MEF2C and the genetics of major depression

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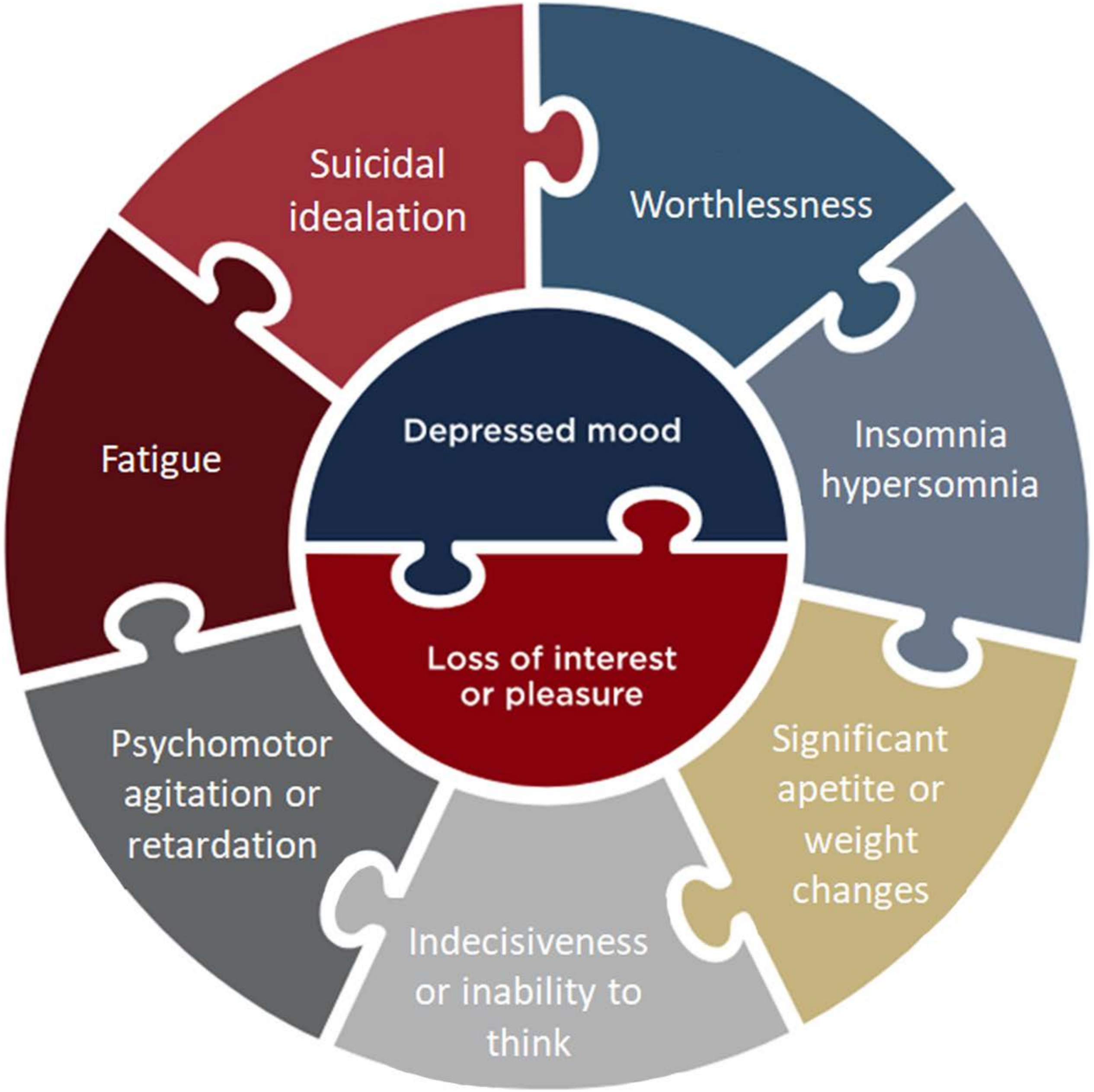
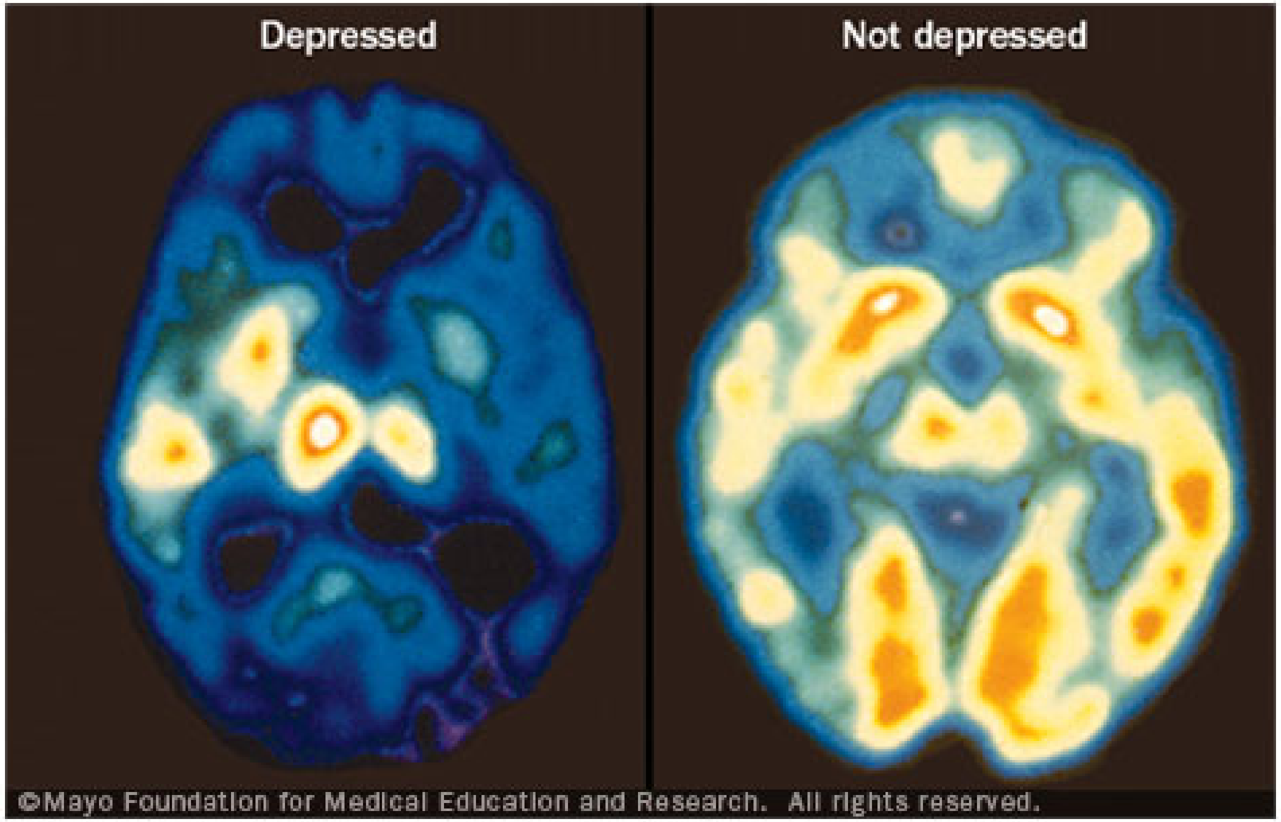
Major depression: its more than just the blues



Does major depression have a biological cause?



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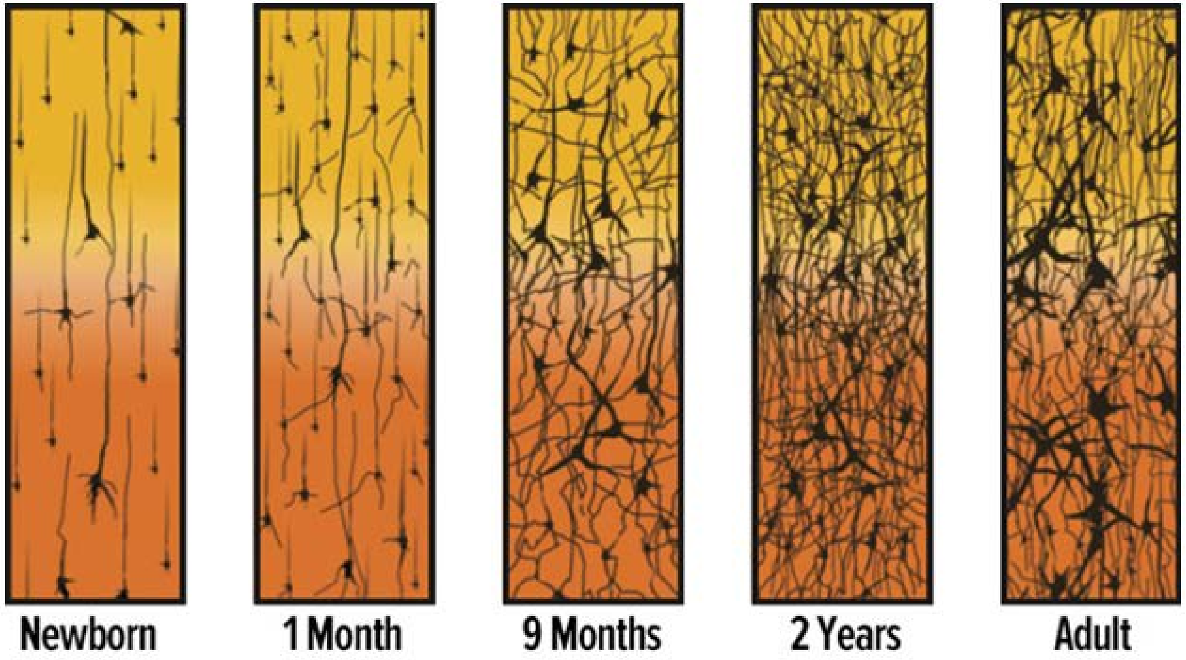
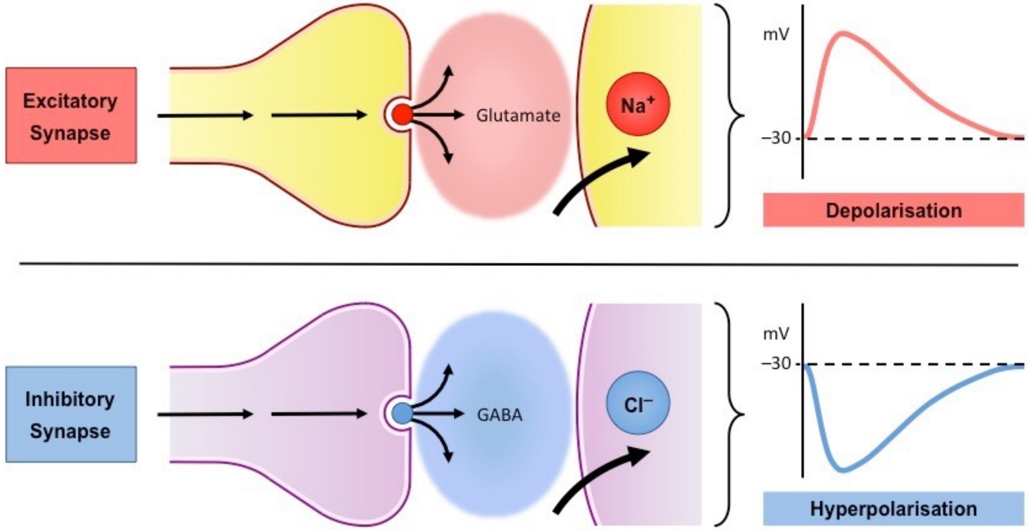
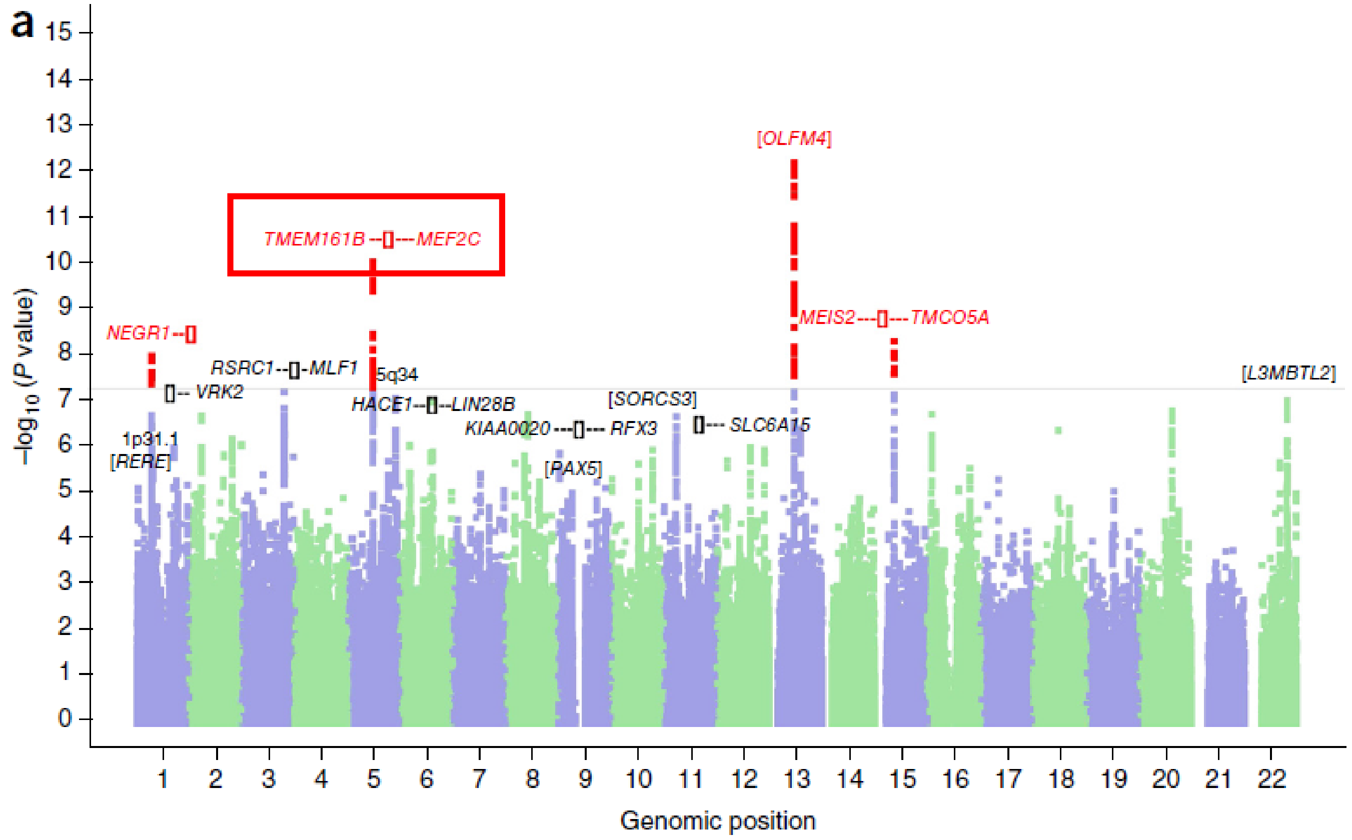
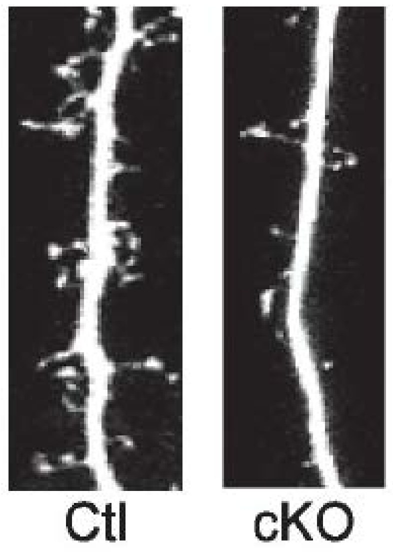




Imbalance in synaptic density leads to a higher risk of depression

Myocyte Enhancer Factor 2C (MEF2C) in depression

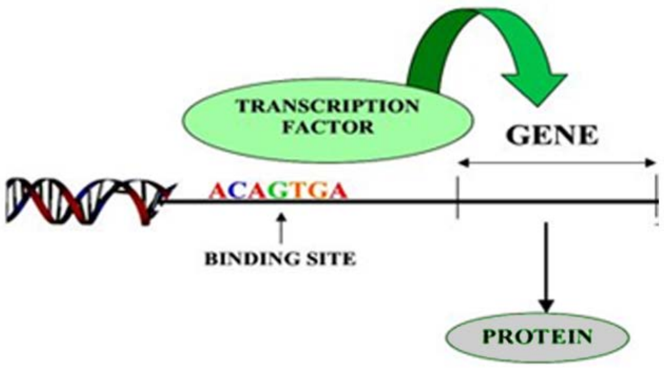




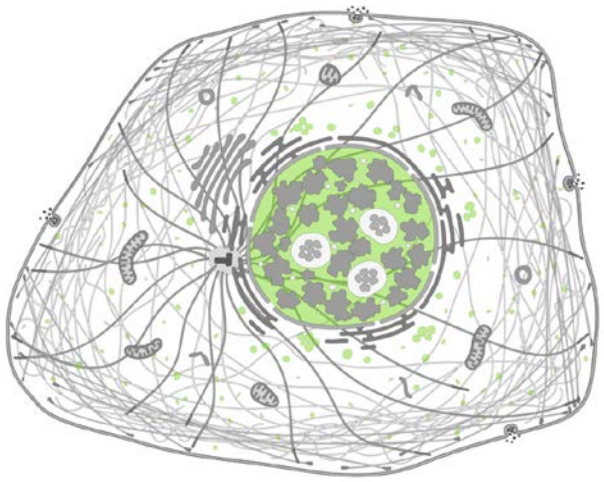
MEF2C regulates development of neurons and synaptic density

What is MEF2C?

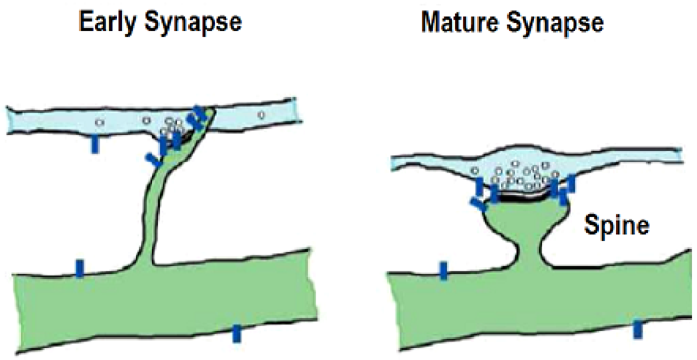
Molecular function



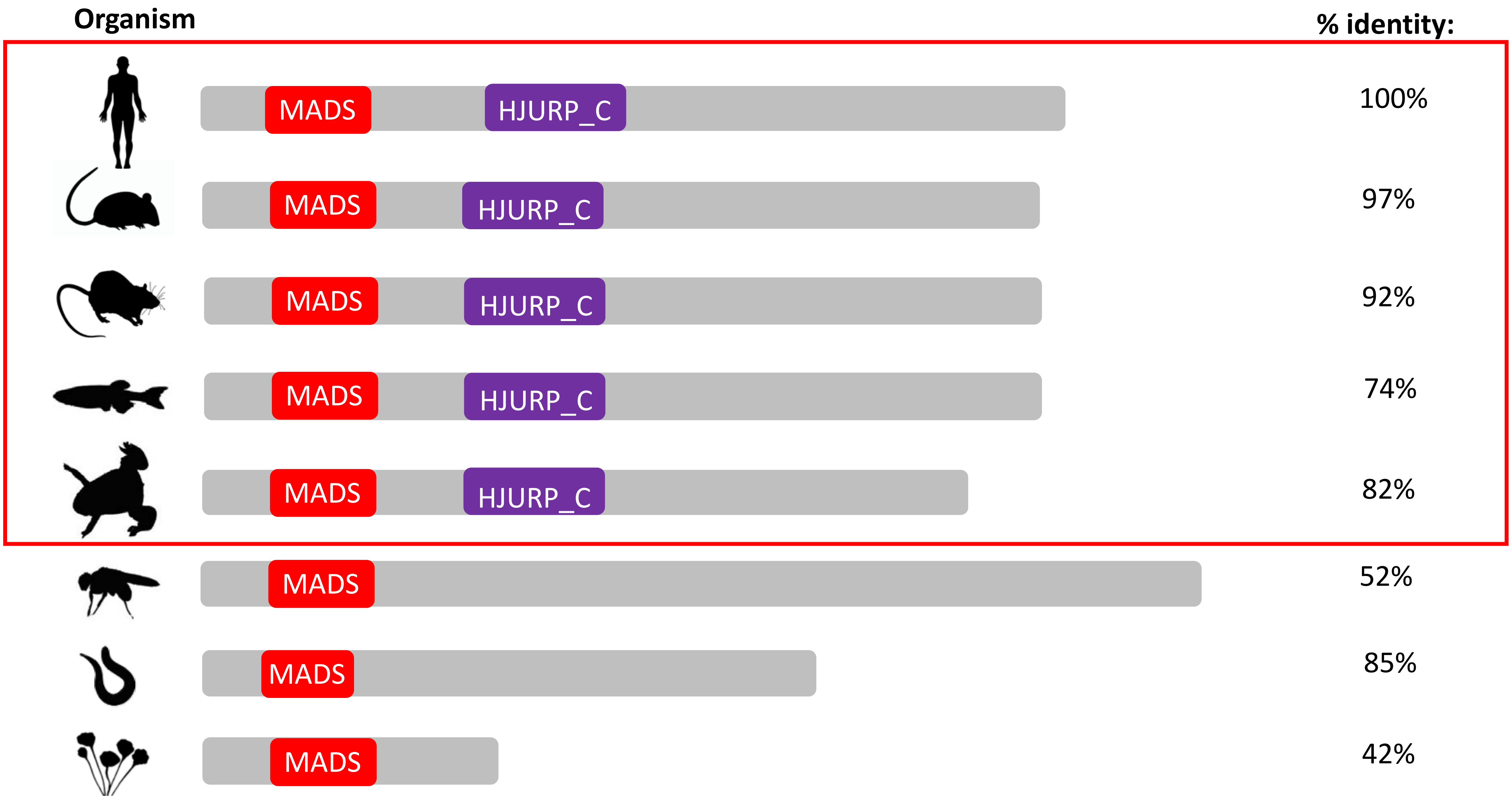
Cellular Component



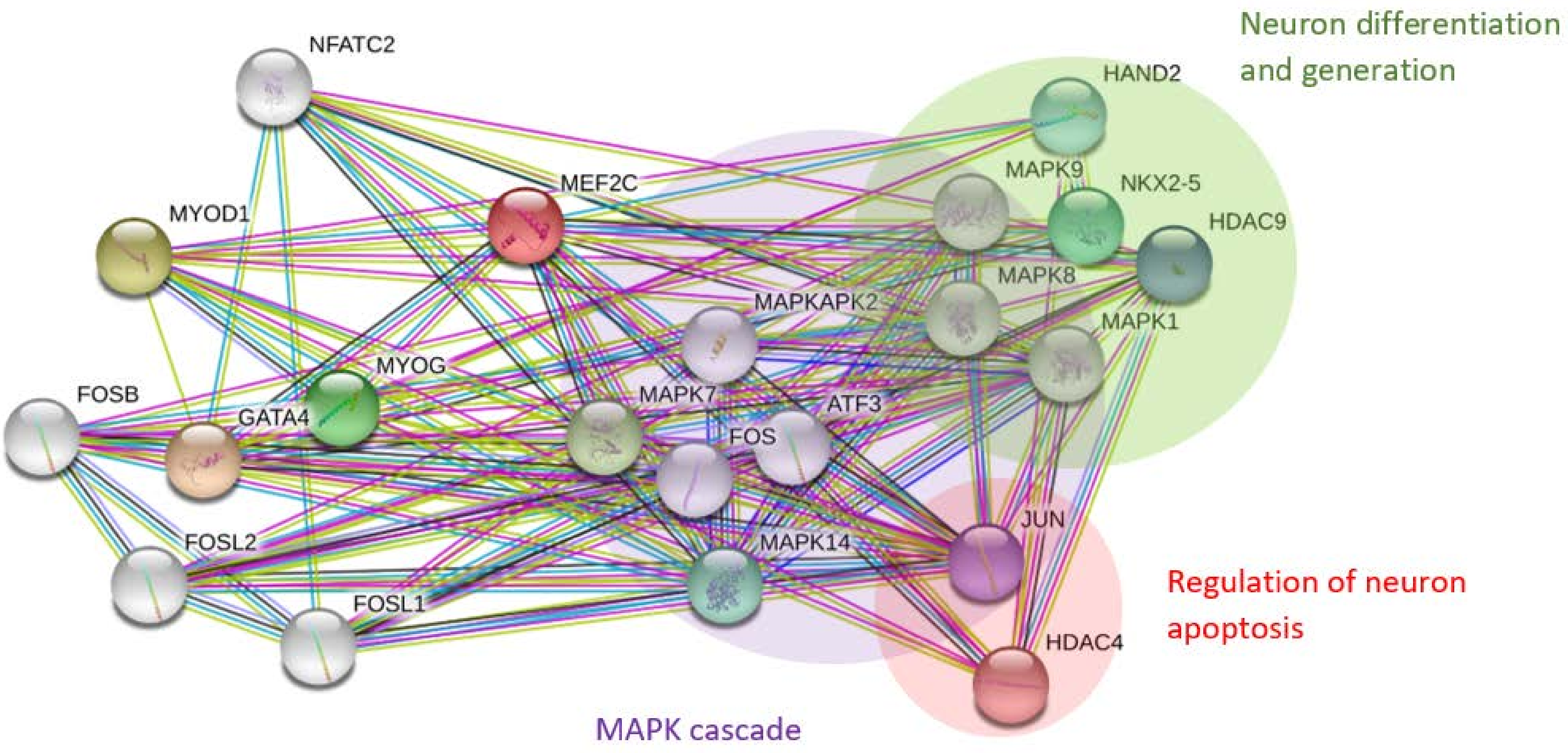
Biological process



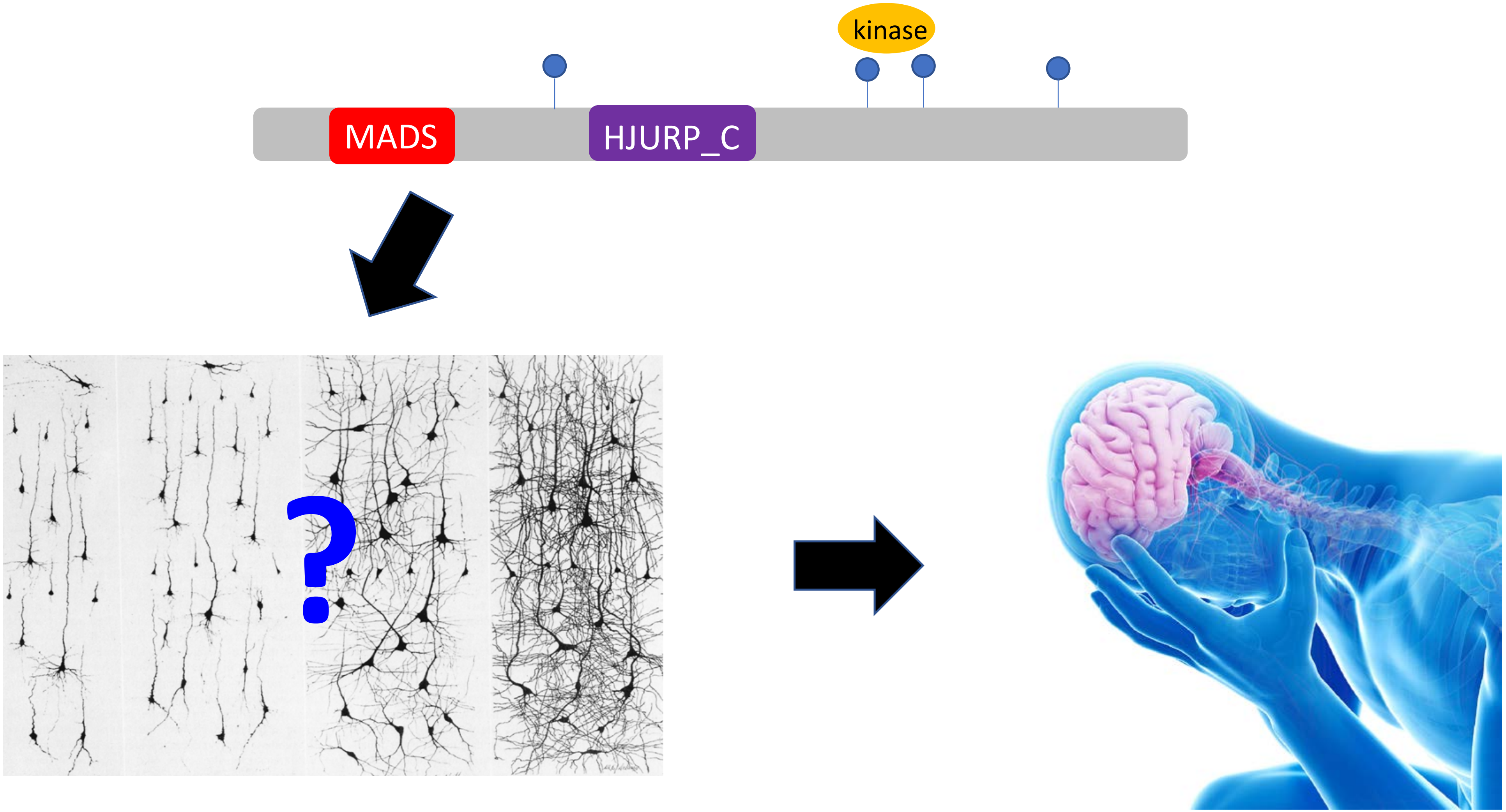
Conservation of MEF2C across homologs



MEF2C protein interaction network



What is the gap in knowledge?

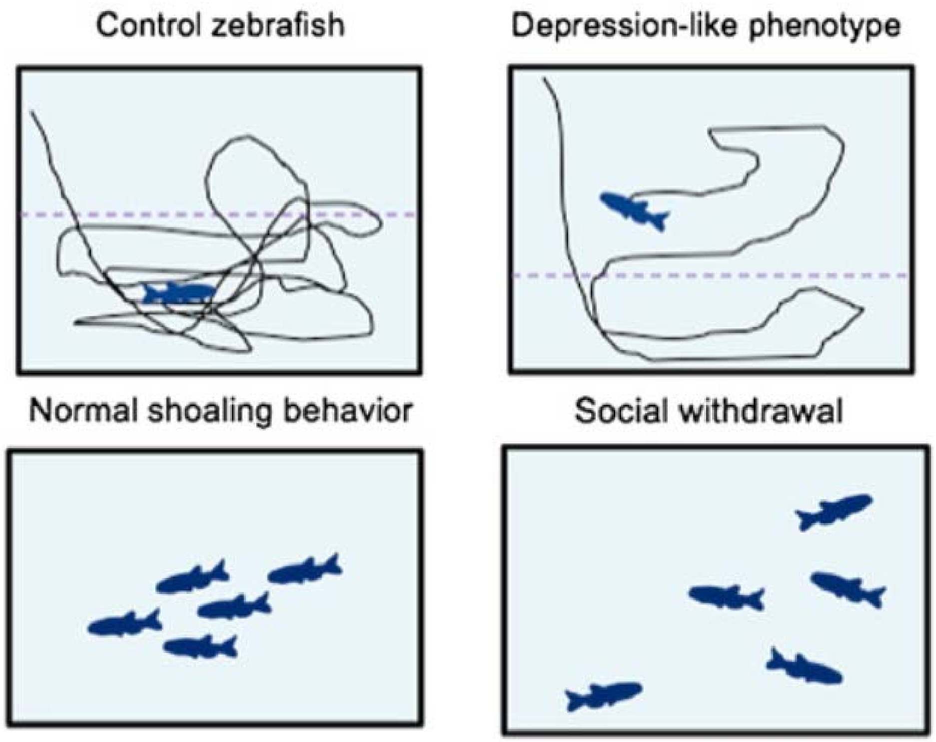


Unclear how phosphorylation of MEF2C regulates synaptic density in depression

Zebrafish as a model organism

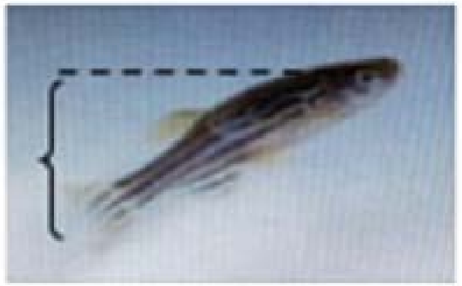
- Highly conserved neural structures

- Observable phenotypes



Normal tail phenotype

'Droopy tail' phenotype

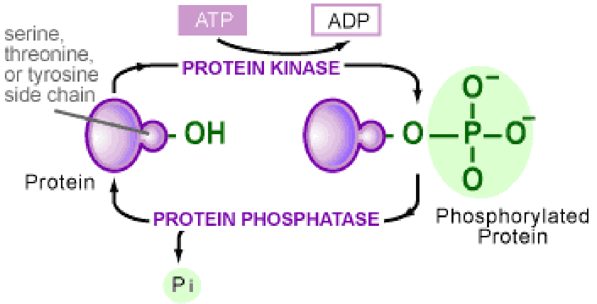


What is the primary goal?

Understand the role of MEF2C phosphorylation sites in the regulation of synapse elimination in development

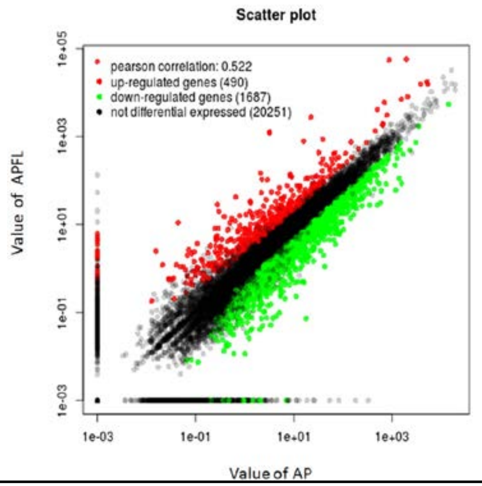
Aim 1:

Identify conserved phosphorylation sites



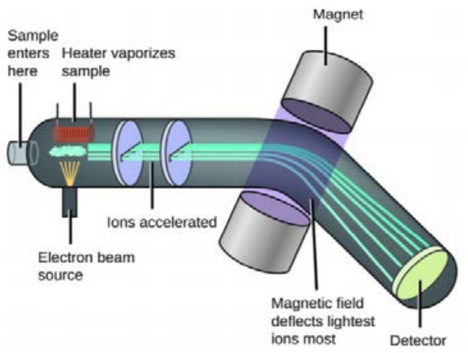
Aim 2:

Identify differently expressed genes involved in synapse development



Aim 3:

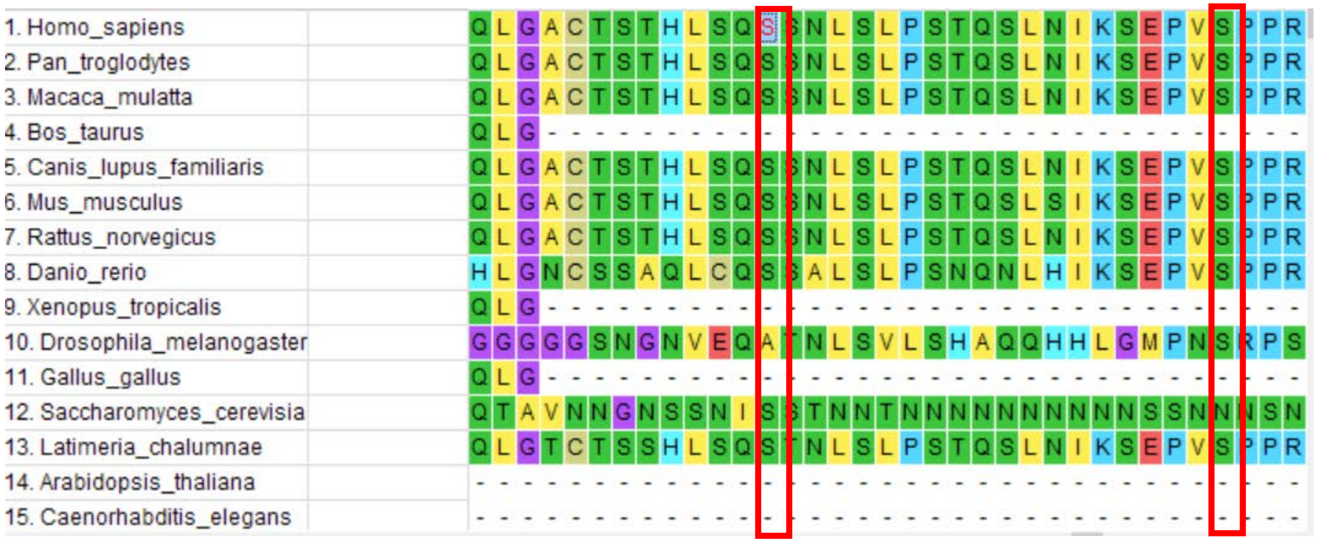
Identifying kinases responsible for MEF2C phosphorylation



Aim 1: Identifying conserved phosphorylation sites across MEF2C homologs

Sequence allignment → CRISPR/Cas 9 → Behavioral screen → Immunohistochemistry

MEGA



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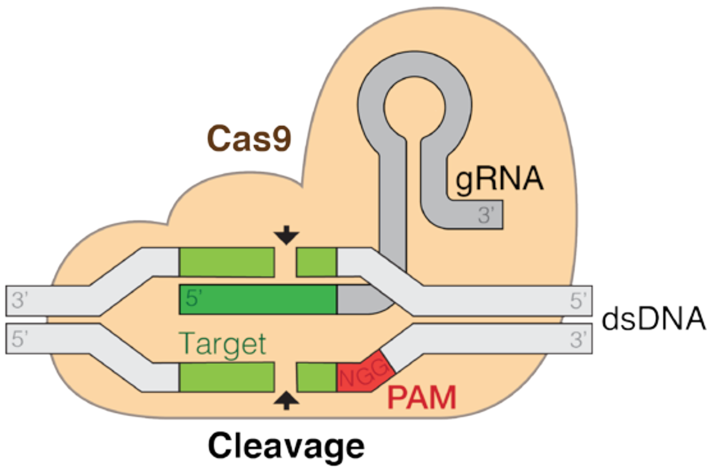
Sequence allignment → **CRISPR/Cas 9** → Behavioral screen → Immunohistochemistry



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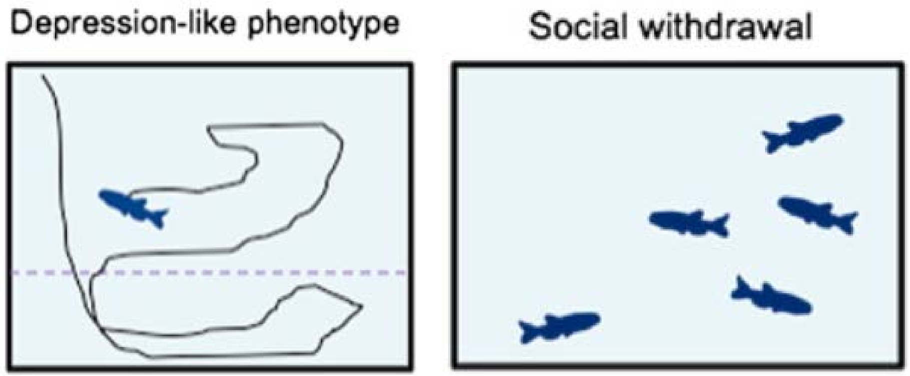
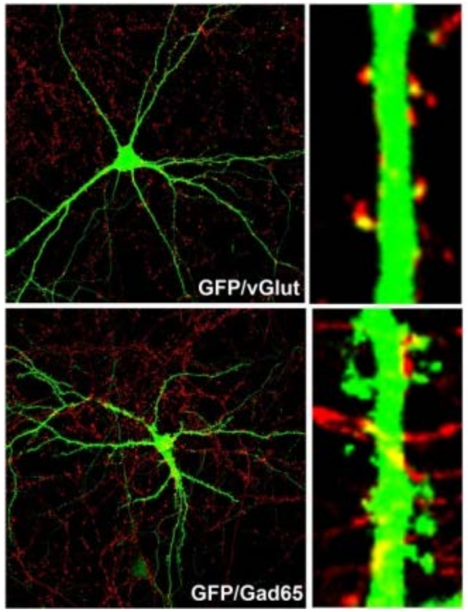
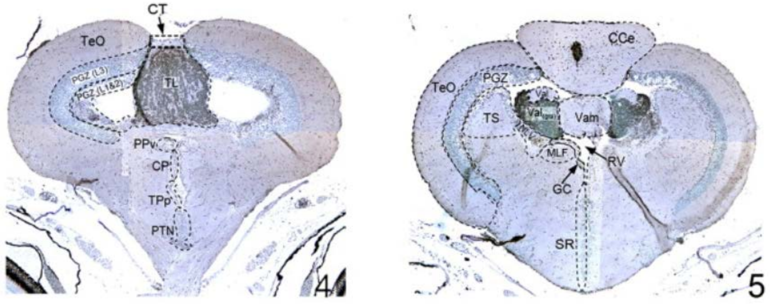


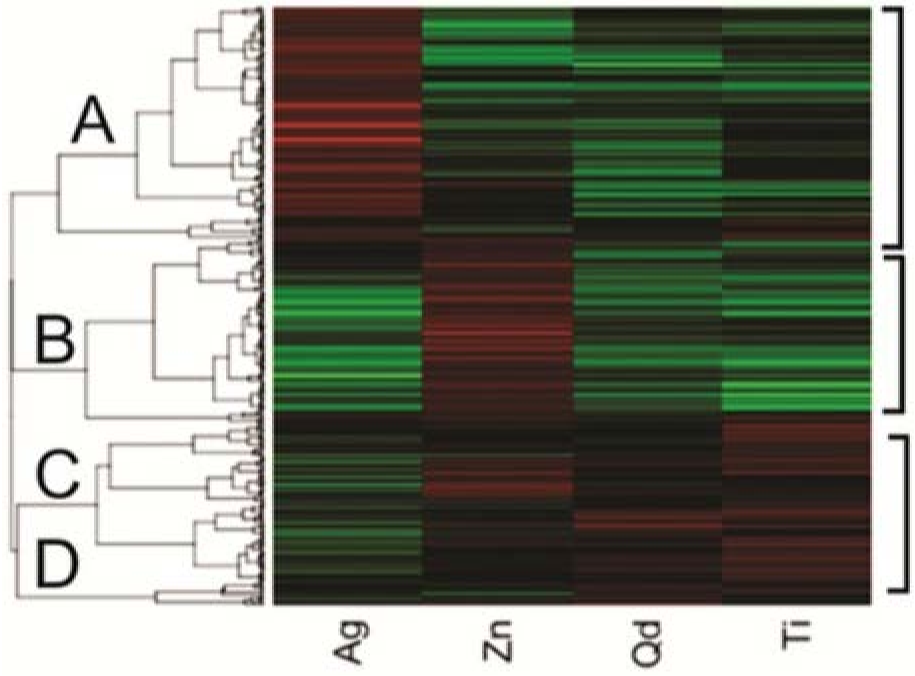


Hypothesis: Zebrafish with mutations in conserved phosphorylation sites will have depressive phenotypes and abnormal synaptic density

Aim 2: Identifying differently expressed genes involved in synaptic regulation

RNA-seq → Gene Ontology → CRISPR/Cas 9 → Immunohistochemistry





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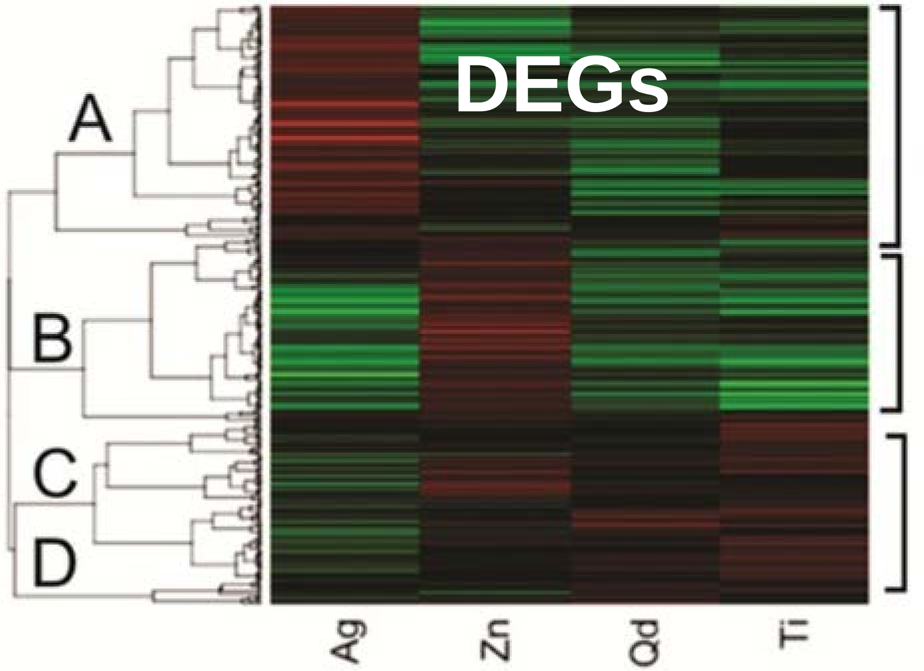
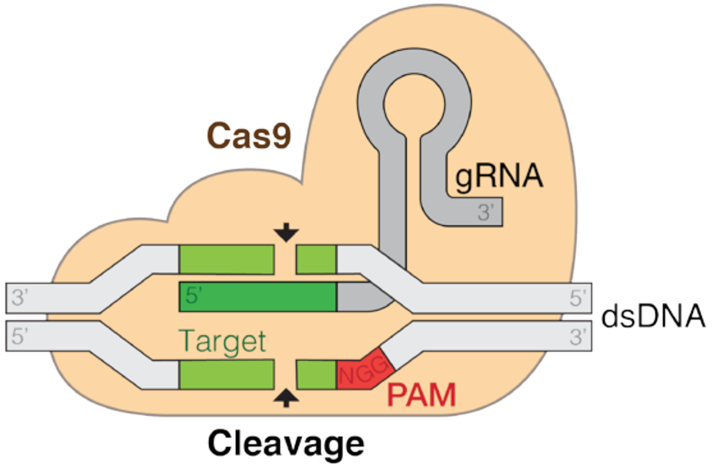
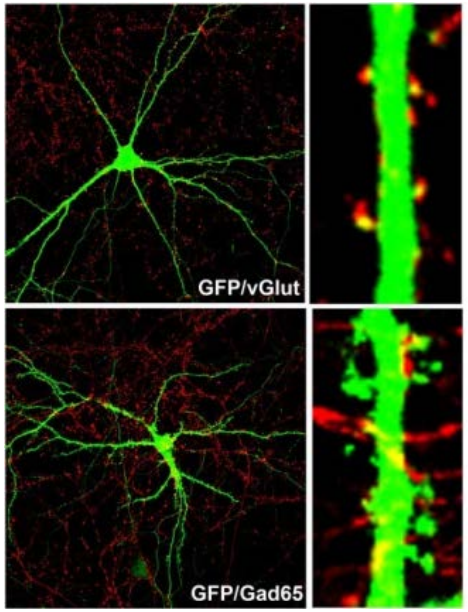


GENEONTOLOGY
Unifying Biology

Aim 2: Identifying differently expressed genes involved in synaptic regulation

RNA-seq → Gene Ontology → CRISPR/Cas 9 → Immunohistochemistry

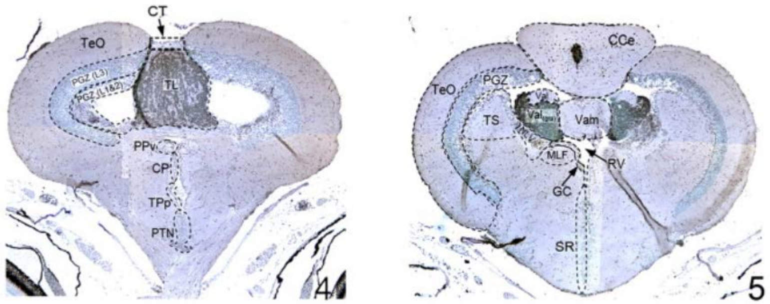


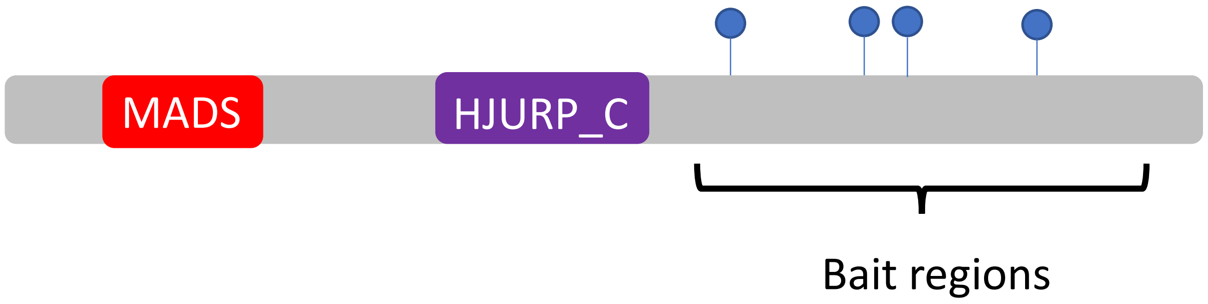


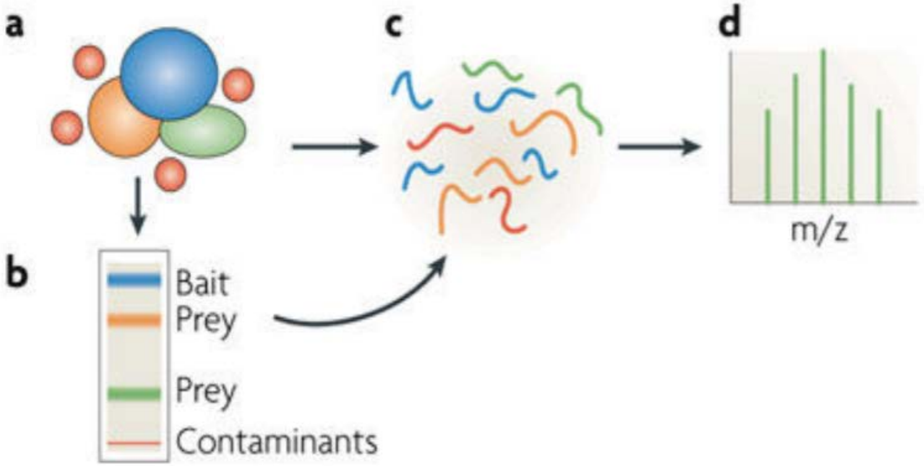
Hypothesis: Mutants with depressive phenotypes have different gene expression profiles for genes involved in neuron development

Aim 3: Identifying kinases responsible for MEF2C phosphorylation important in synaptic regulation

Pulldown/ MS → Gene Ontology → CRISPR/Cas 9 → Immunohistochemistry







Aim 3: Identifying kinases responsible for MEF2C phosphorylation important in synaptic density

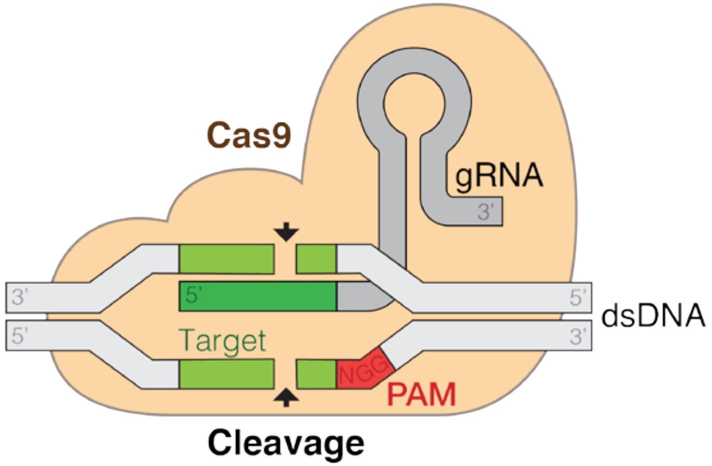
Pulldown/MS → **Gene Ontology** → CRISPR/Cas9 → Immunohistochemistry

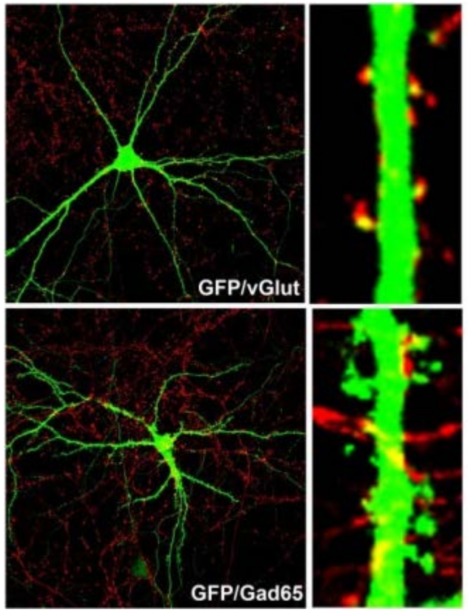
GENEONTOLOGY
Unifying Biology

→ **Comparison of proteins that bind to WT and mutants**

Aim 3: Identifying kinases responsible for MEF2C phosphorylation important in synaptic density

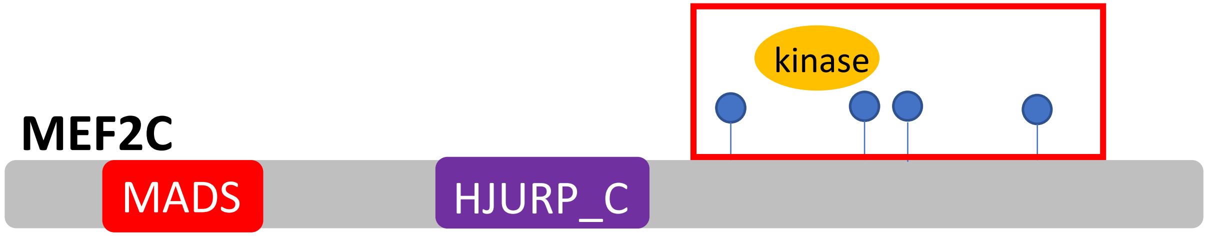
Pulldown/ MS → Gene Ontology → CRISPR/Cas 9 → Immunohistochemistry



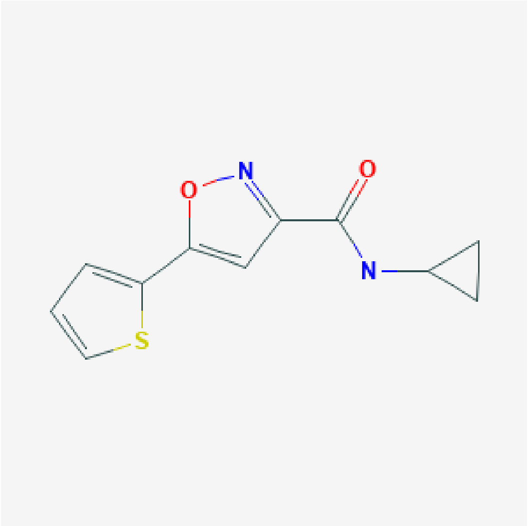


Hypothesis: Kinases that bind to WT but not mutant MEF2C are important in phosphorylation of MEF2C

Future Directions



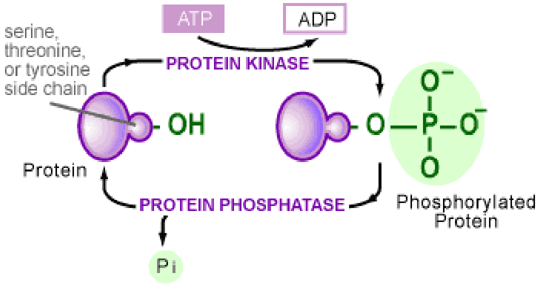
Targeting kinases/phosphorylation sites involved in regulation of synaptic density



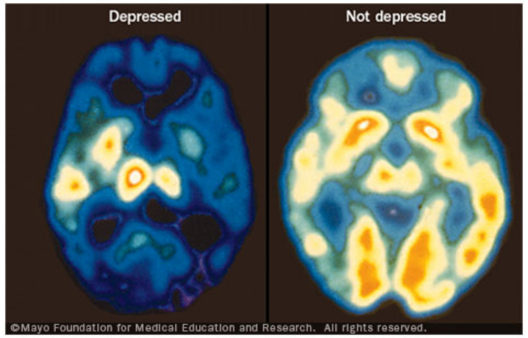
Drugs that treat neuron imbalance

Summary

Synaptic imbalance leads to depression



Phosphorylation of MEF2C is linked to regulation of synaptic density



Understanding how MEF2C regulates synaptic density is important in understanding depression

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QUESTIONS?