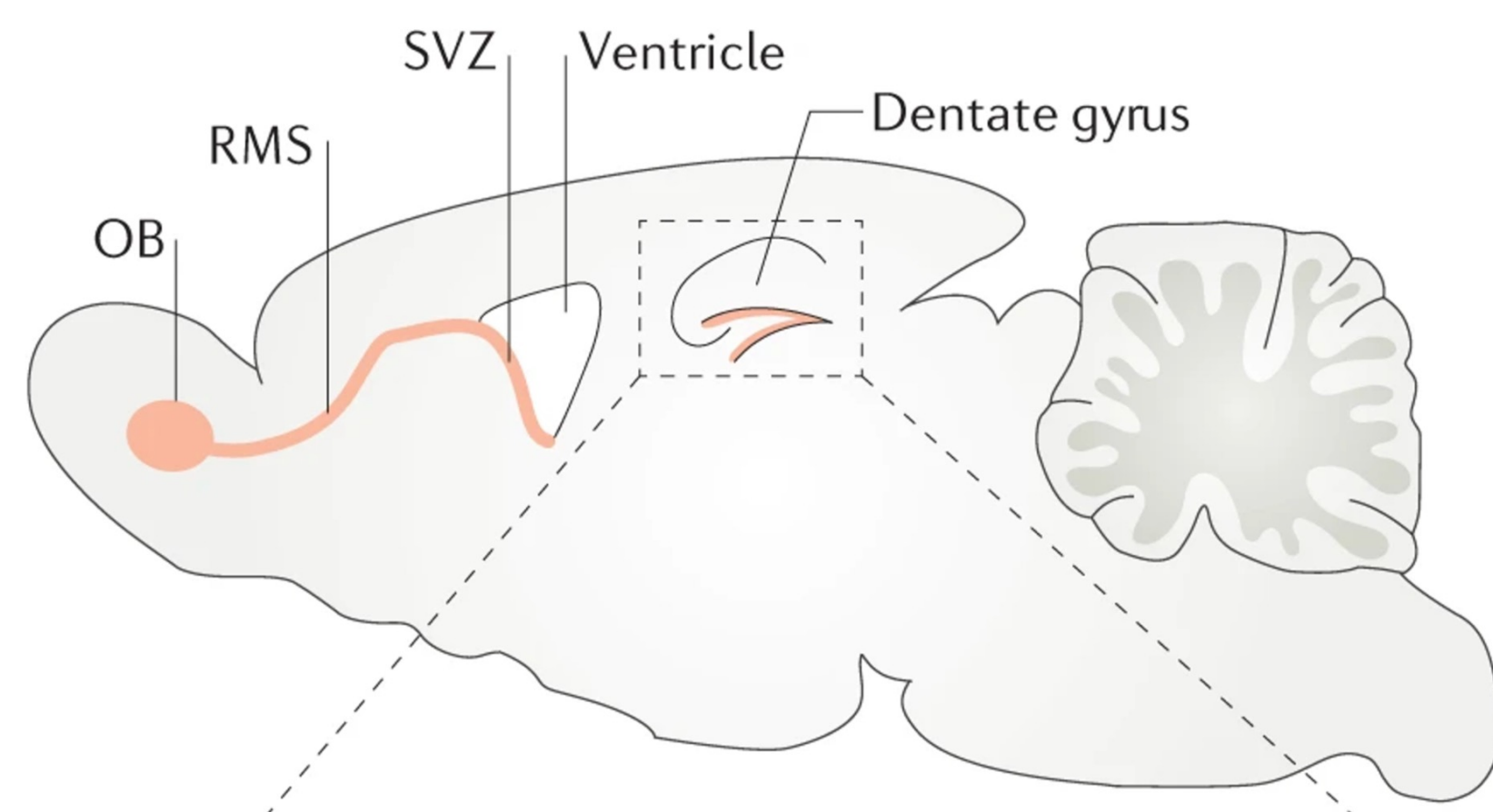
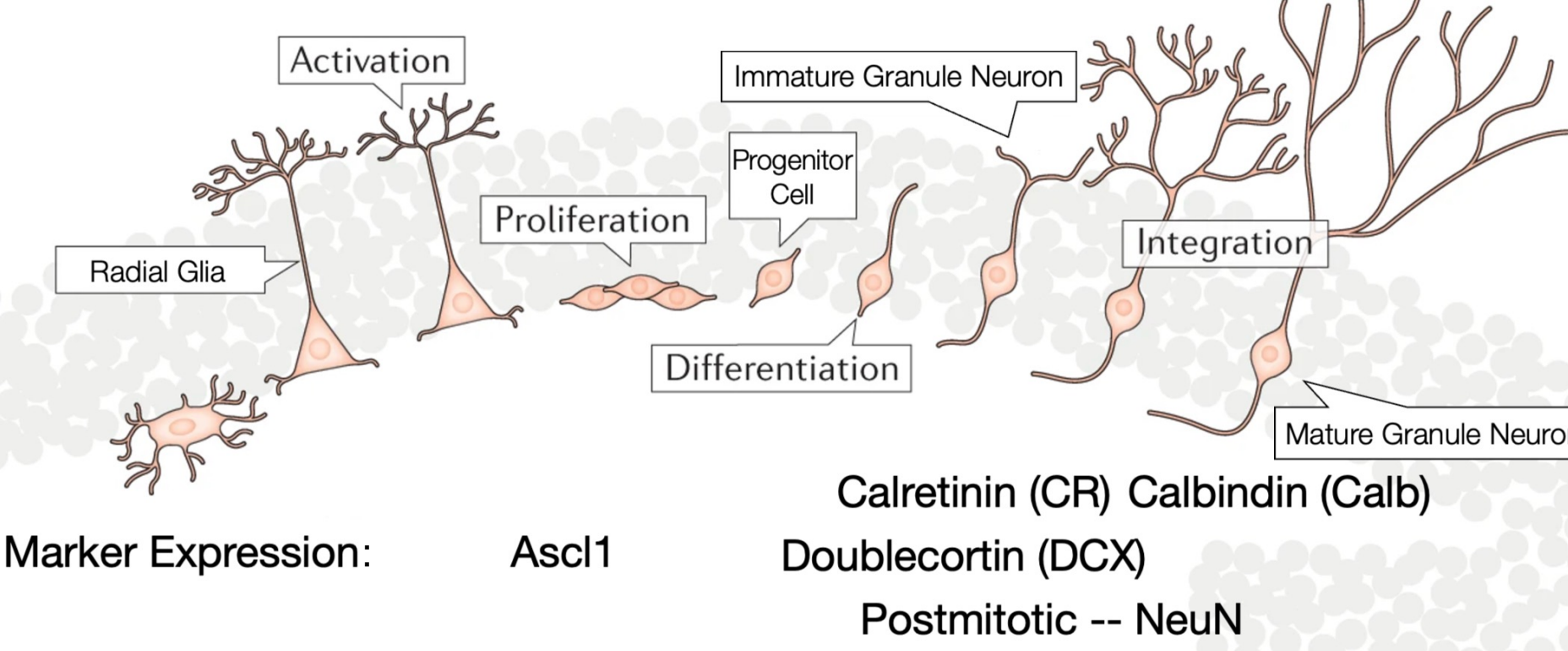


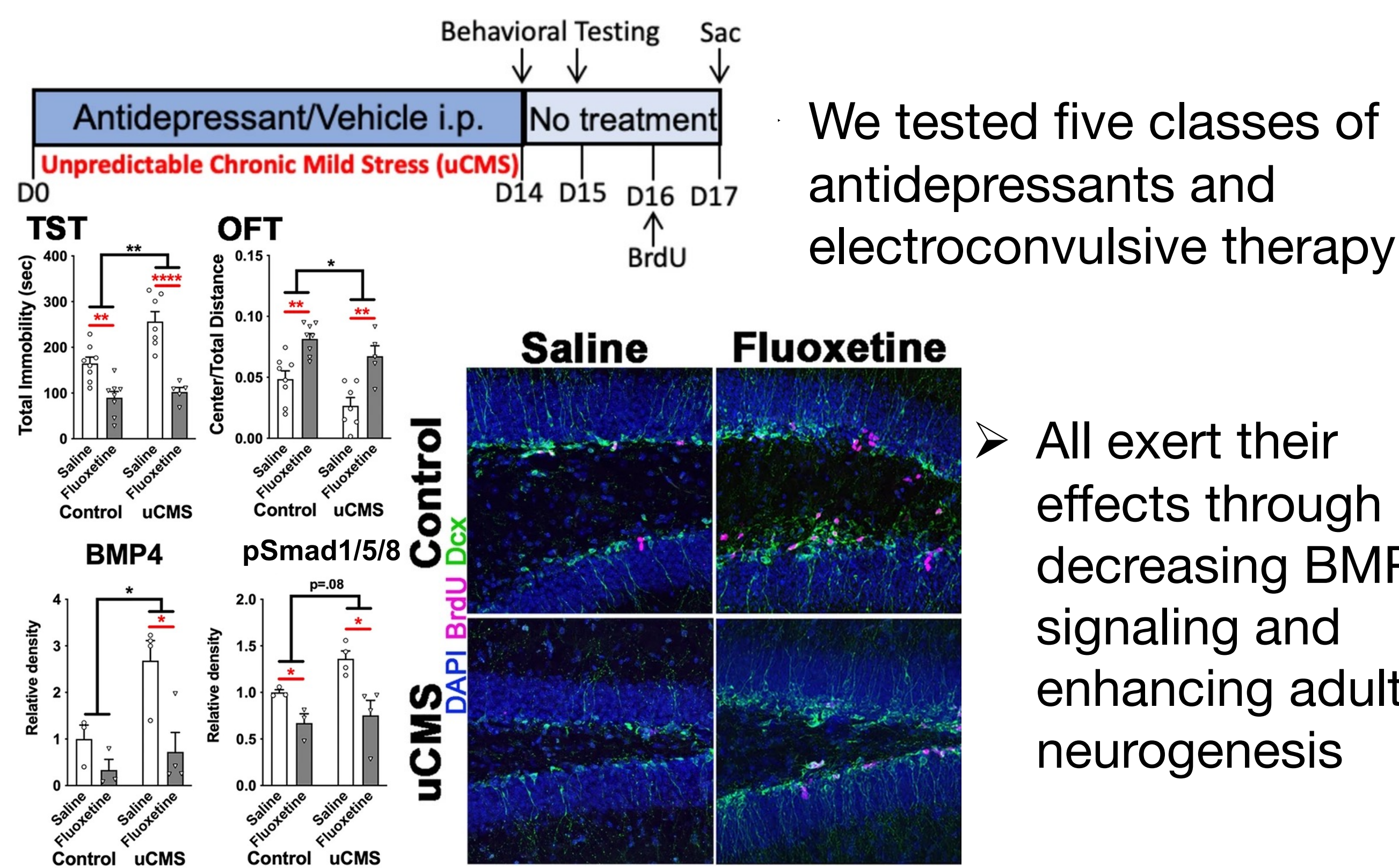
## Adult Hippocampal Neurogenesis



BMP receptors are expressed across these populations

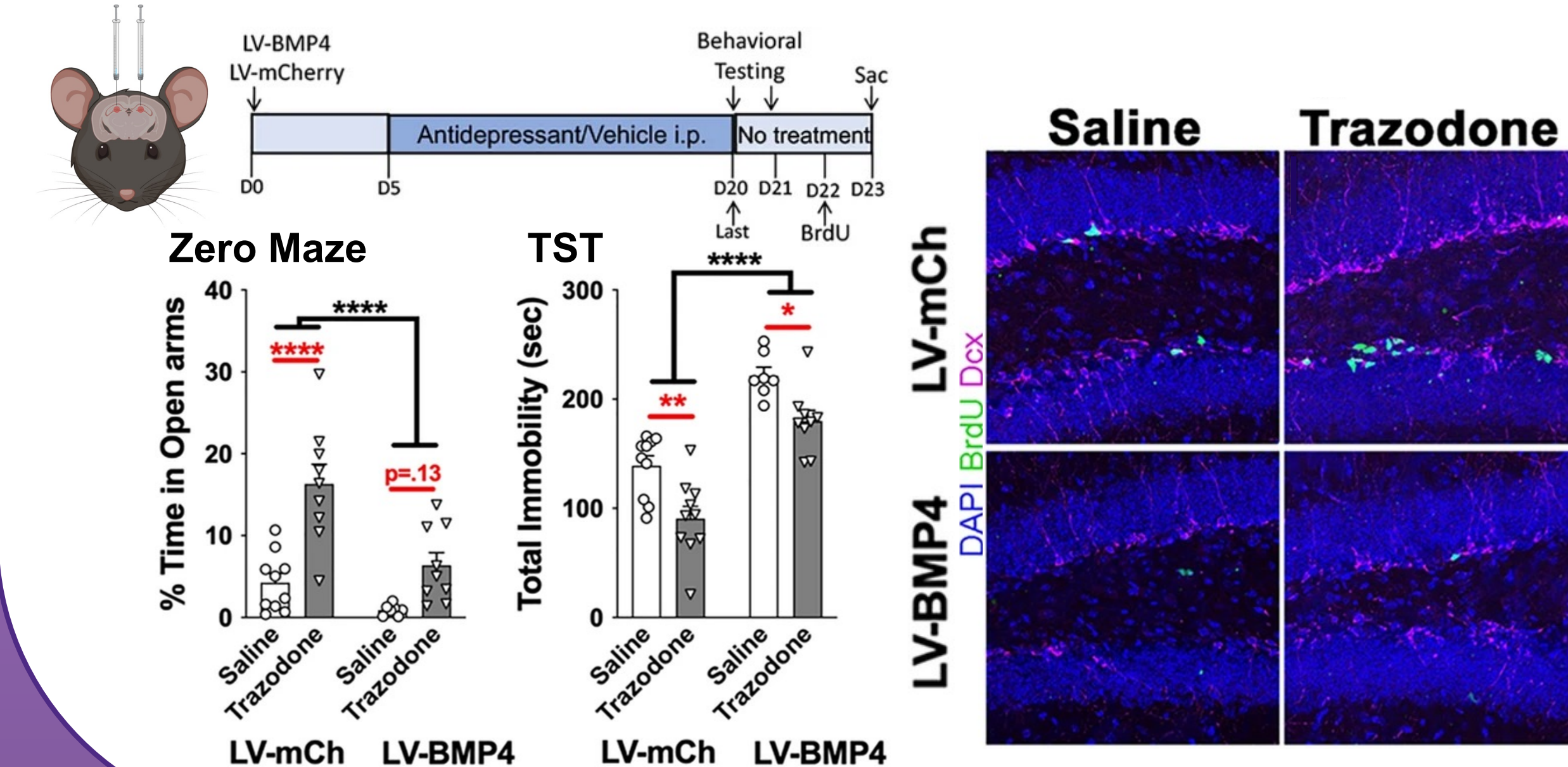


## Stress Increases BMP Signaling and Reduces Adult Neurogenesis

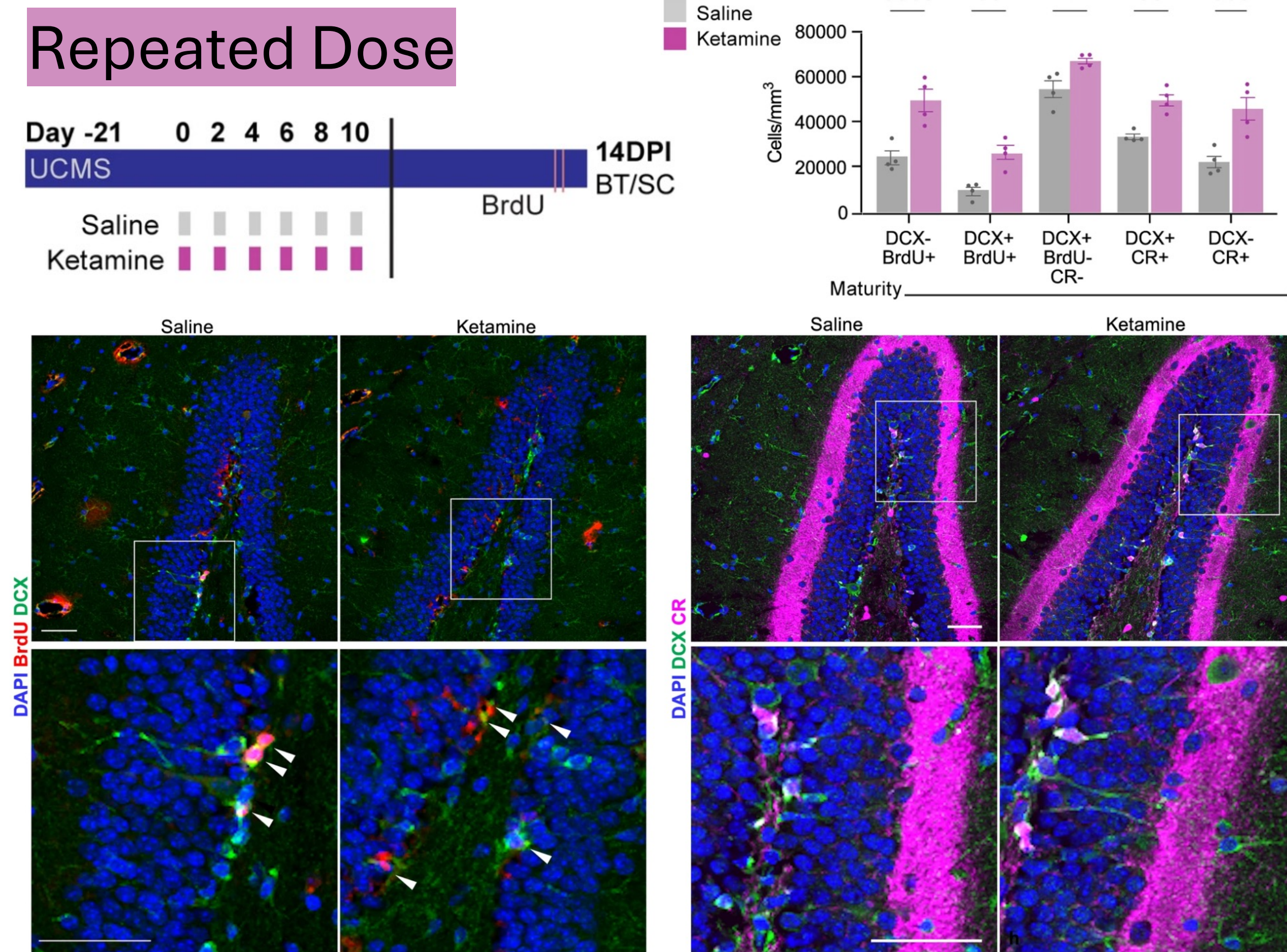


## Increasing BMP Signaling Abolishes the Effects of Antidepressants

Preventing BMP signaling decrease blocks their effects

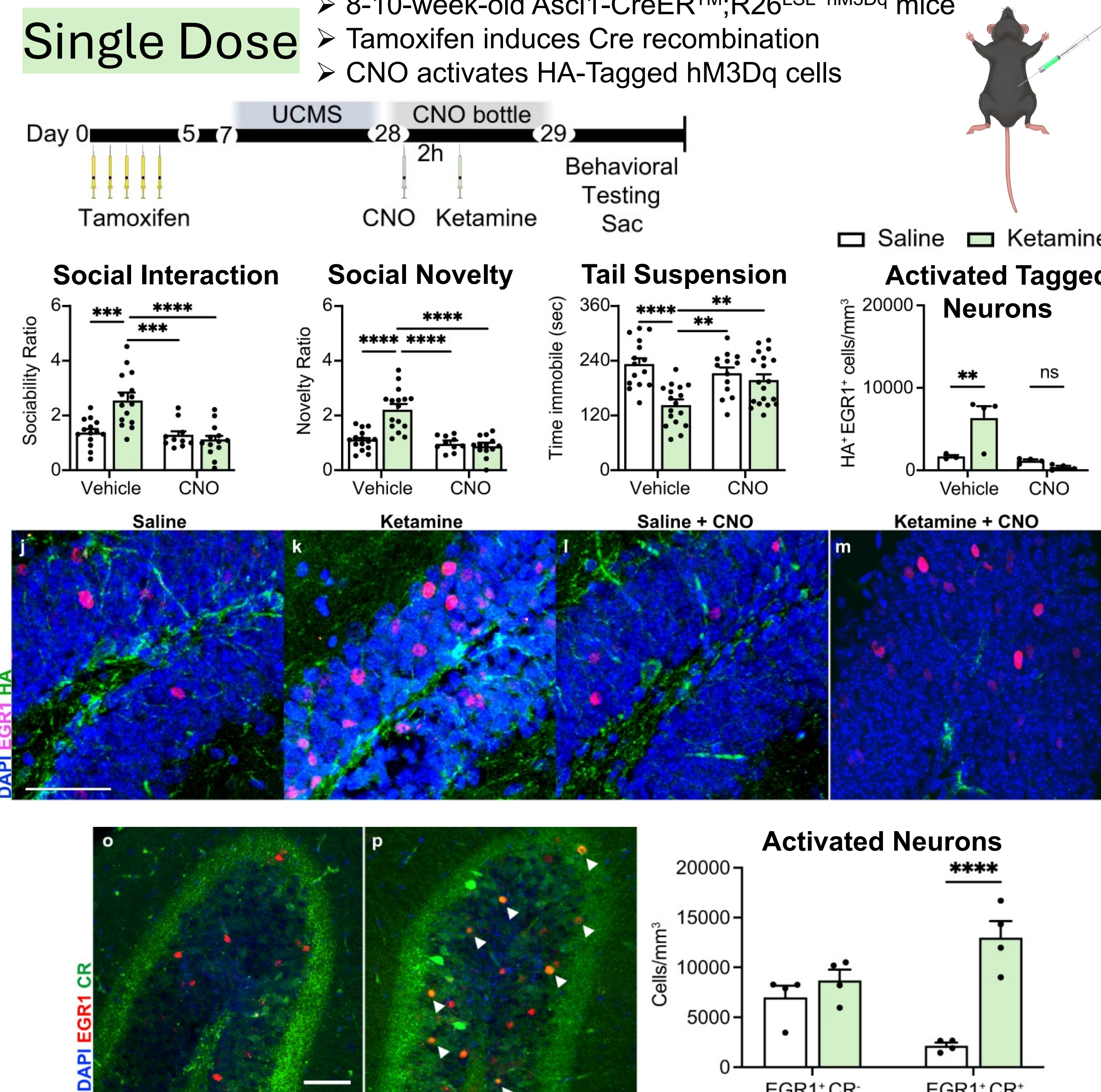


## Increased Adult Neurogenesis Mediates Ketamine's Sustained Effects

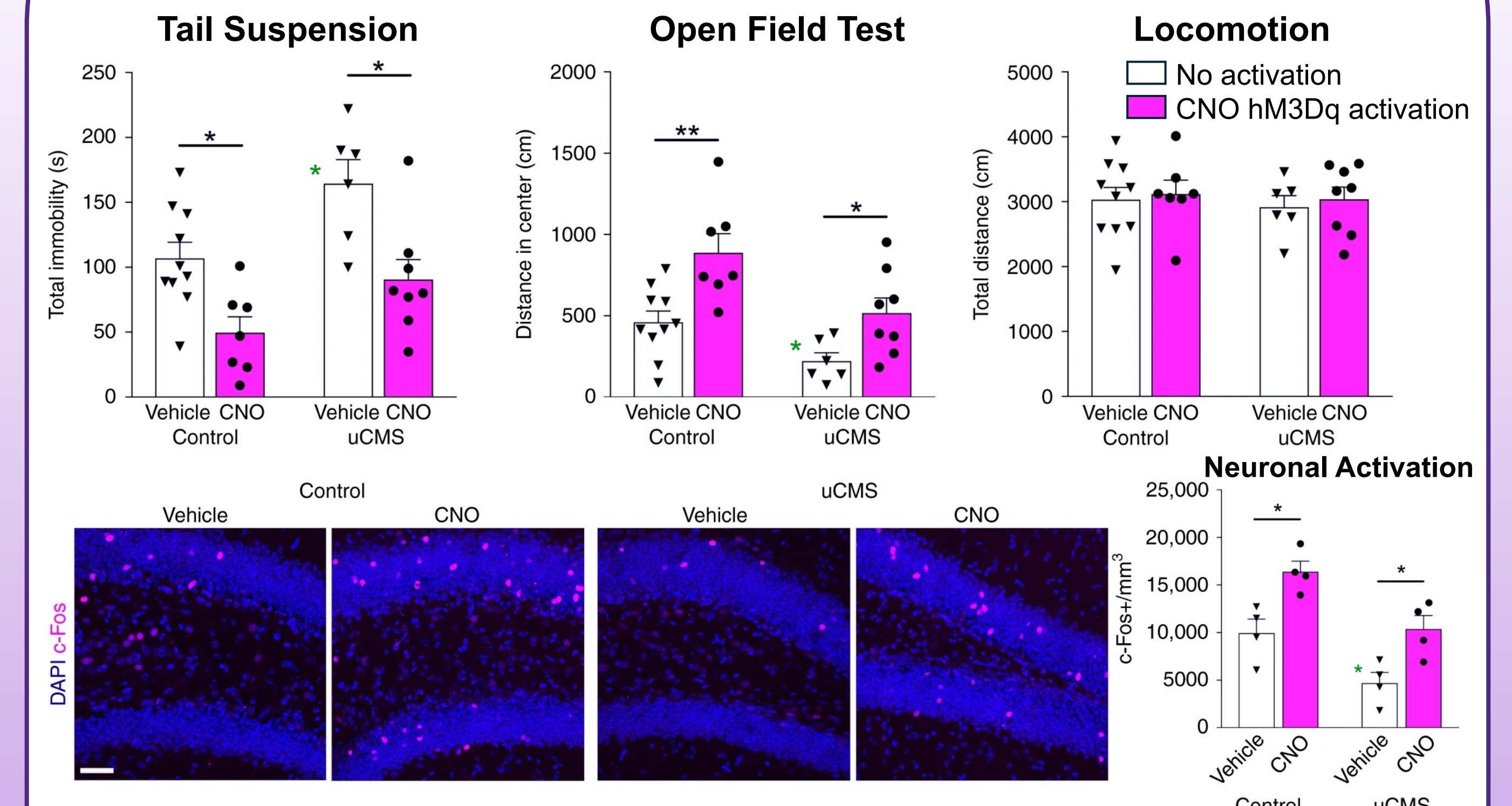


Repeated ketamine increased neuronal precursor division and accelerated neuronal maturation

## Immature Granule Neuron Activation Drives Ketamine's Rapid Effects



## Activation of Newborn Granule Neurons Produces Antidepressant-like Effects



Acute activation of newborn dentate gyrus neurons improves affective behavior performance and reverses the negative behavioral effects of chronic stress

## Conclusions:

- Hippocampal bone morphogenetic protein (BMP) signaling increases in the unpredictable chronic mild stress (UCMS) model. This increase is sufficient to worsen affective behavior performance and abolish sustained, long-term antidepressant effects
- For multiple antidepressant treatments, decreasing hippocampal BMP signaling is a common mechanism that increases adult hippocampal neurogenesis
- As a rapid-acting antidepressant, a single dose of ketamine activates immature granule neurons; this activation is both necessary and sufficient to produce antidepressant-like effects

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- Rawat, R., Tunc-Ozcan, E., Dunlop, S. *et al.* Ketamine's rapid and sustained antidepressant effects are driven by distinct mechanisms. *Cell Mol Life Sci* **81**, 105 (2024).
- Rawat, R., Tunc-Ozcan, E., McGuire, T.L., Peng, C.Y., & Kessler, J.A. Ketamine activates adult-born immature granule neurons to rapidly alleviate depression-like behaviors in mice. *Nat Commun* **13**, 2650 (2022).
- Tunc-Ozcan, E., Peng, C.Y., Zhu, Y. *et al.* Activating newborn neurons suppresses depression and anxiety-like behaviors. *Nat Commun* **10**, 3768 (2019).

All data are presented as means±s.e.m. \**p*<0.05, \*\**p*<0.01, \*\*\**p*<0.001, \*\*\*\**p*<0.0001