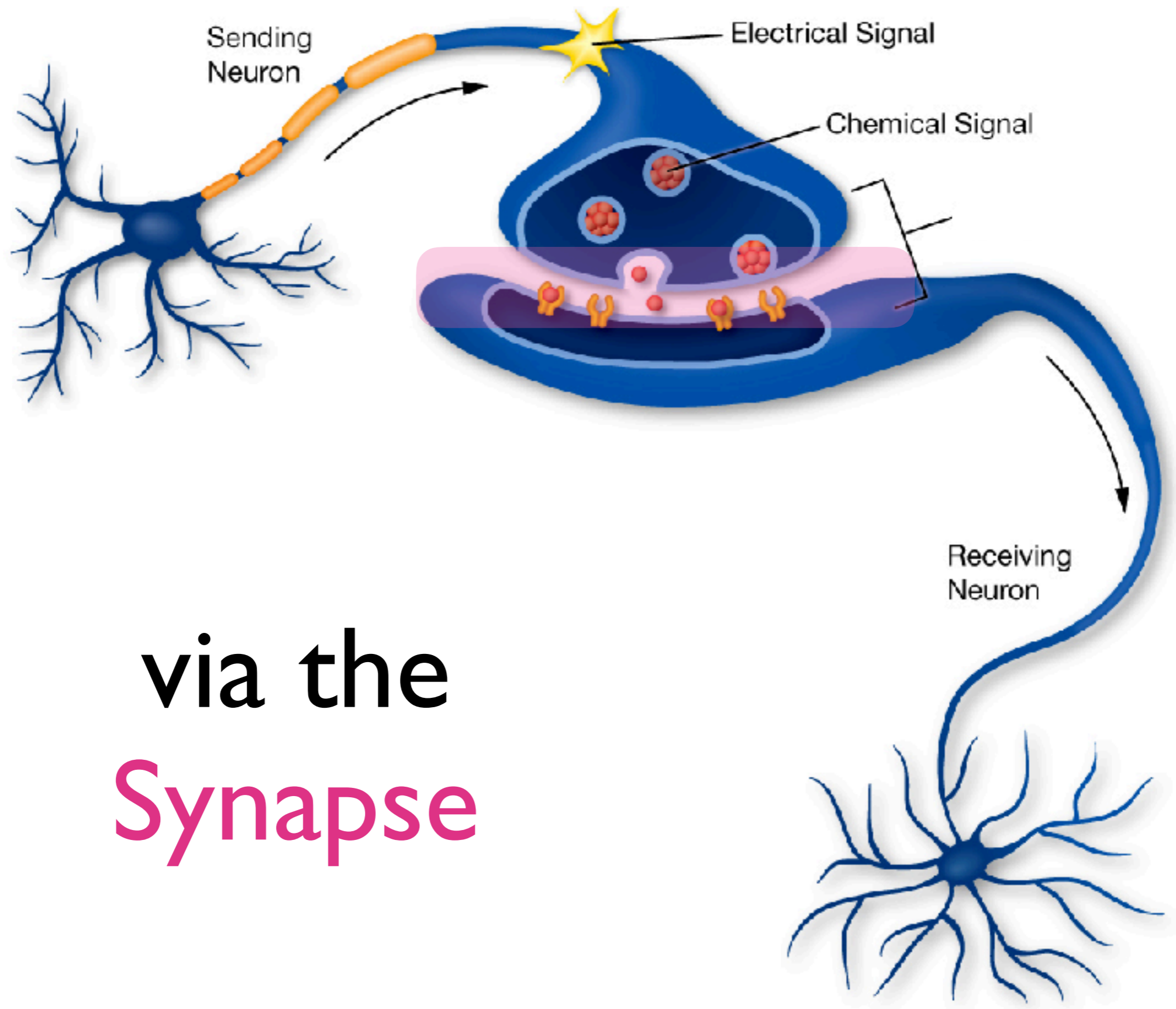
# How do neurons communicate?



# How do neurons communicate?

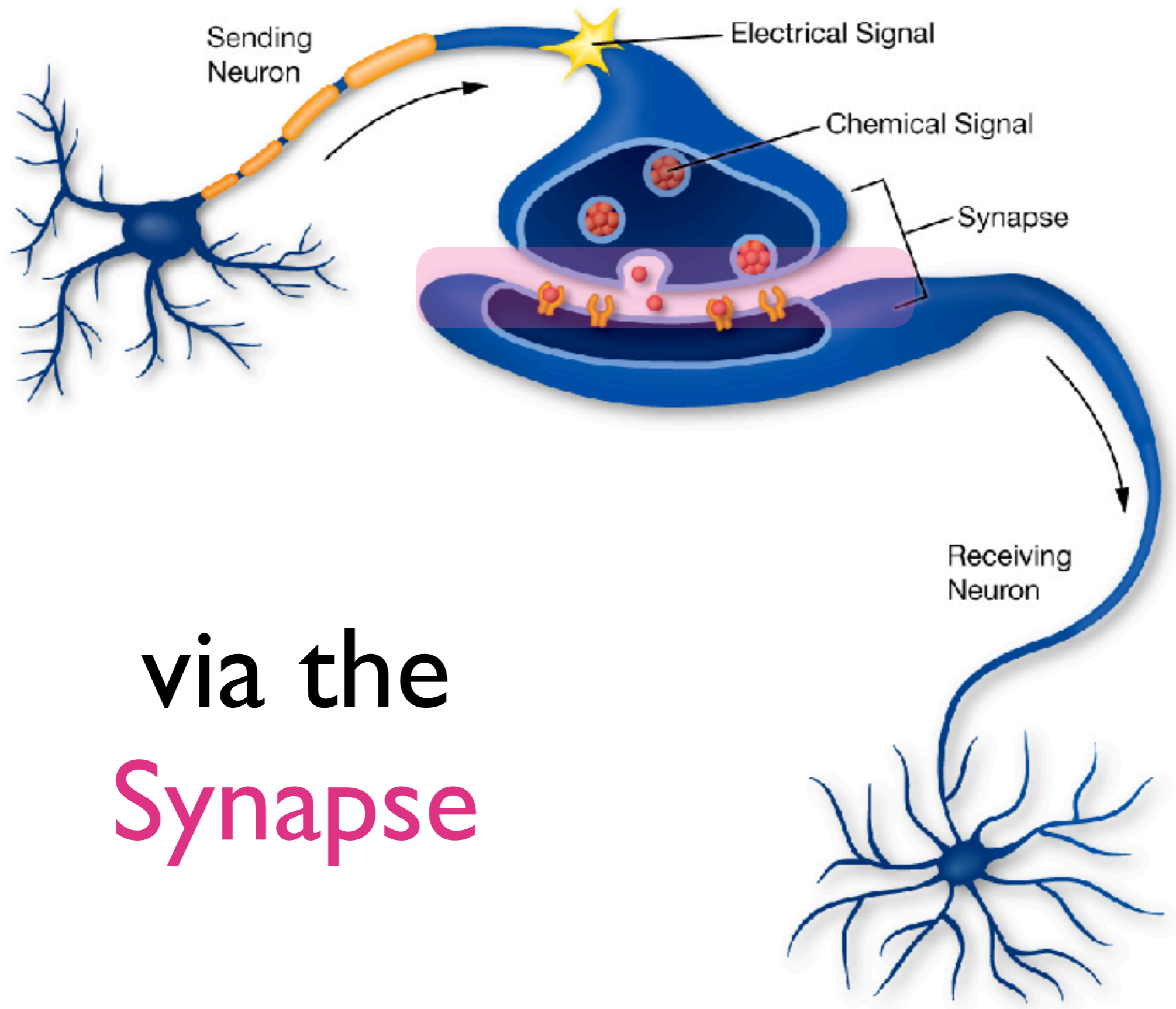


# How do neurons communicate?



via the  
**Synapse**

# How do neurons communicate?



via the  
**Synapse**

# What gene is associated with Alcohol Dependence?



**NRXN3**

# What gene is associated with Alcohol Dependence?



## NRXN3

### Cellular Component

A diagram of a synapse showing the interaction between an axon and a dendritic spine. The axon side includes the presynaptic terminal with Ca<sup>2+</sup> channels and a-Neurexin. The dendritic spine side includes receptor proteins and Neuroigin. A synaptic cleft separates the two. A legend shows a-Neurexin with C and N domains, and Neuroigin with N and C domains. Below the diagram is the text 'Presynaptic Membrane'.

Presynaptic Membrane

### Molecular Function

A diagram illustrating cell adhesion. It shows a branching cell structure on the left and a magnified view of a cell membrane on the right. The magnified view shows a-Neurexin (green) and Neuroigin (purple) interacting with an AMPA glutamate receptor (pink) on the cell membrane. Below the diagram is the text 'Cell Adhesion'.

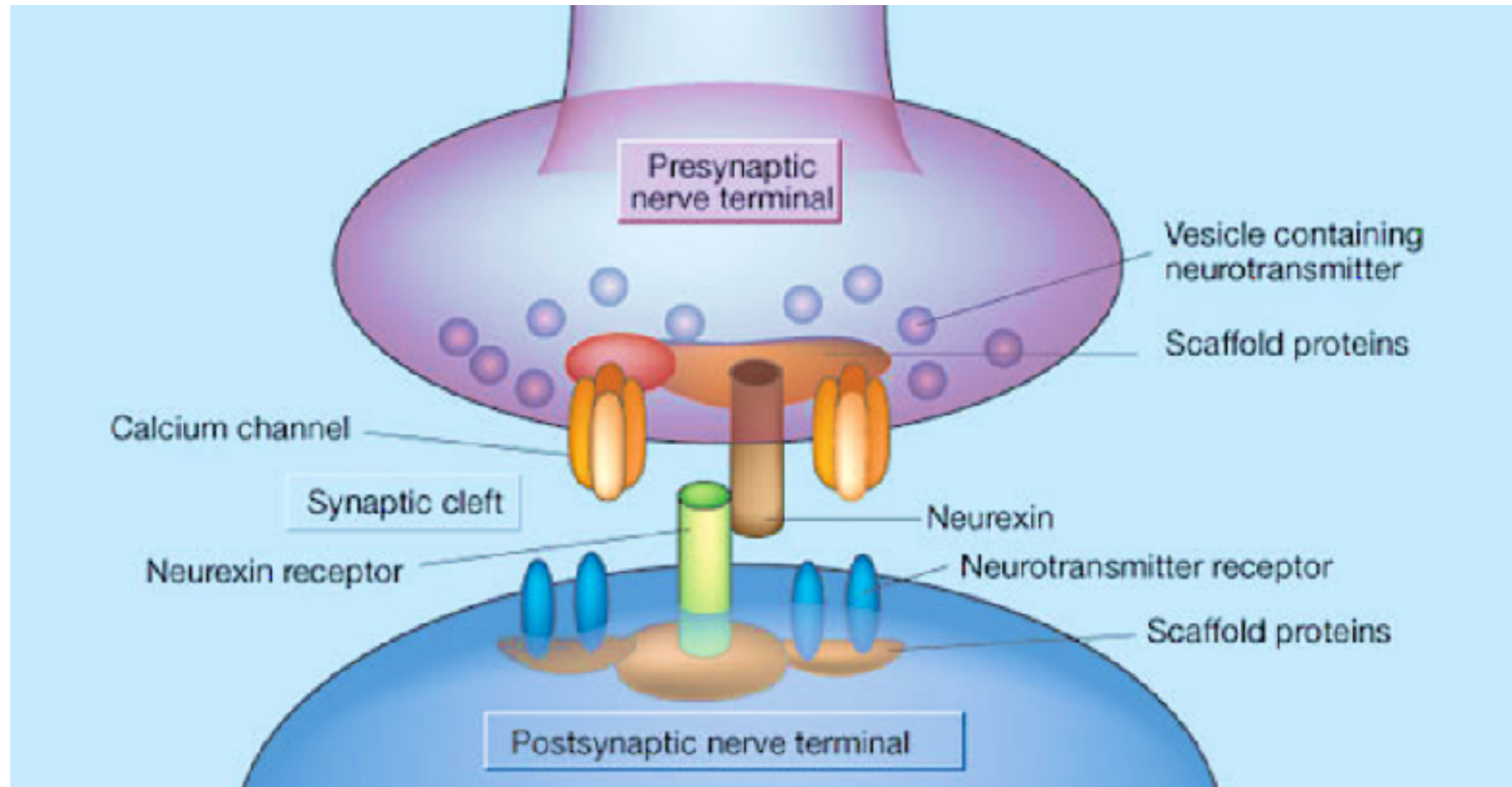
Cell Adhesion

### Biological Process

A diagram illustrating the biological process of synaptogenesis in three stages: Axon Guidance, Axon Guidance, and Synapse Formation. The first stage shows a neurite extending from a cell membrane. The second stage shows the neurite branching. The third stage shows the formation of a presynapse with synaptic vesicles and a postsynapse. Labels include 'neurite axons', 'postsynapse', 'synaptic vesicles', 'presynapse', and 'postsynapse'. Below the diagram is the text 'Synaptogenesis'.

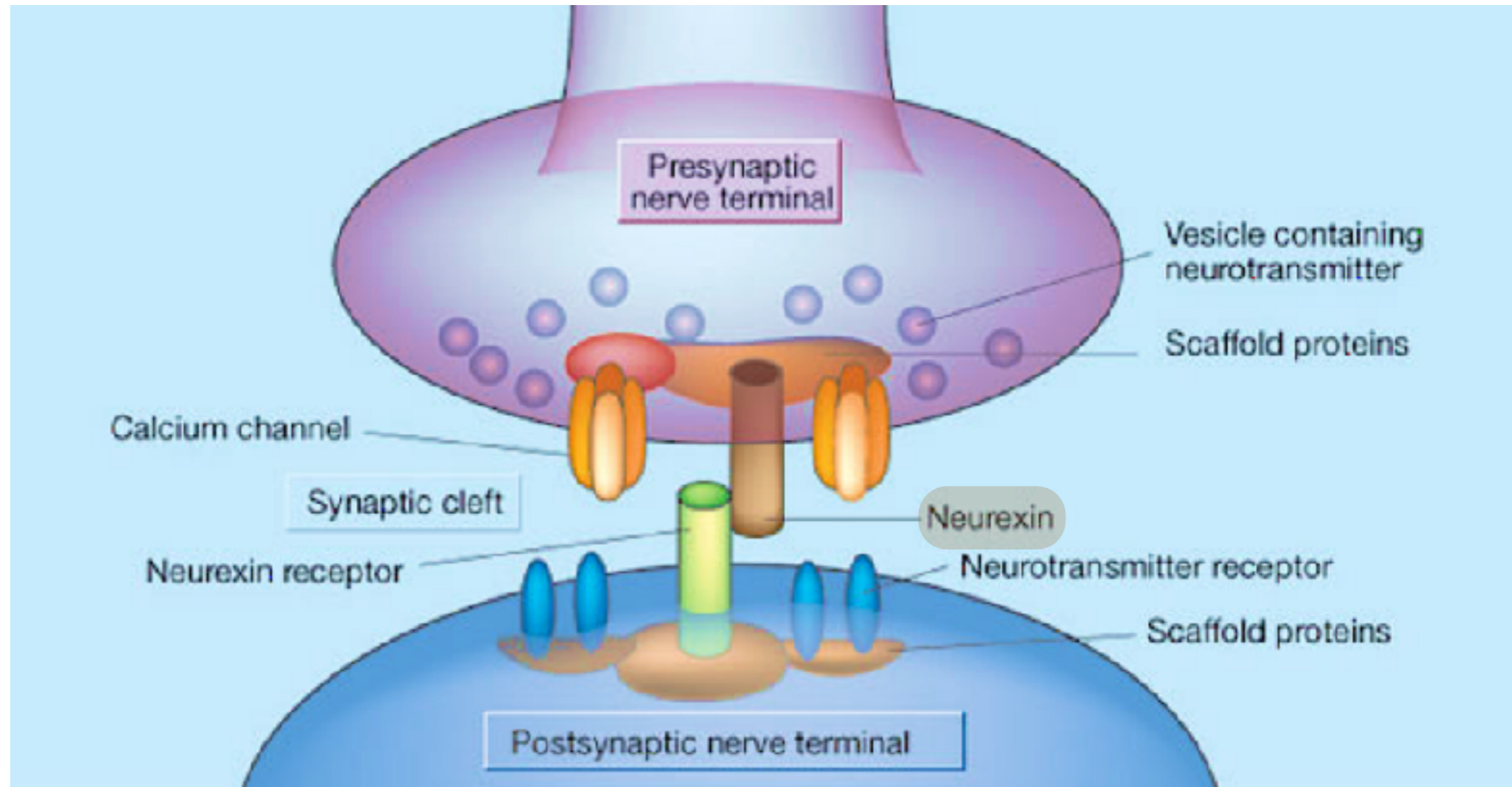
Synaptogenesis

# Neurexins

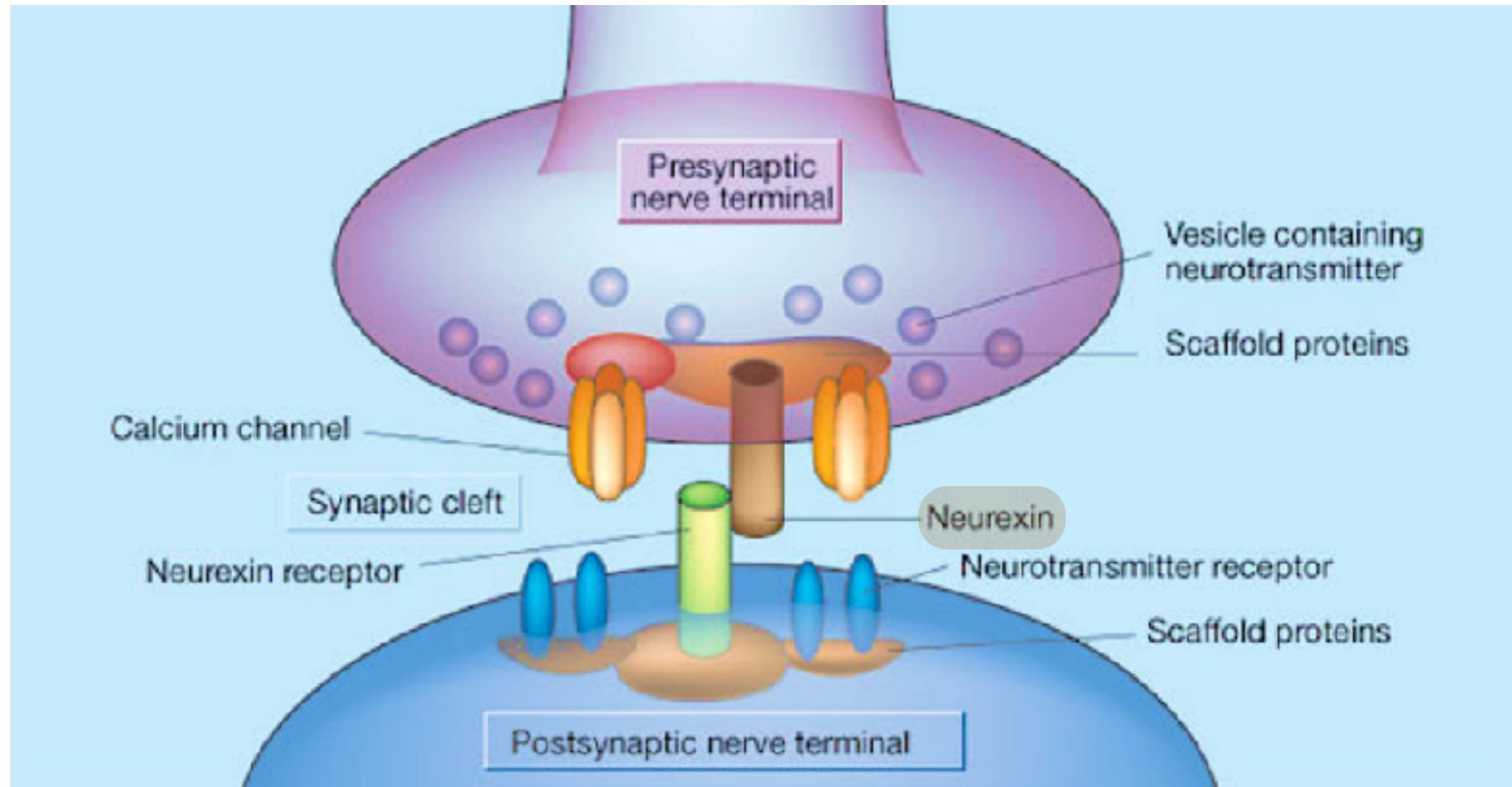




# Neurexins

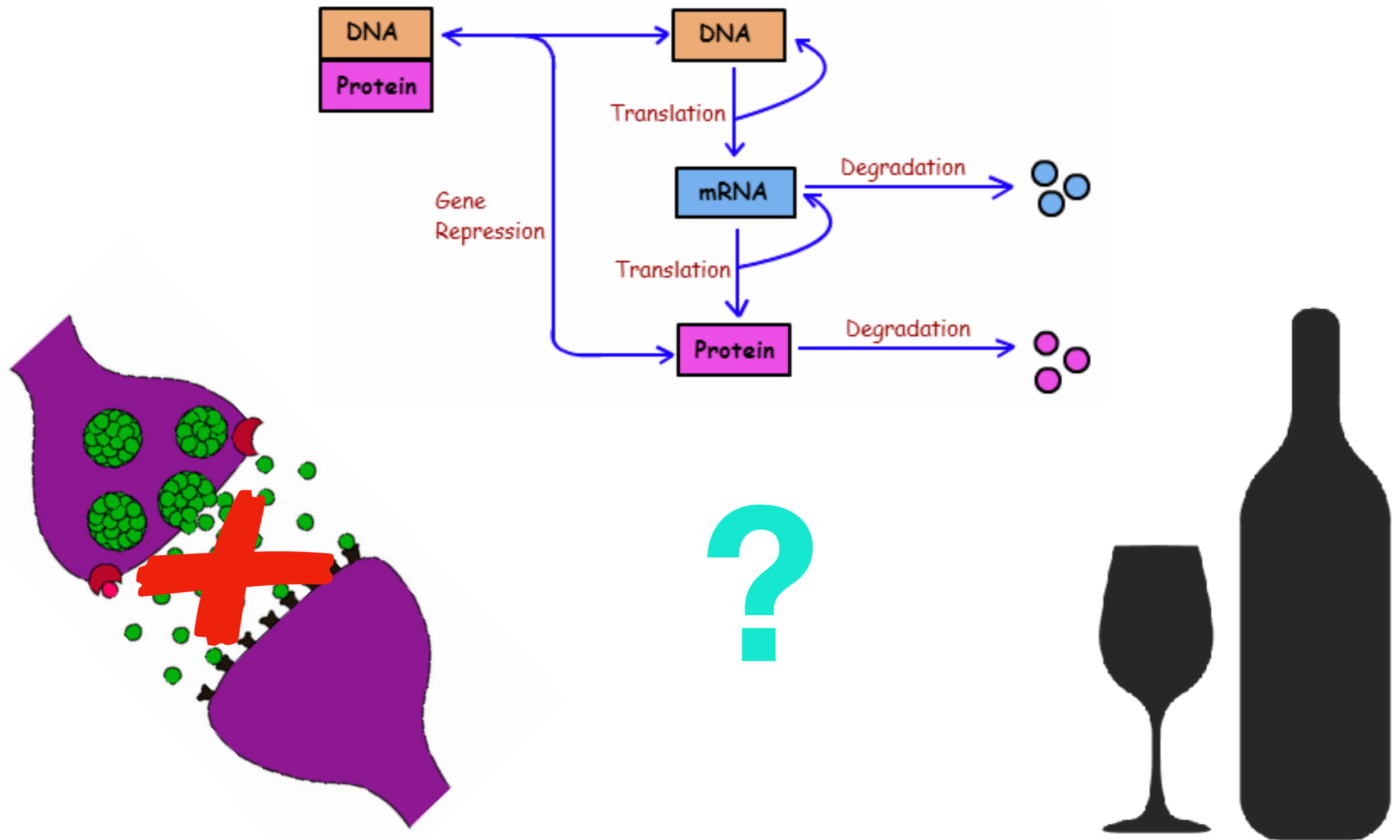


# Neurexins



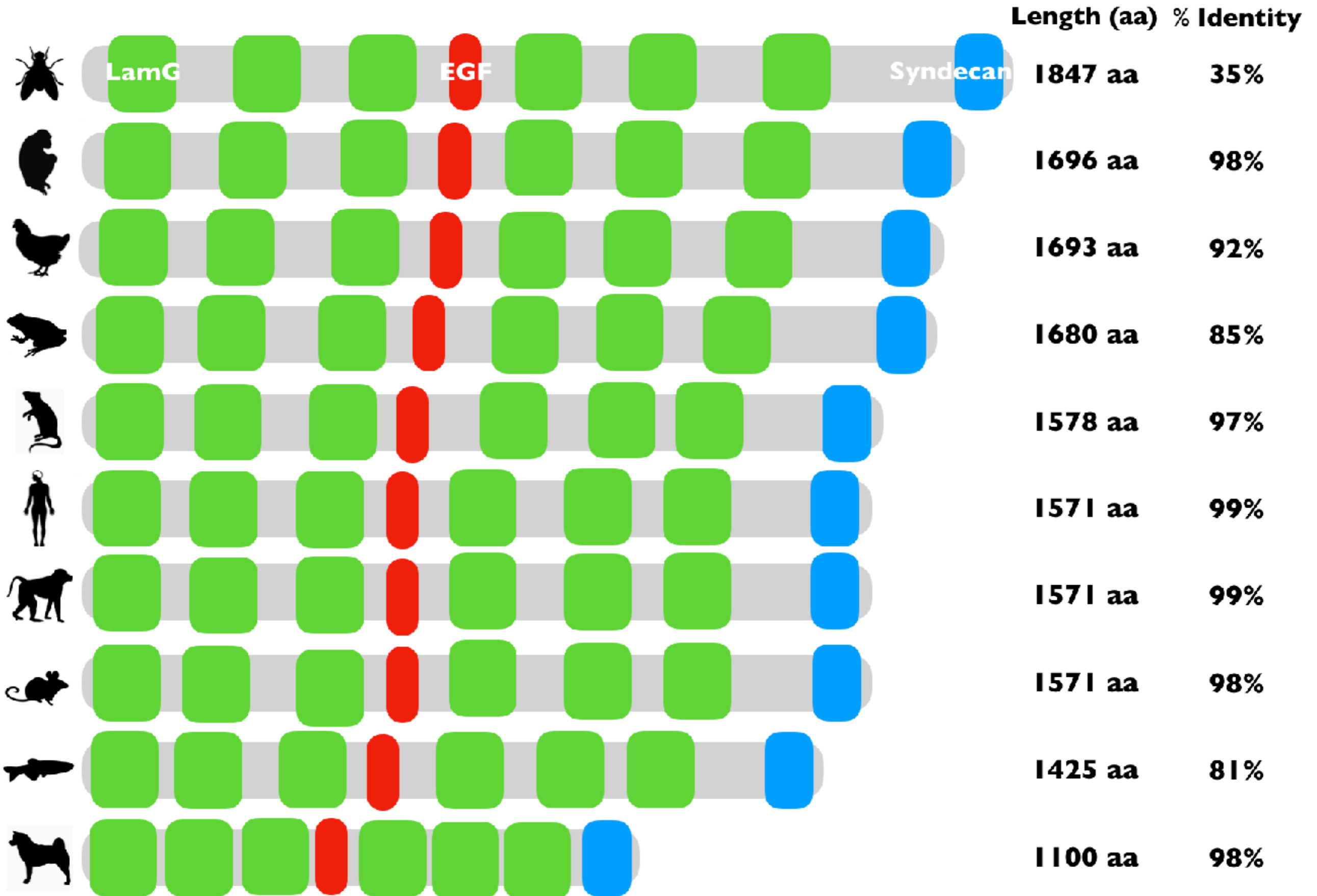
Synaptic cell adhesion molecules that connect neurons and mediate signaling

# What is the gap in knowledge?

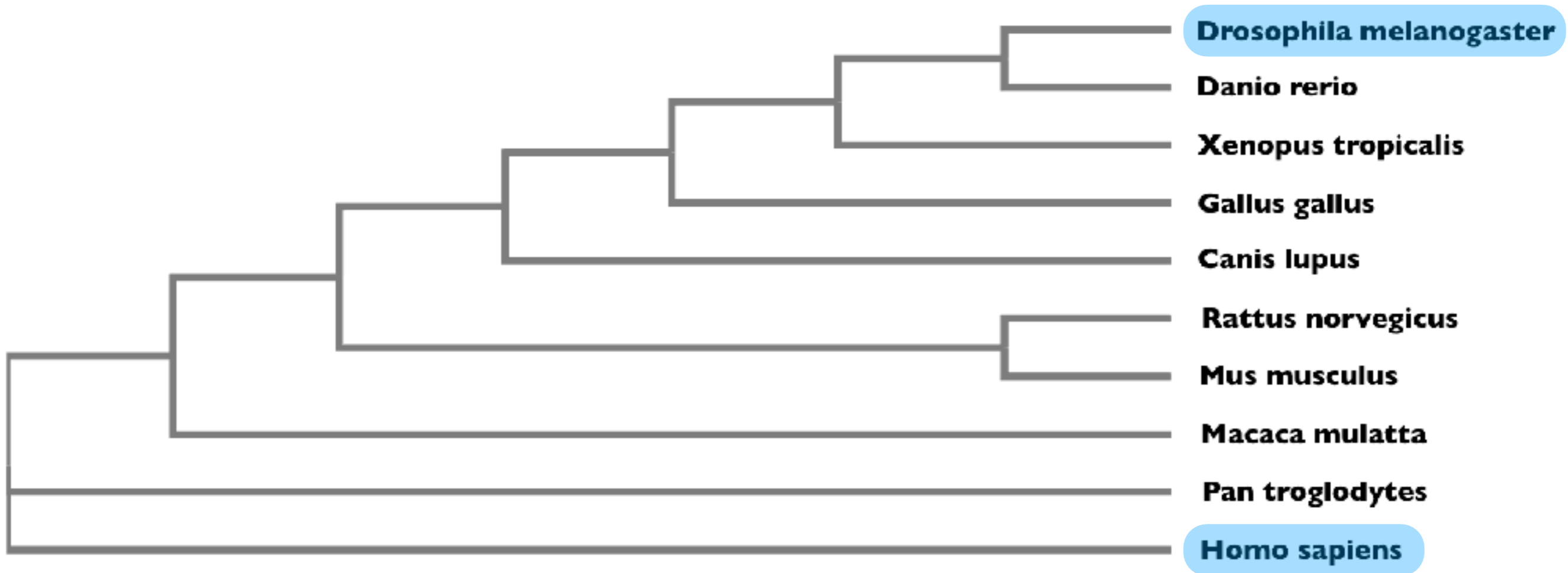


The molecular mechanisms through which **NRXN3** polymorphisms lead to alcohol dependence and synaptic dysfunction remain unclear

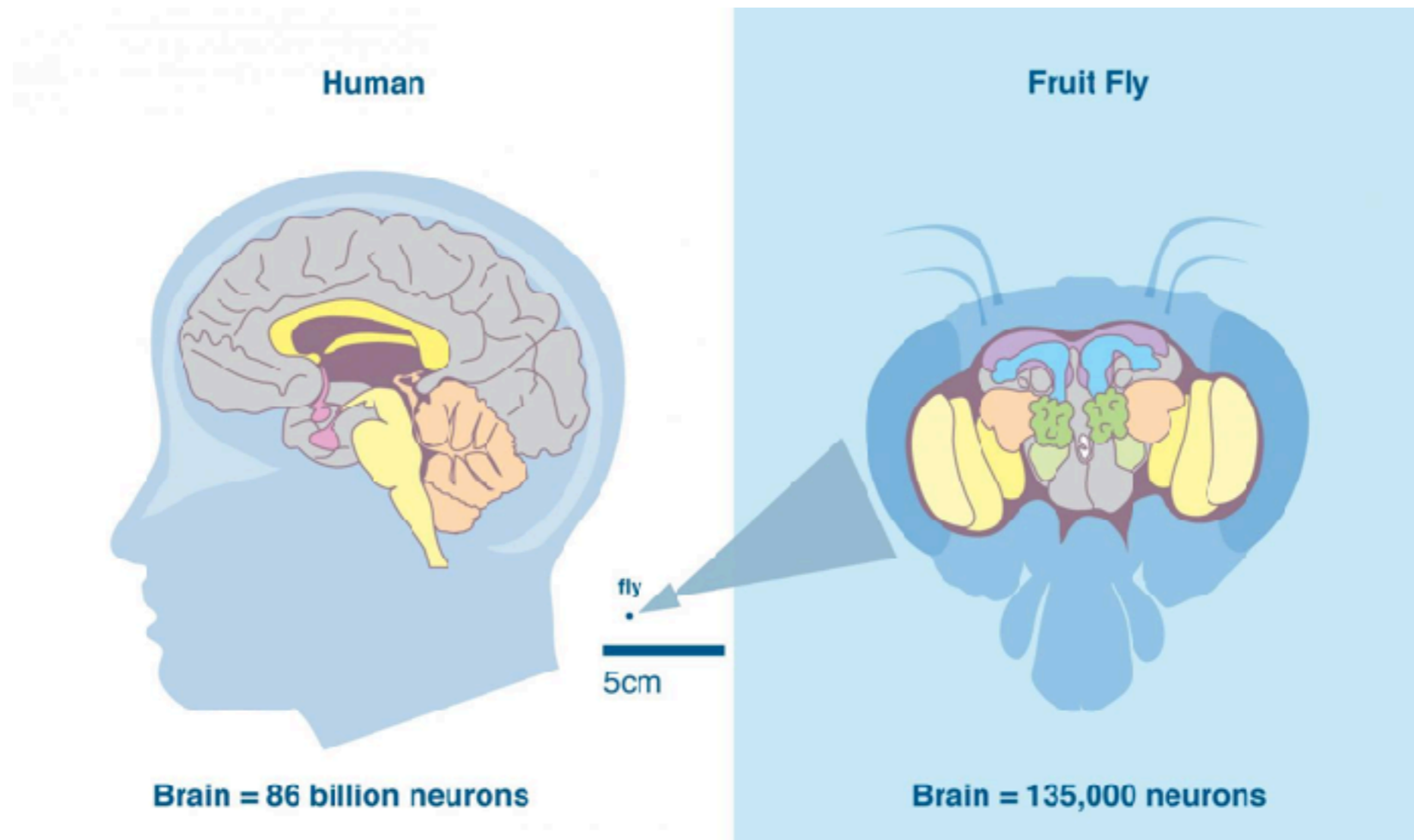
# Is NRXN3 conserved across species?



# Phylogeny



# Model Organism



**Well Conserved**

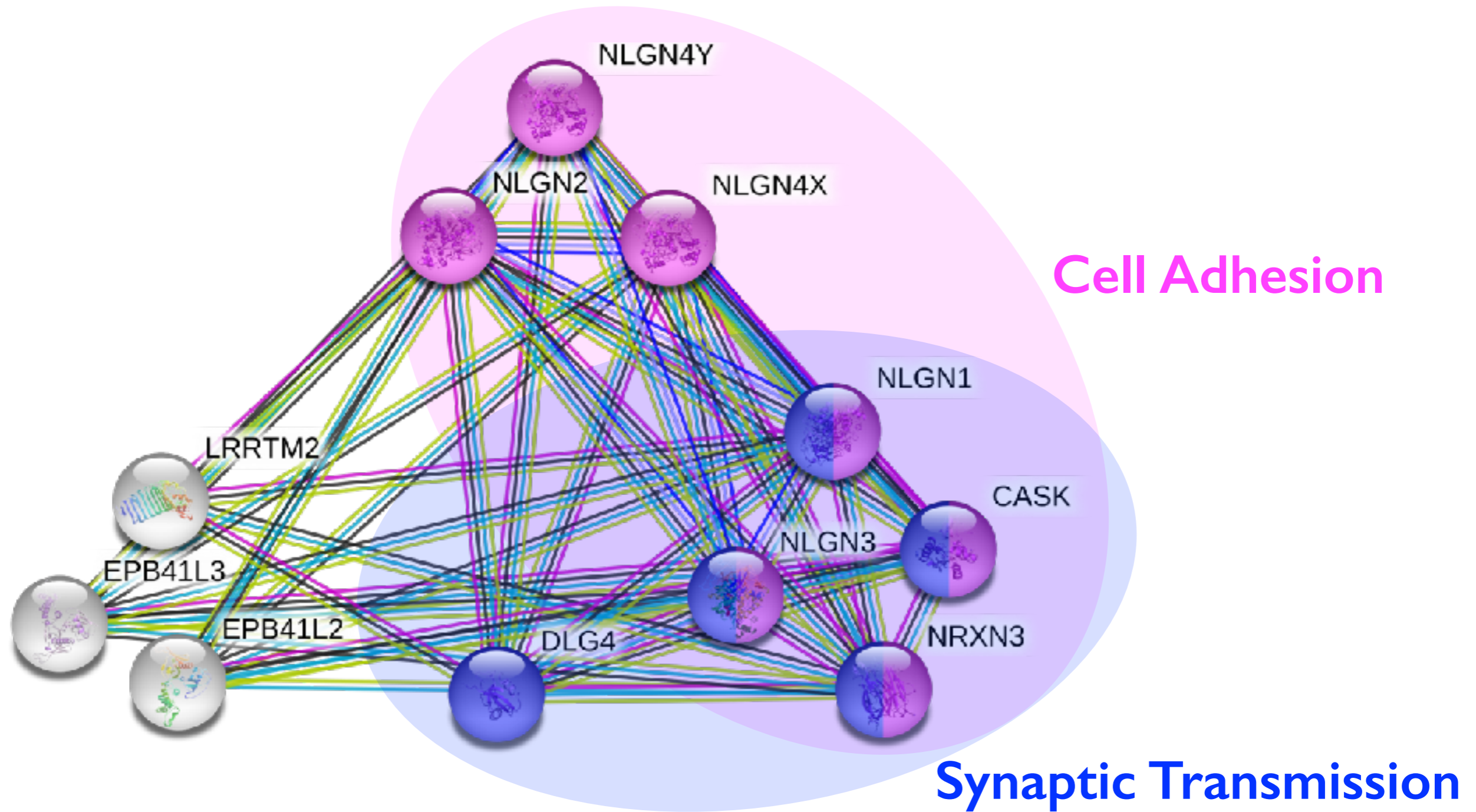
**Short Generation Time**

**Cheap**

**Easy to Access Structures**

**Exhibit Similar Phenotypes to Humans**

# What proteins interact with NRXN3?



CASK is a serine protein kinase that helps control expression of other genes involved in brain development

# What is the primary goal?



To better understand how *NRXN3* mRNA regulation contributes to synaptic dysfunction and ultimately alcohol dependence.

## Aim 1

Characterize conserved amino acids of *NRXN3* crucial for proper synaptic function

## Aim 2

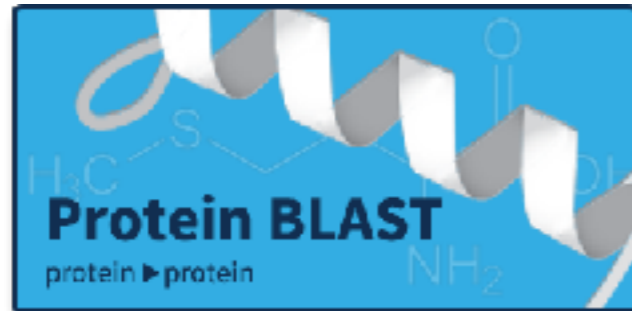
Identify small molecules that rescue *NRXN3* mutant phenotypes

## Aim 3

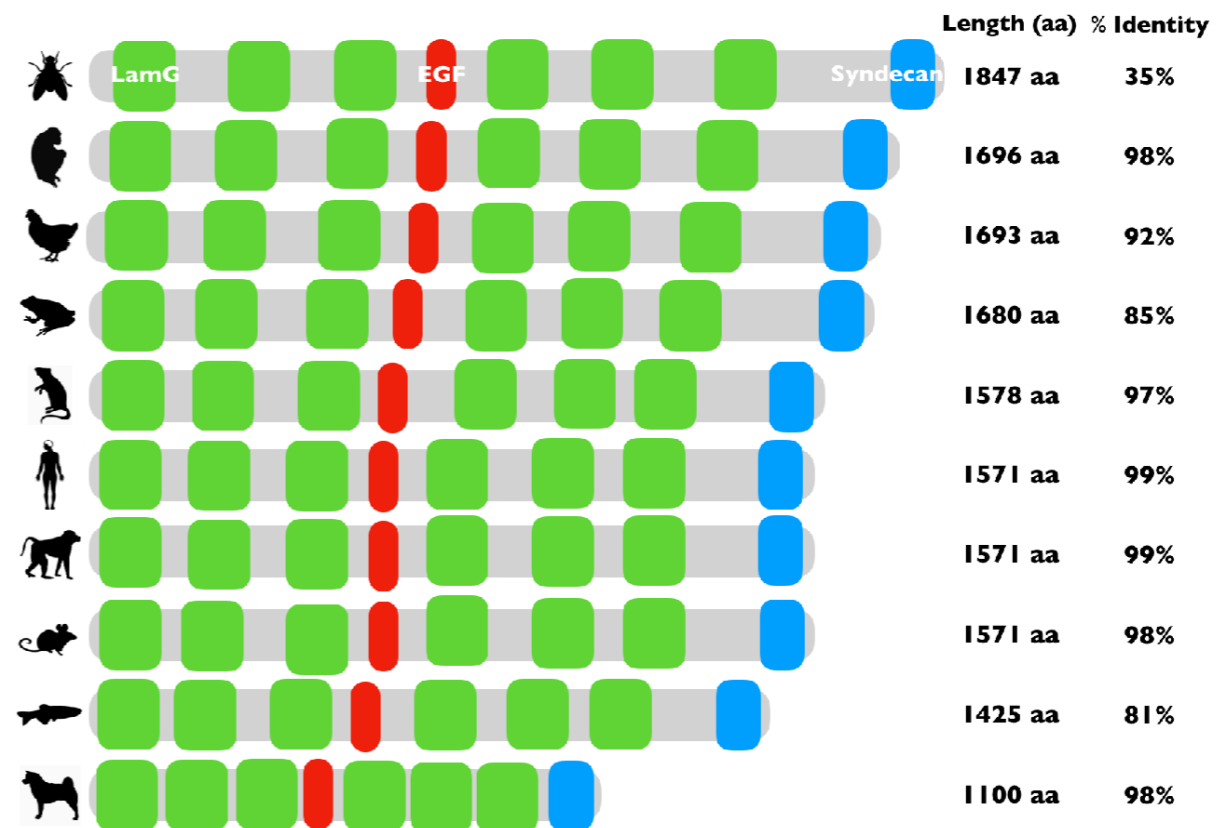
Identify and mutate phosphorylation sites in *NRXN3* to observe effects in the pathway



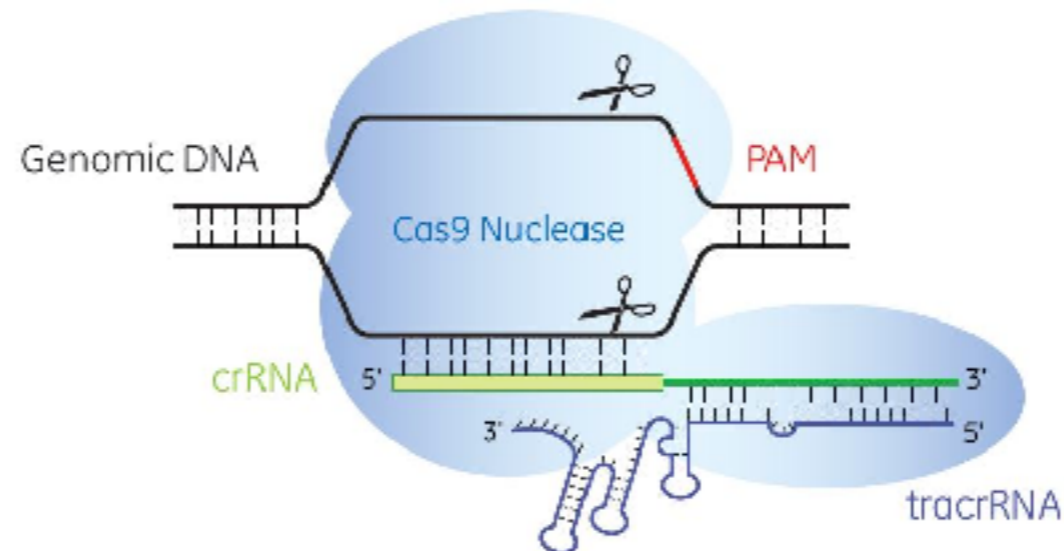
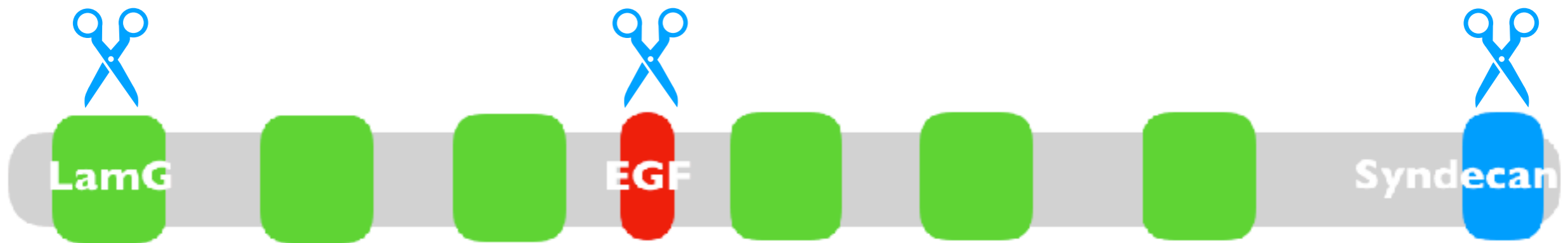
# Aim I: Characterize conserved amino acids of NRXN3 crucial for proper synaptic function



Sequence Alignment



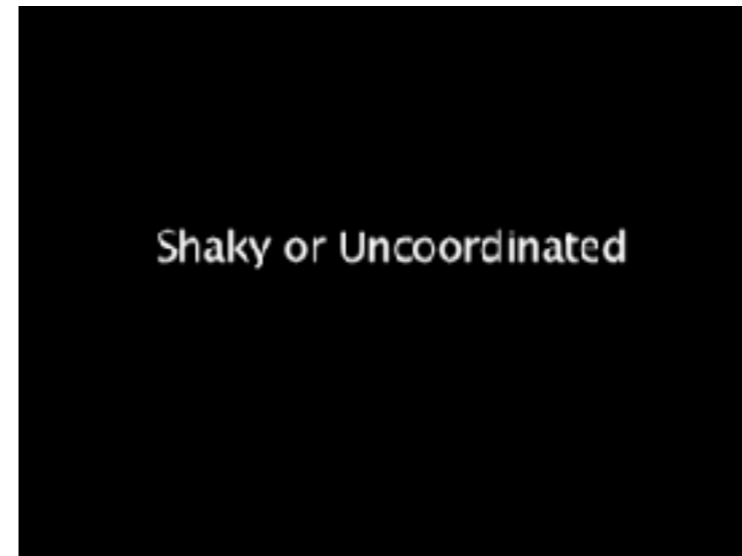
# Aim I: Characterize conserved amino acids of NRXN3 crucial for proper synaptic function



# Aim I: Characterize conserved amino acids of NRXN3 crucial for proper synaptic function



Wild Type  
Coordinated



Mutant  
Uncoordinated

**Hypothesis:** Specific conserved amino acids in NRXN3 correlate with proper synaptic function and decreased alcohol dependence.

# Aim I: Characterize conserved amino acids of NRXN3 crucial for proper synaptic function



Wild Type  
Coordinated



Shaky or Uncoordinated



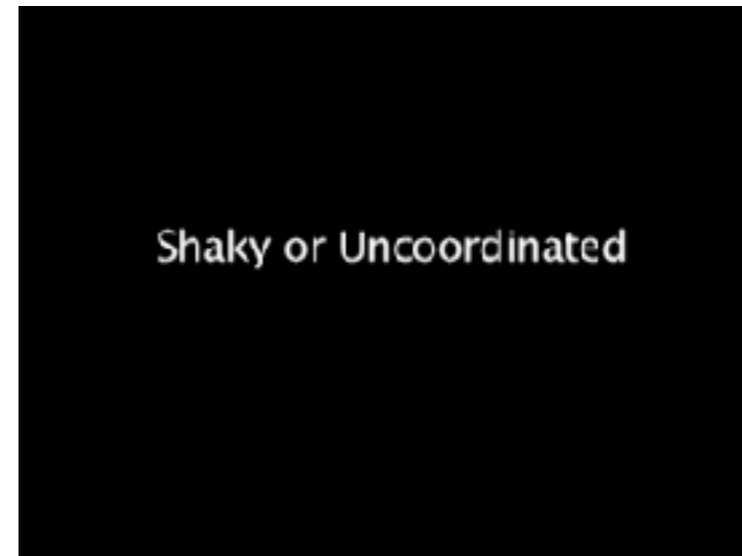
Mutant  
Uncoordinated

**Hypothesis:** Specific conserved amino acids in NRXN3 correlate with proper synaptic function and decreased alcohol dependence.

# Aim I: Characterize conserved amino acids of NRXN3 crucial for proper synaptic function



Wild Type  
Coordinated



Mutant  
Uncoordinated

**Hypothesis:** Specific conserved amino acids in NRXN3 correlate with proper synaptic function and decreased alcohol dependence.

# **Aim 2:** Identify small molecules that rescue **NRXN3** mutant phenotypes



# **Aim 2:** Identify small molecules that rescue **NRXN3** mutant phenotypes



**Wild Type**  
**Coordinated**

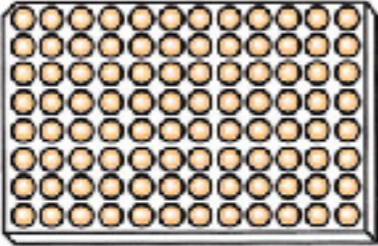


**Mutant**  
**Uncoordinated**

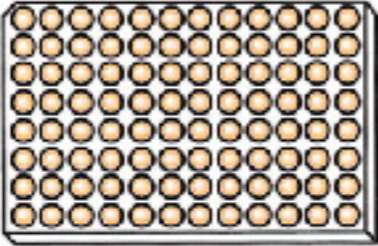
# Aim 2: Identify small molecules that rescue NRXN3 mutant phenotypes



**Wild Type  
Coordinated**




**Mutant  
Uncoordinated**

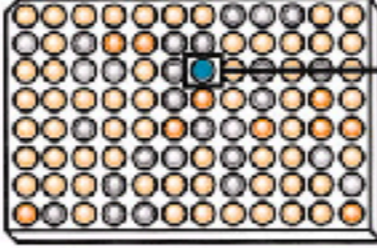
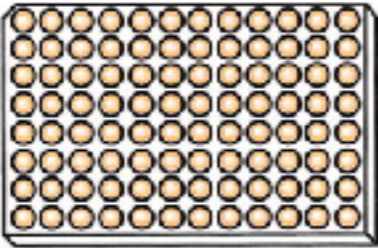




# Aim 2: Identify small molecules that rescue NRXN3 mutant phenotypes

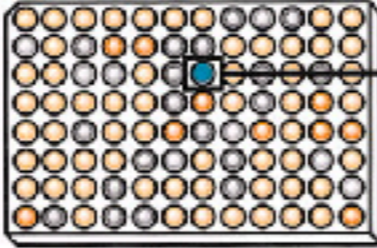
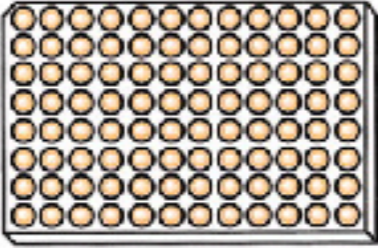


  
**Wild Type**  
**Coordinated**



Screen for phenotypic changes ←


  
**Mutant**  
**Uncoordinated**

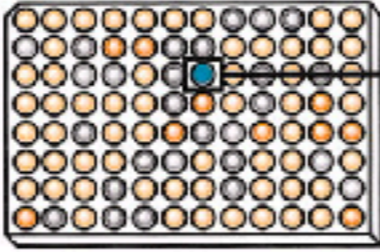
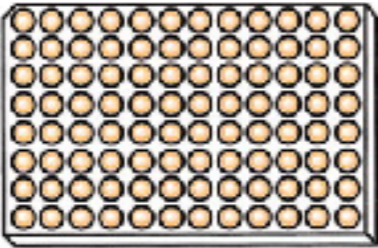


Screen for phenotypic changes ←

# Aim 2: Identify small molecules that rescue NRXN3 mutant phenotypes

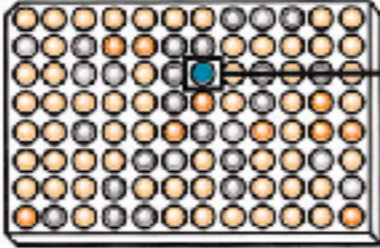
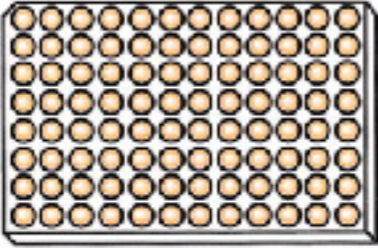


  
Wild Type  
Coordinated

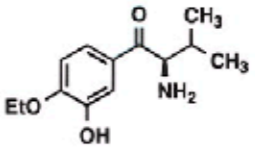


Screen for phenotypic changes

  
Mutant  
Uncoordinated




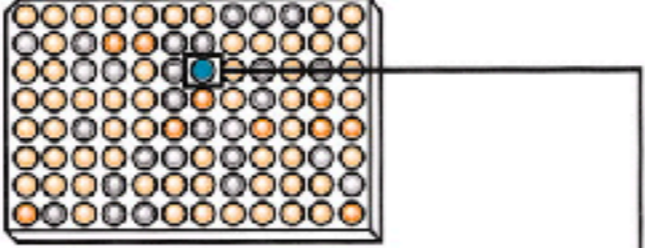
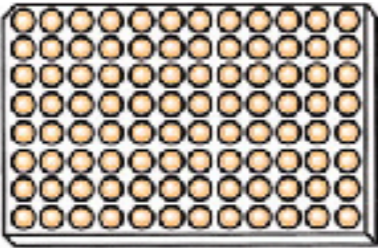
Screen for phenotypic changes



# Aim 2: Identify small molecules that rescue NRXN3 mutant phenotypes



  
**Wild Type**  
**Coordinated**

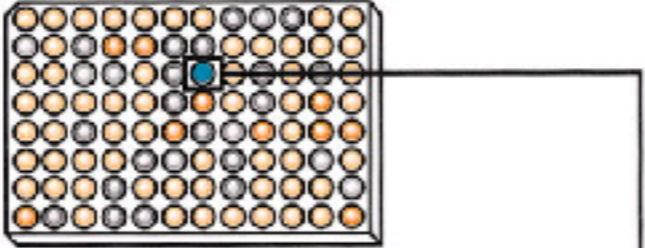
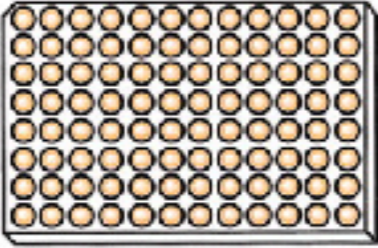


Screen for phenotypic changes

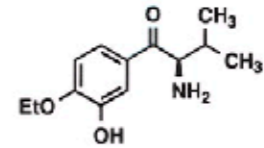


  
**Coordinated**

  
**Mutant**  
**Uncoordinated**




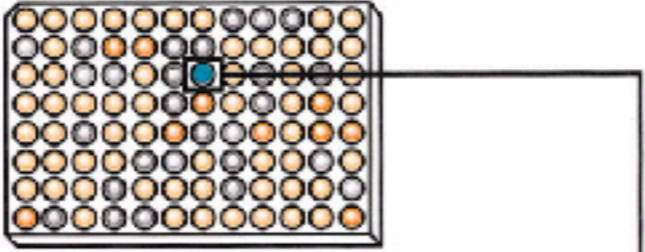
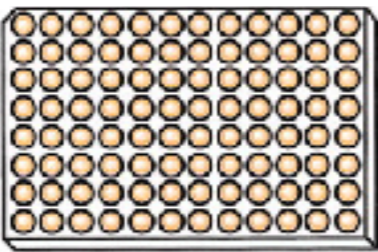
Screen for phenotypic changes



# Aim 2: Identify small molecules that rescue NRXN3 mutant phenotypes



  
**Wild Type**  
**Coordinated**

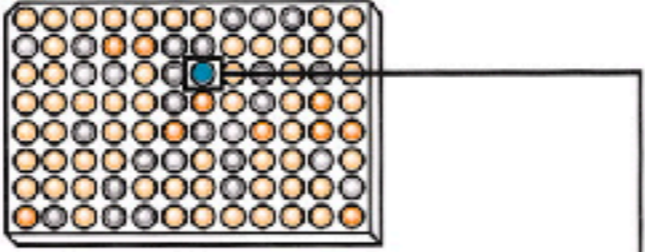
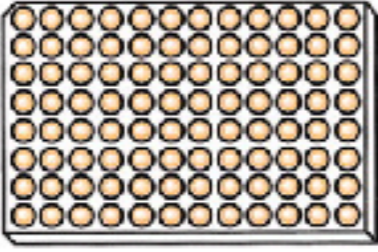


*Screen for phenotypic changes*

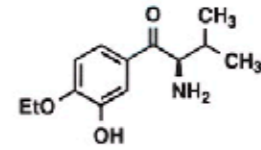


  
**Coordinated**

  
**Mutant**  
**Uncoordinated**



*Screen for phenotypic changes*



  
**Coordinated**

# **Aim 2:** Identify small molecules that rescue **NRXN3** mutant phenotypes



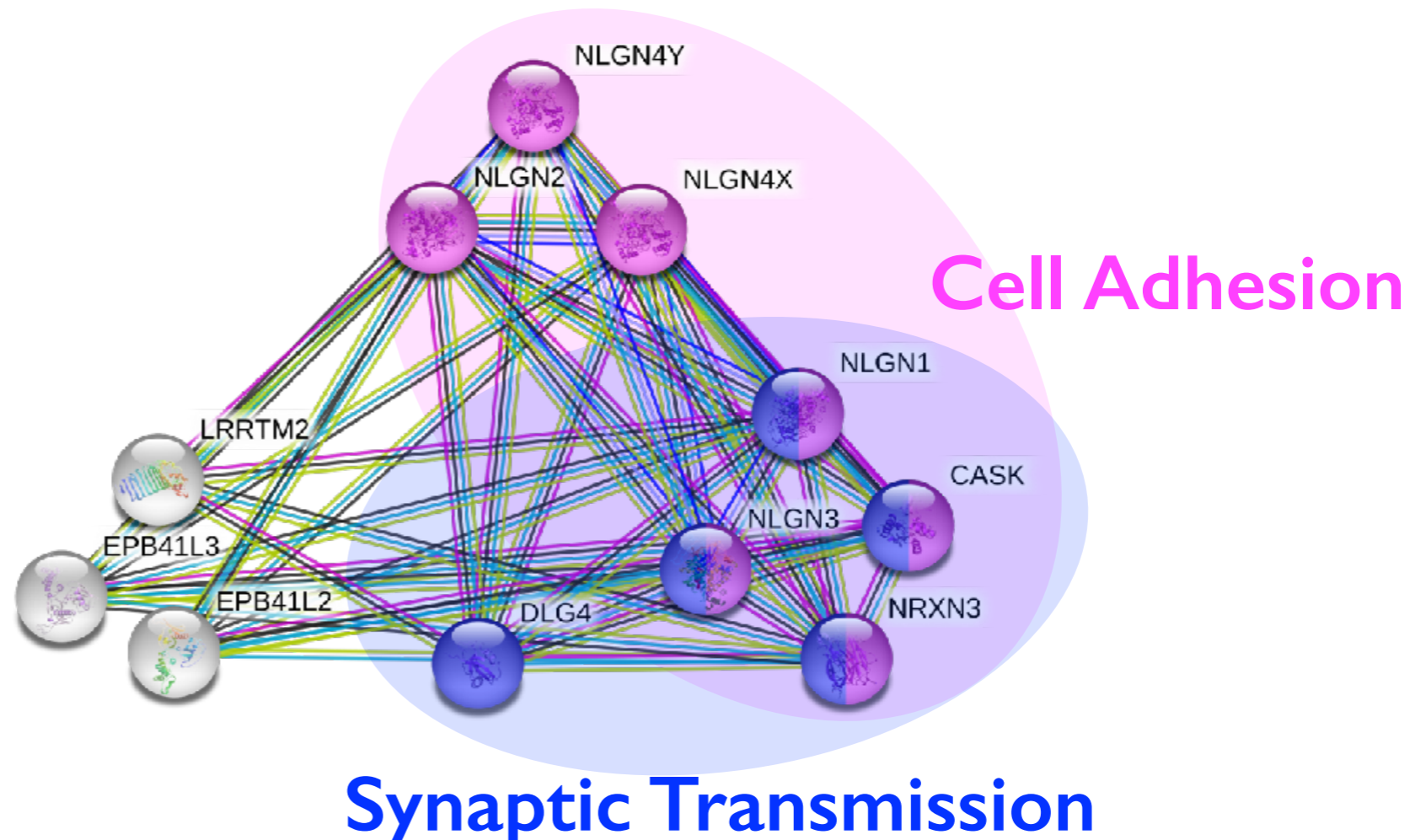
**Wild Type  
Coordinated**

**Hypothesis:** Small molecules that rescue the **NRXN3** mutant phenotypes will restore proper synaptic function.

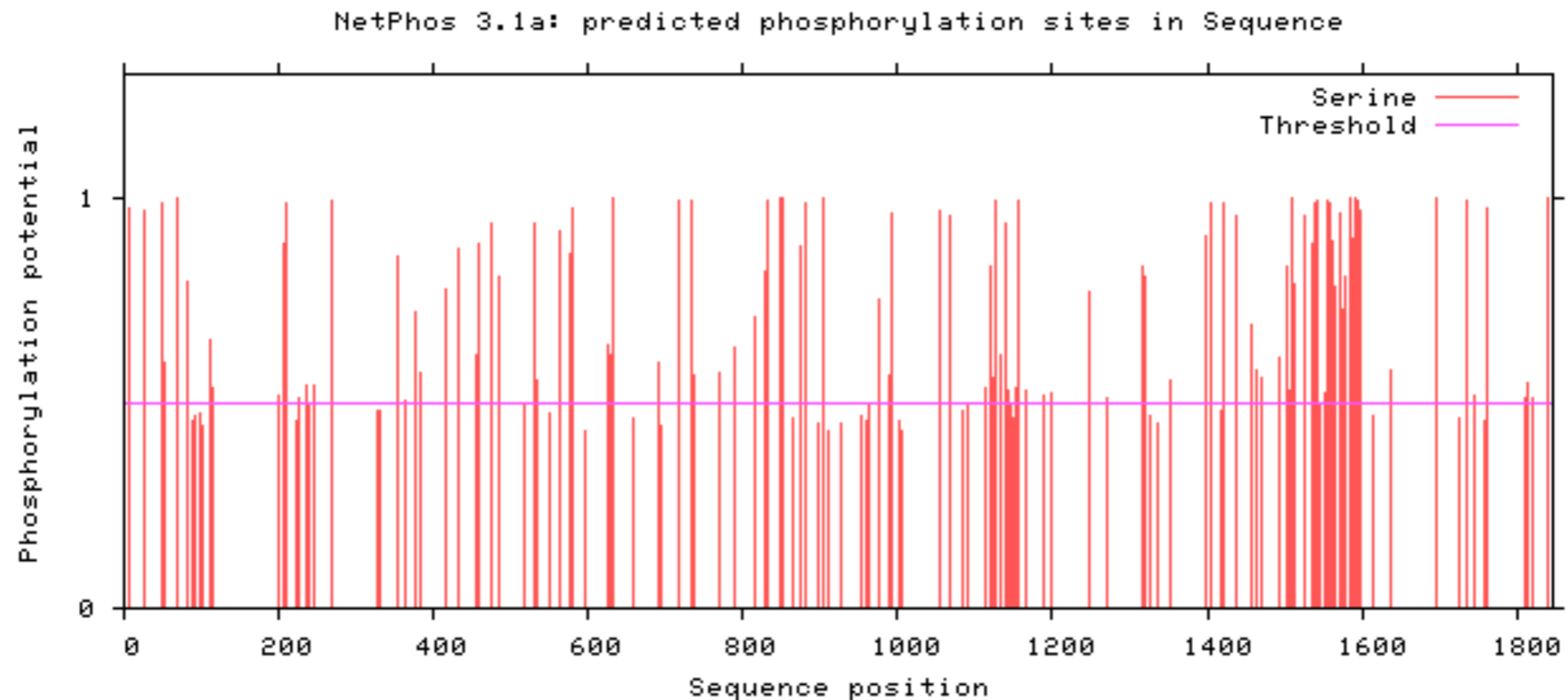
# Aim 3: Identify and mutate phosphorylation sites in NRXN3 important for synaptic function



STRING



# Aim 3: Identify and mutate phosphorylation sites in NRXN3 important for synaptic function



CASK phosphorylates Neurexins

# **Aim 3:** Identify and mutate phosphorylation sites in **NRXN3** important for synaptic function



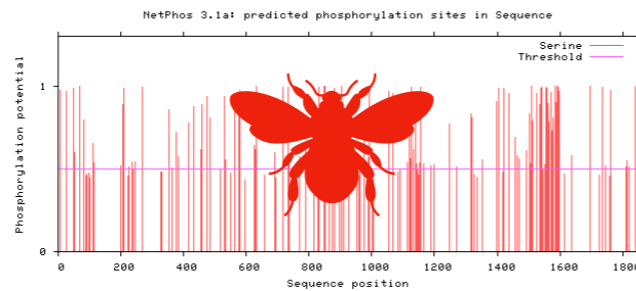


# **Aim 3:** Identify and mutate phosphorylation sites in **NRXN3** important for synaptic function



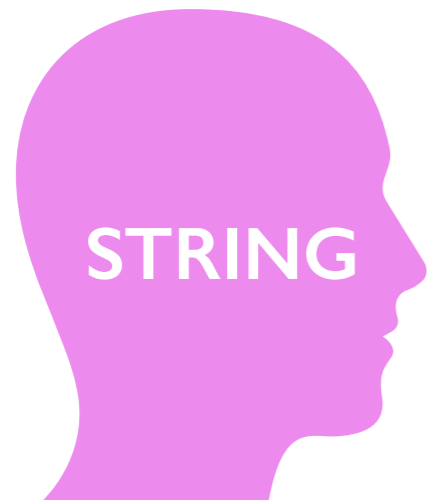
**Wild Type**  
**Coordinated**


# Aim 3: Identify and mutate phosphorylation sites in NRXN3 important for synaptic function

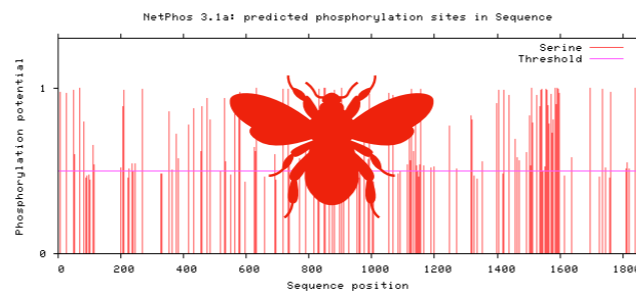


Mutated  
Serine Sites

# Aim 3: Identify and mutate phosphorylation sites in NRXN3 important for synaptic function



  
Wild Type  
Coordinated



Compare

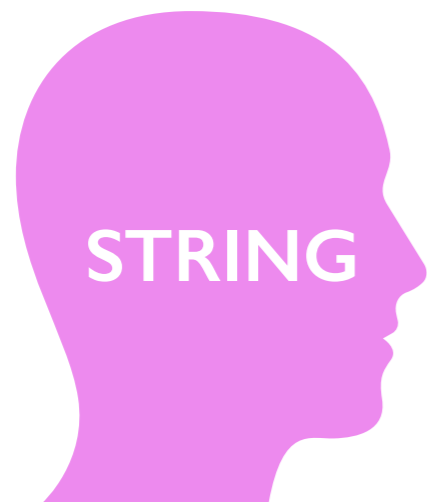


and

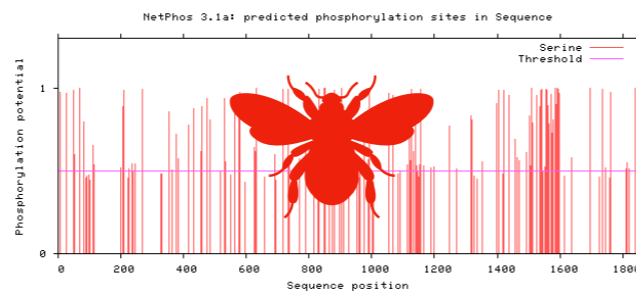


Mutated  
Serine Sites

# Aim 3: Identify and mutate phosphorylation sites in **NRXN3** important for synaptic function



Wild Type  
Coordinated



Compare



and



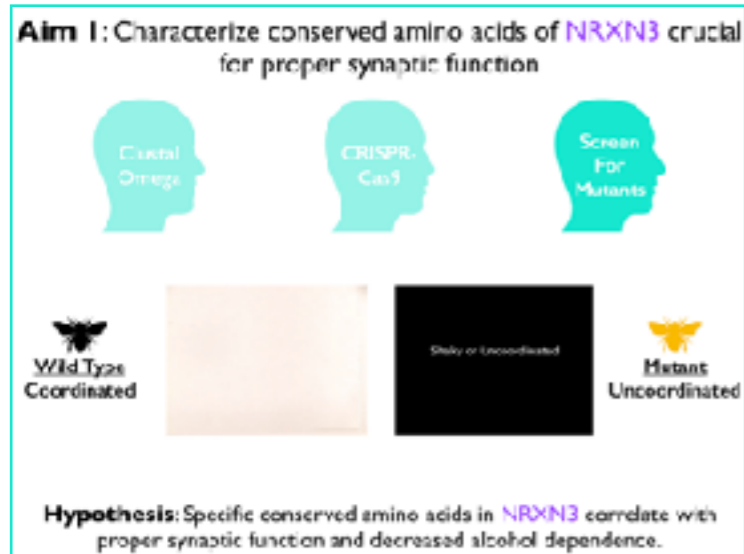
Mutated  
Serine Sites

**Hypothesis:** Mutating the most highly conserved serine phosphorylation site in **NRXN3** will result in decreased phosphorylation and improper synaptic function.

# Future Directions



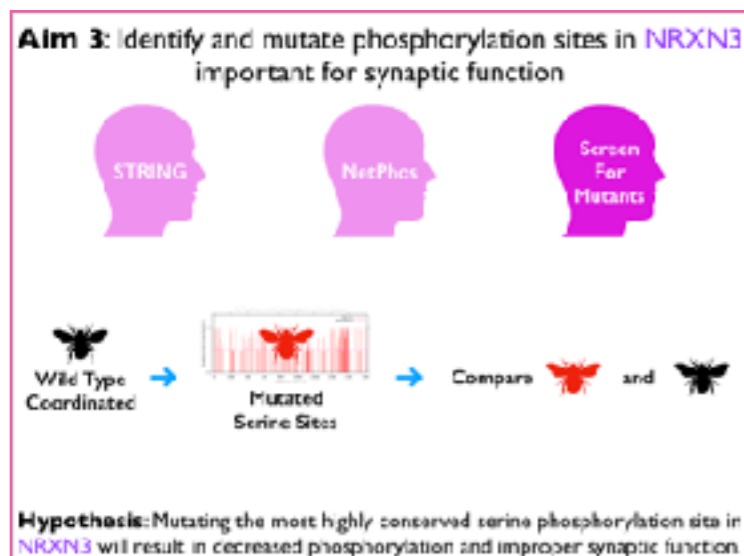
# Conclusion



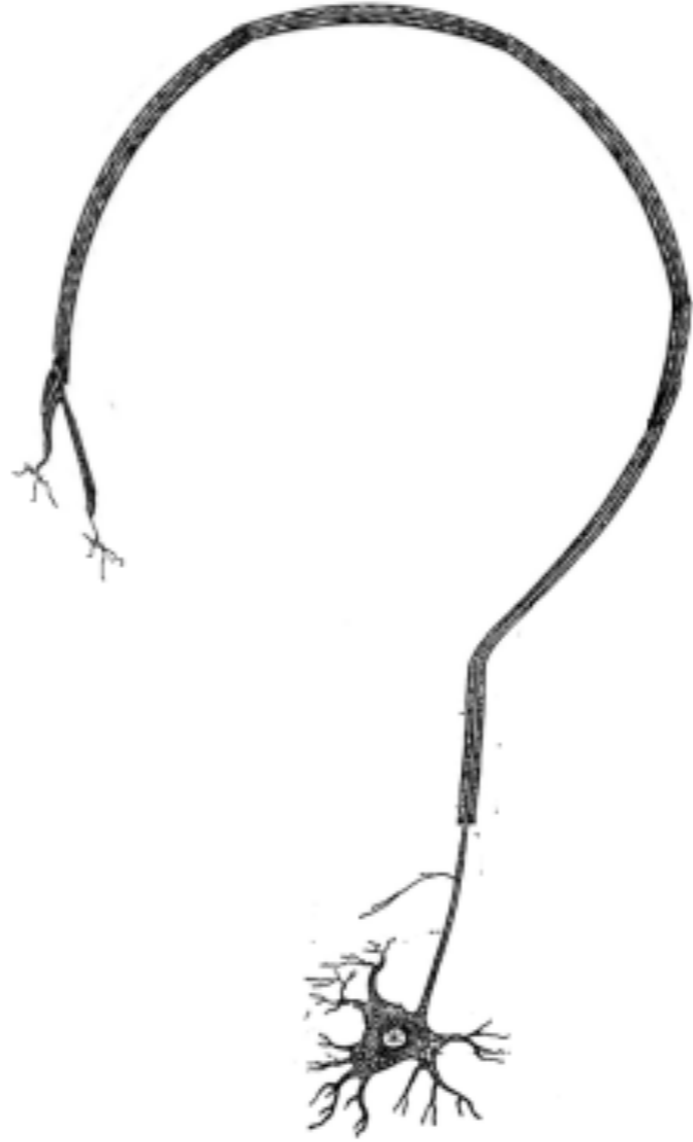
Specific conserved amino acids in **NRXN3** correlate with proper synaptic function and decreased alcohol dependence.



Small molecules that rescue the **NRXN3** mutant phenotypes will restore proper synaptic function.



Mutating the most highly conserved serine phosphorylation site in **NRXN3** will result in decreased phosphorylation and improper synaptic function.



# References

<https://forwhomthegearturns.files.wordpress.com/2015/12/vintage-martini-black-white.jpg?w=590>

[http://www.thepantheronline.com/site/wp-content/uploads/2014/11/Features\\_blackout\\_opt.png](http://www.thepantheronline.com/site/wp-content/uploads/2014/11/Features_blackout_opt.png)

<https://www.addictions.com/wp-content/uploads/2017/09/Sept-15-Drinking-Around-the-World-Section-4.jpg>

<http://static1.uk.businessinsider.com/image/54f8bb16dd089566438b462f/heres-what-alcohol-does-to-your-brain-and-body.jpg>

<http://learn.genetics.utah.edu/content/neuroscience/neurons/neurons-2.jpg>

<https://ars.els-cdn.com/content/image/1-s2.0-S0028390811000359-gr1.jpg>

<http://www.jneurosci.org/content/jneuro/24/42/9244/F1.large.jpg?width=800&height=600&carousel=1>

<https://www.neuroskills.com/images/synaptogenesis.jpg>

[https://www.researchgate.net/profile/J\\_Littleton/publication/10690680/figure/fig1/AS:304803294007308@1449682176735/A-neurexin-based-adhesion-complex-in-synapsesIn-this-model-which-incorporates-the.png](https://www.researchgate.net/profile/J_Littleton/publication/10690680/figure/fig1/AS:304803294007308@1449682176735/A-neurexin-based-adhesion-complex-in-synapsesIn-this-model-which-incorporates-the.png)

<https://biology.tutorvista.com/cell/gene-regulation.html>

<https://images.vexels.com/media/users/3/137130/isolated/preview/7411ac190a0efd344066e2c01bc17c36-wine-bottle-glass-silhouette-by-vexels.png>

<https://static1.squarespace.com/static/52ec8c1ae4b047ccc14d6f29/t/5705bcb60442628269048e4b/1490436869202/synapse1.jpg>

[https://string-db.org/cgi/input.pl?sessionId=jhq1yYAK6Hi9&input\\_page\\_show\\_search=on](https://string-db.org/cgi/input.pl?sessionId=jhq1yYAK6Hi9&input_page_show_search=on)

<https://3c1703fe8d.site.internapcdn.net/newman/gfx/news/hires/2016/10-newresearchc.jpg>

<https://blast.ncbi.nlm.nih.gov/images/protein-blast-cover.png>

[http://www.clustal.org/images/clustalo\\_big.png](http://www.clustal.org/images/clustalo_big.png)

[http://dharmacon.horizondiscovery.com/uploadedImages/Products/Gene\\_Editing/\\_assets/crtracr-diagram.jpg](http://dharmacon.horizondiscovery.com/uploadedImages/Products/Gene_Editing/_assets/crtracr-diagram.jpg)

<https://www.youtube.com/watch?v=FVI9FSPnTWk>

[https://youtu.be/3D\\_ZU248roY](https://youtu.be/3D_ZU248roY)

<http://www.plantphysiol.org/content/plantphysiol/133/2/448/F1.large.jpg?width=800&height=600&carousel=1>

[http://2017.igem.org/wiki/images/7/7b/T--SYSU-Software--project\\_string\\_m.png](http://2017.igem.org/wiki/images/7/7b/T--SYSU-Software--project_string_m.png)

<http://superawesomevectors.com/wp-content/uploads/2016/10/pills-vector-illustration-800x566.jpg>

<http://www.consciousentities.com/wp-content/uploads/2014/02/neuron-question.gif>