

# *Psychedelics and Related Plasticity-Promoting Neurotherapeutics*

**David E. Olson**

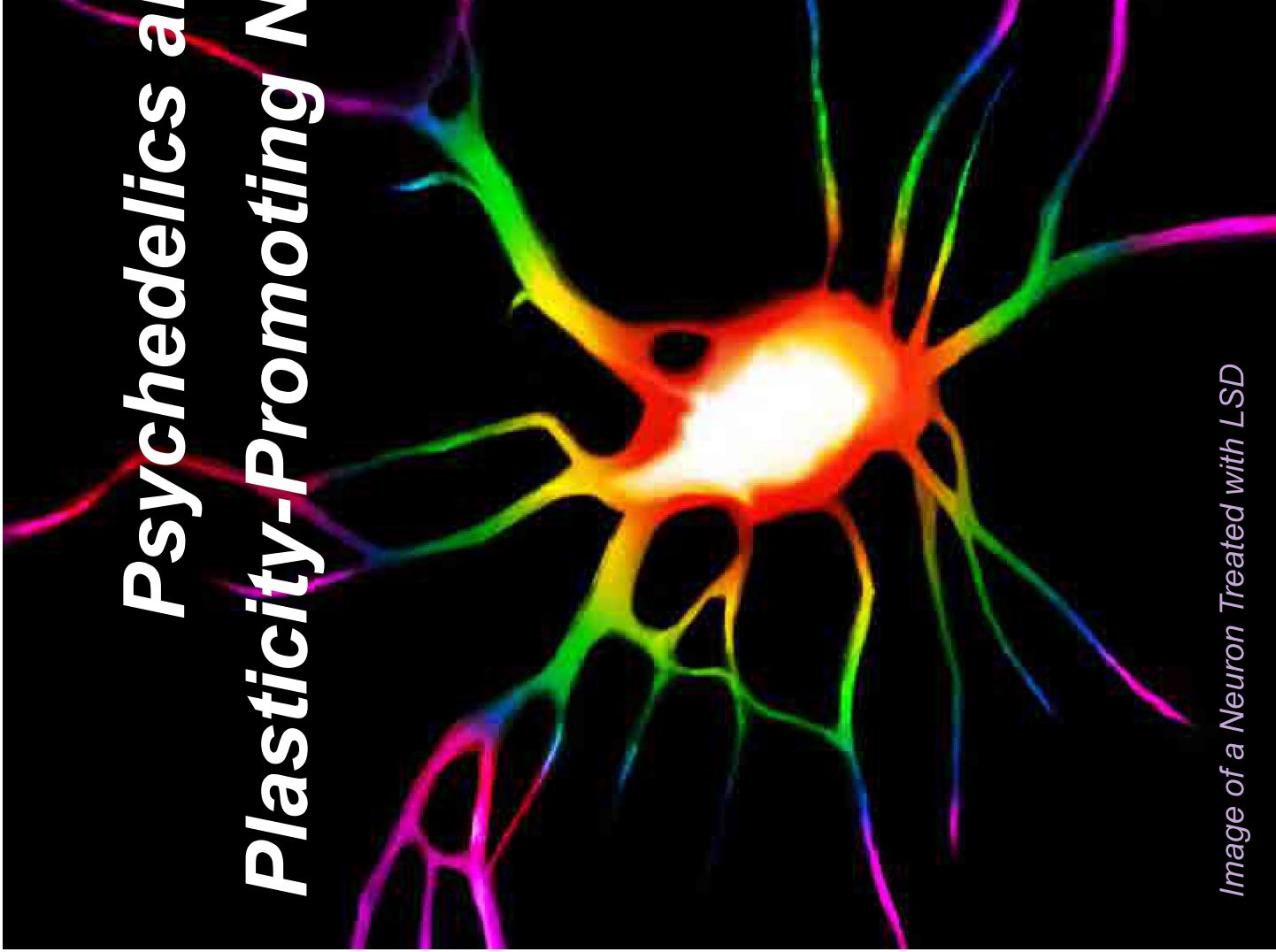
*Department of Chemistry  
Biochemistry & Molecular Medicine  
Center for Neuroscience*

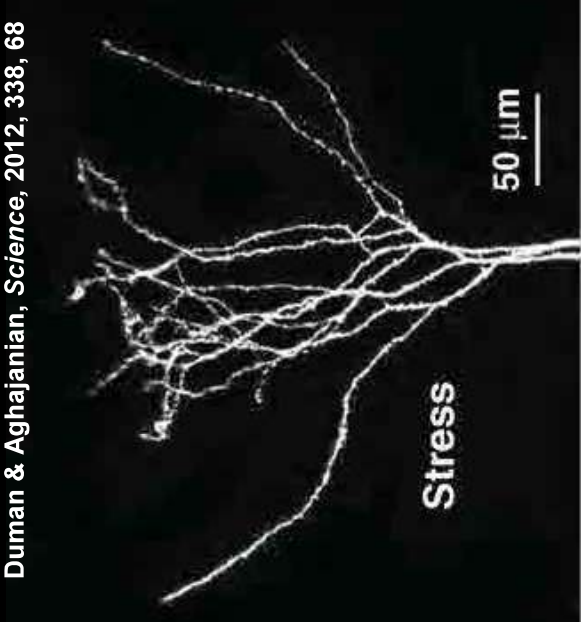
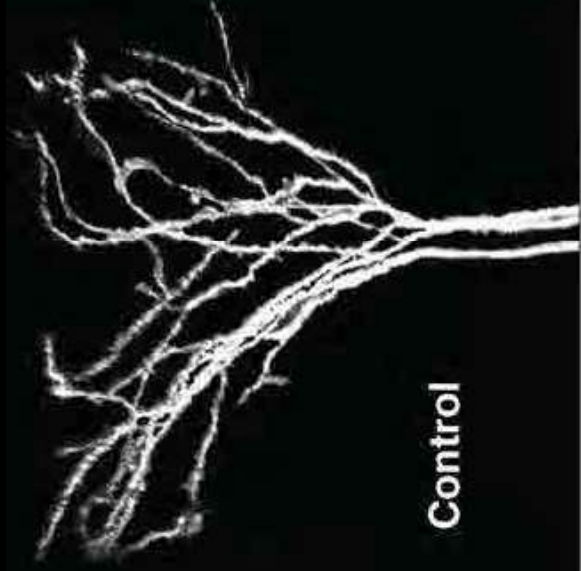
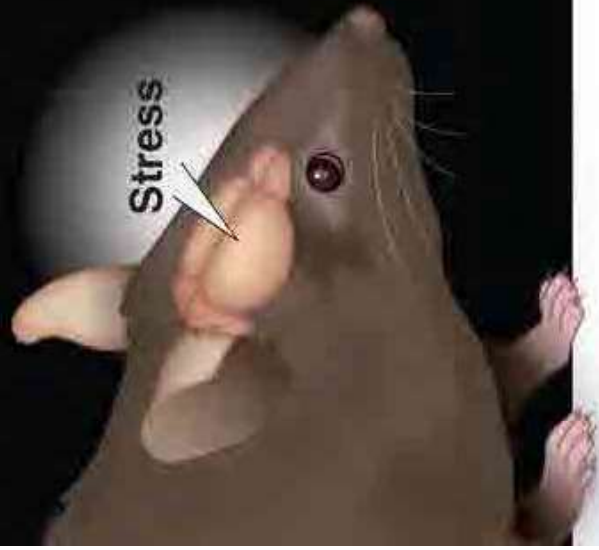
*University of California, Davis*



*Disclosure: DEO is a Co-Founder and  
CIO of Delix Therapeutics, Inc.*

*Image of a Neuron Treated with LSD*





Chemical Imbalance

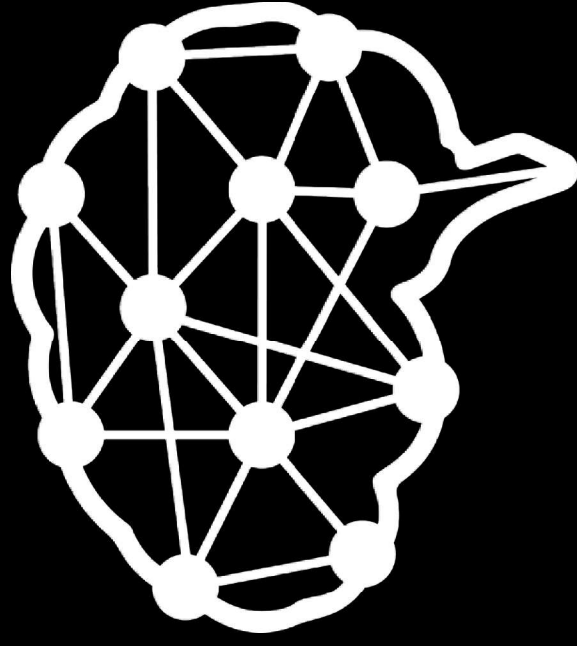
vs

Neural Circuits

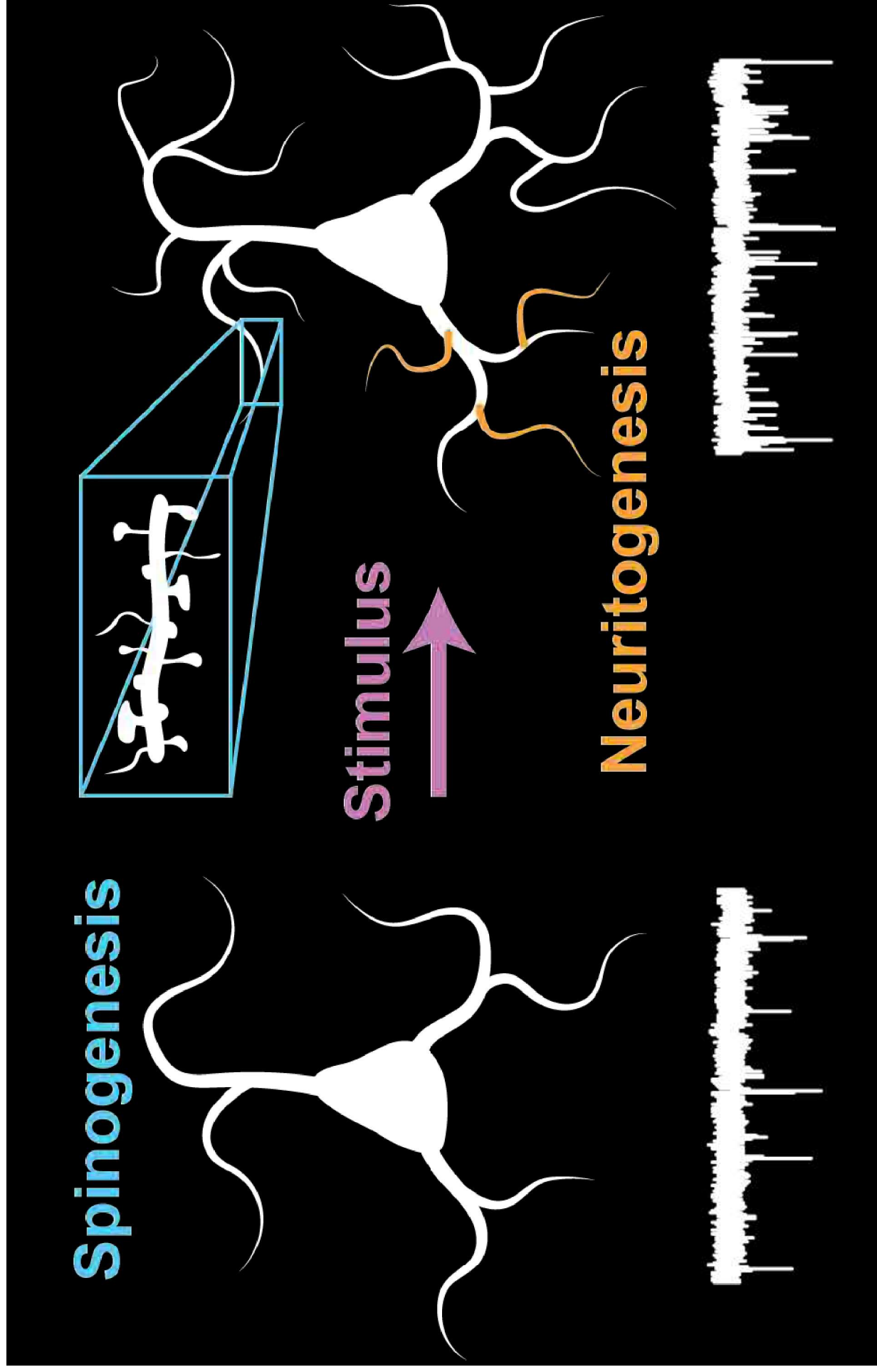
Healthy



Depression



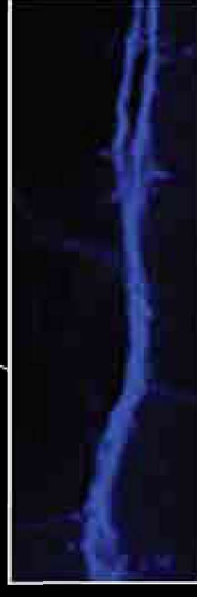
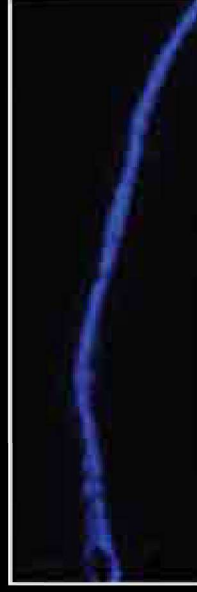
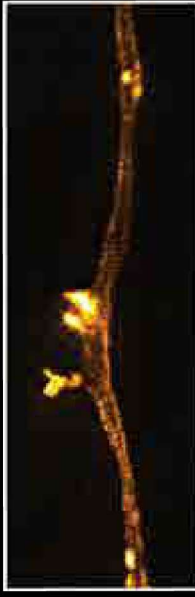
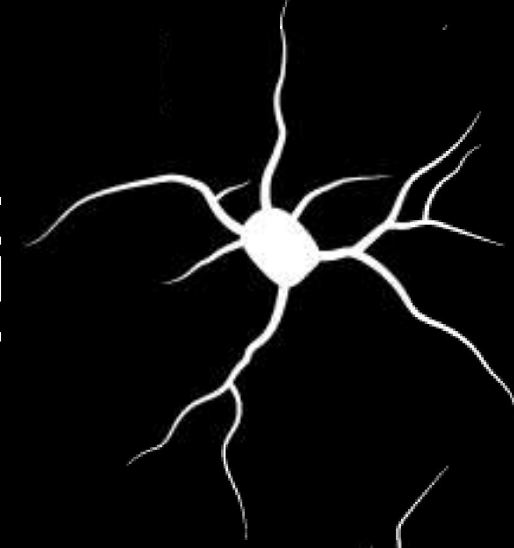
# *Psychoplastogens Promote Neuronal Growth*



DMT

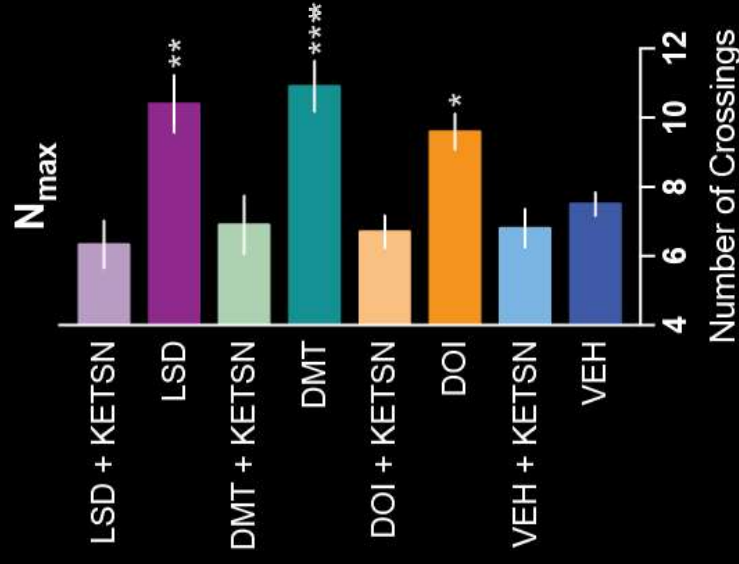
VEH

LSD

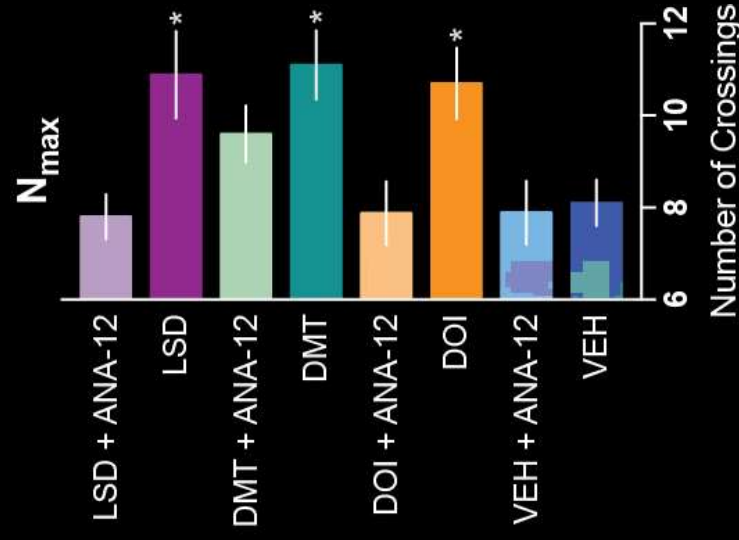


# Mechanism of Psychoplastogenic Effect

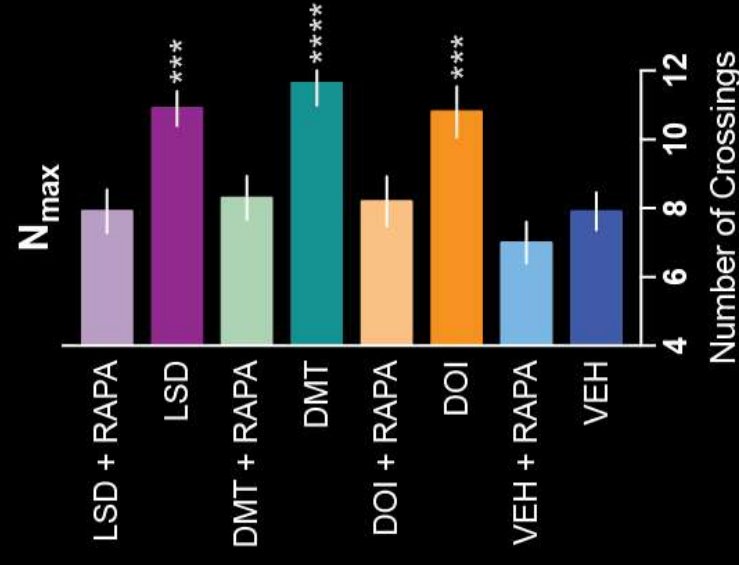
5-HT<sub>2A</sub>

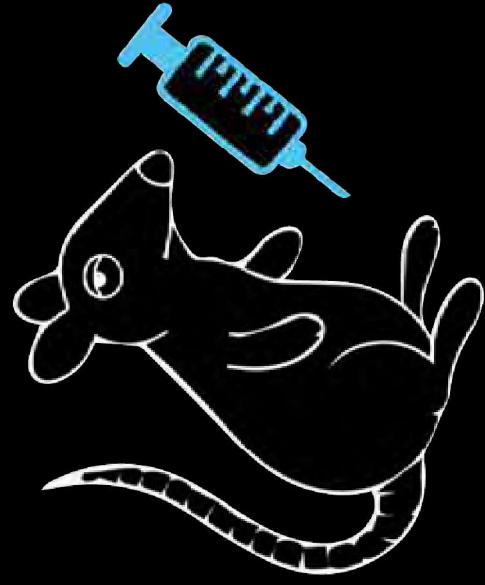


TrkB

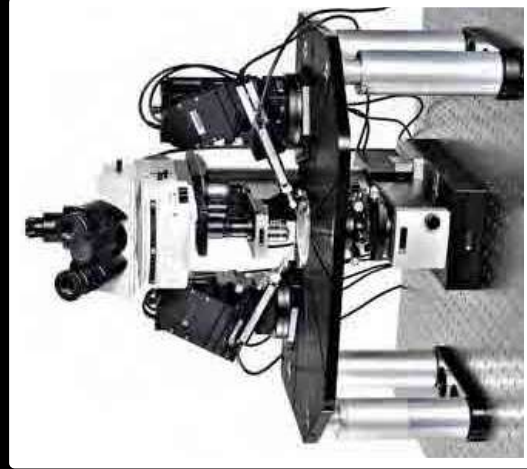


mTOR

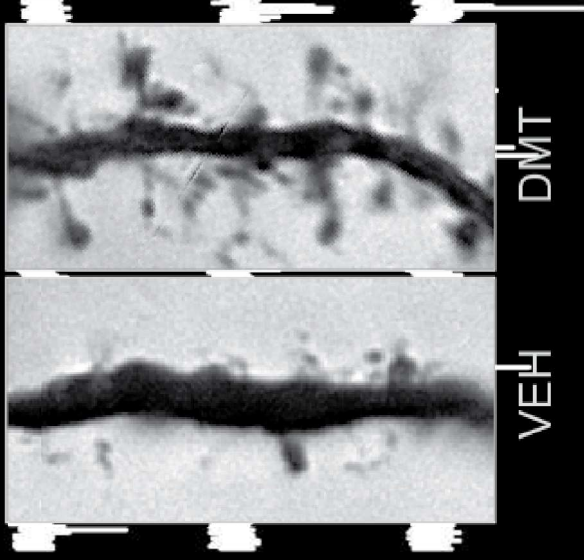




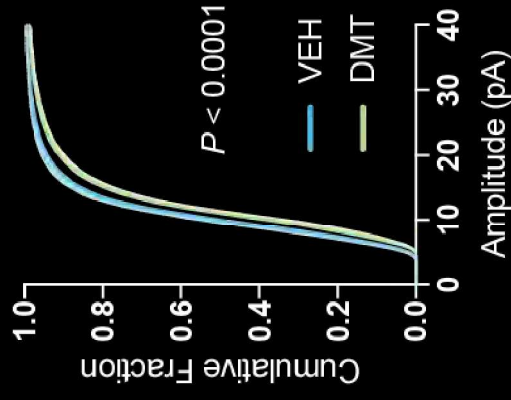
**Dose  
then  
Wait 24 h**



Apical **MT** dendrites



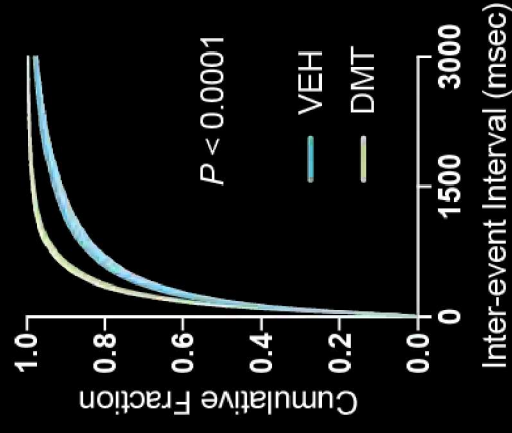
sEPSC Amplitude



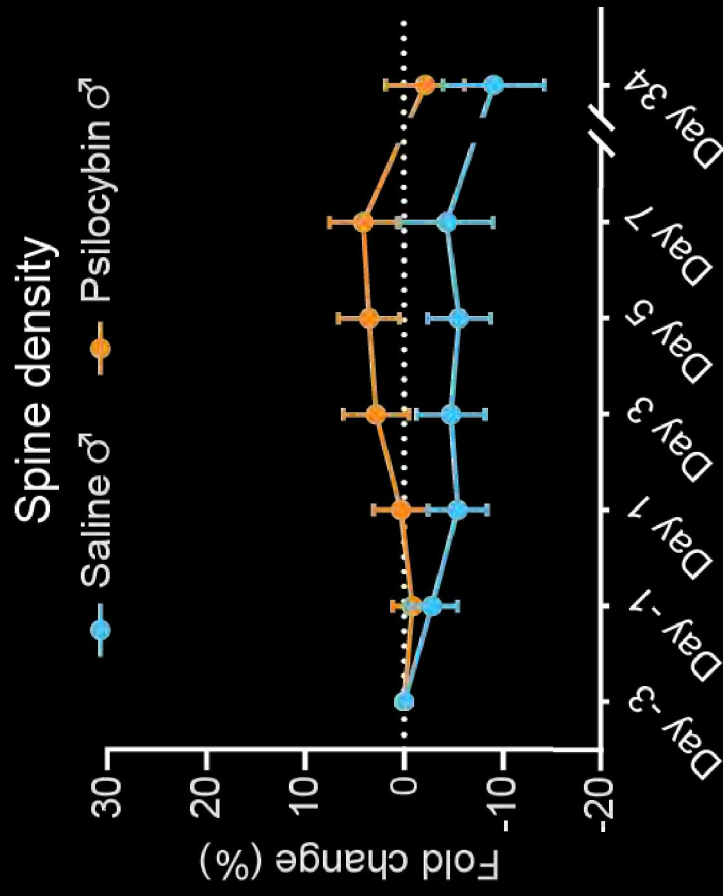
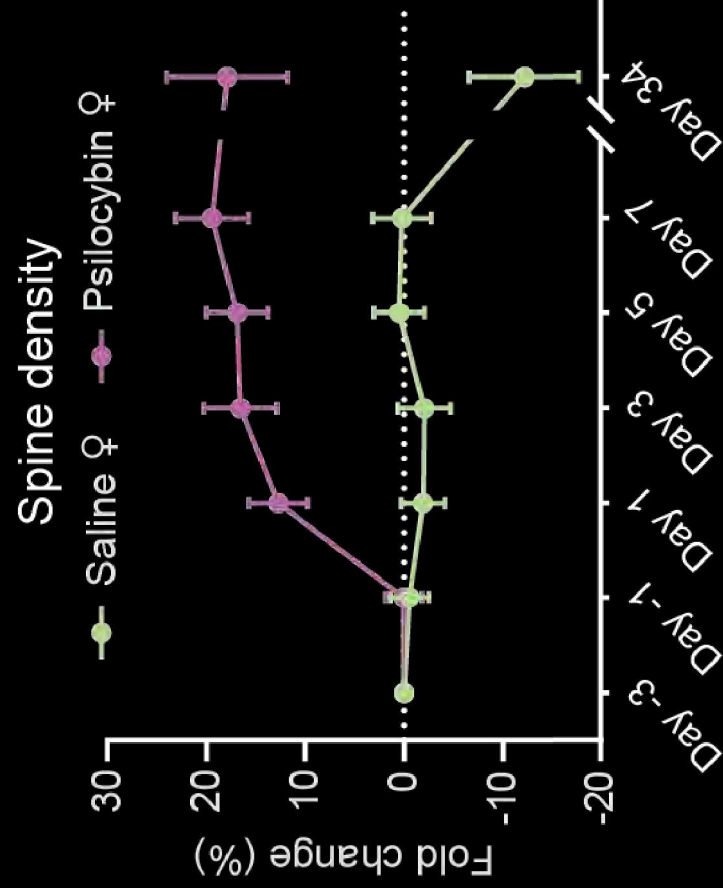
8 **DMT**



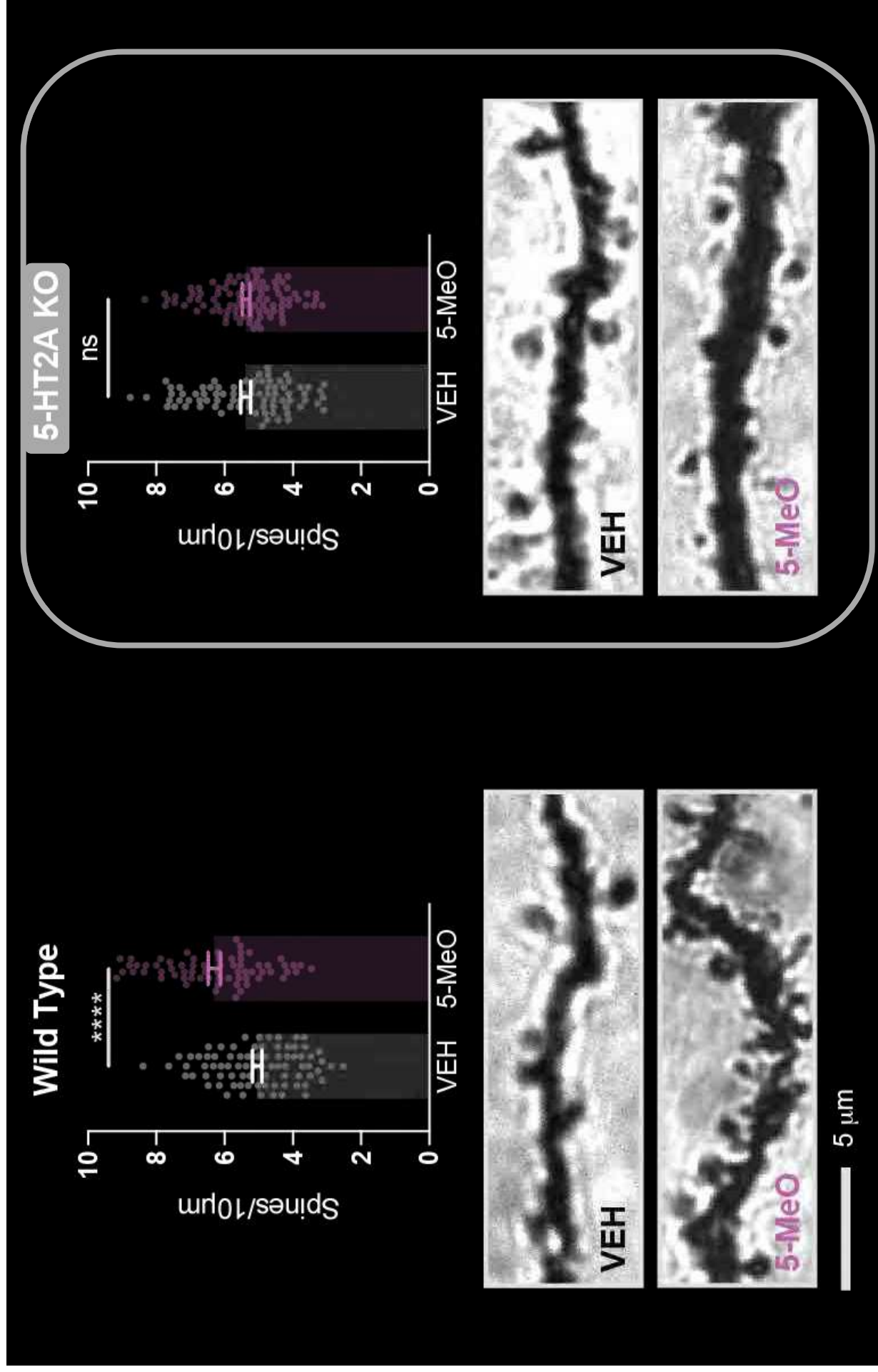
sEPSC Frequency



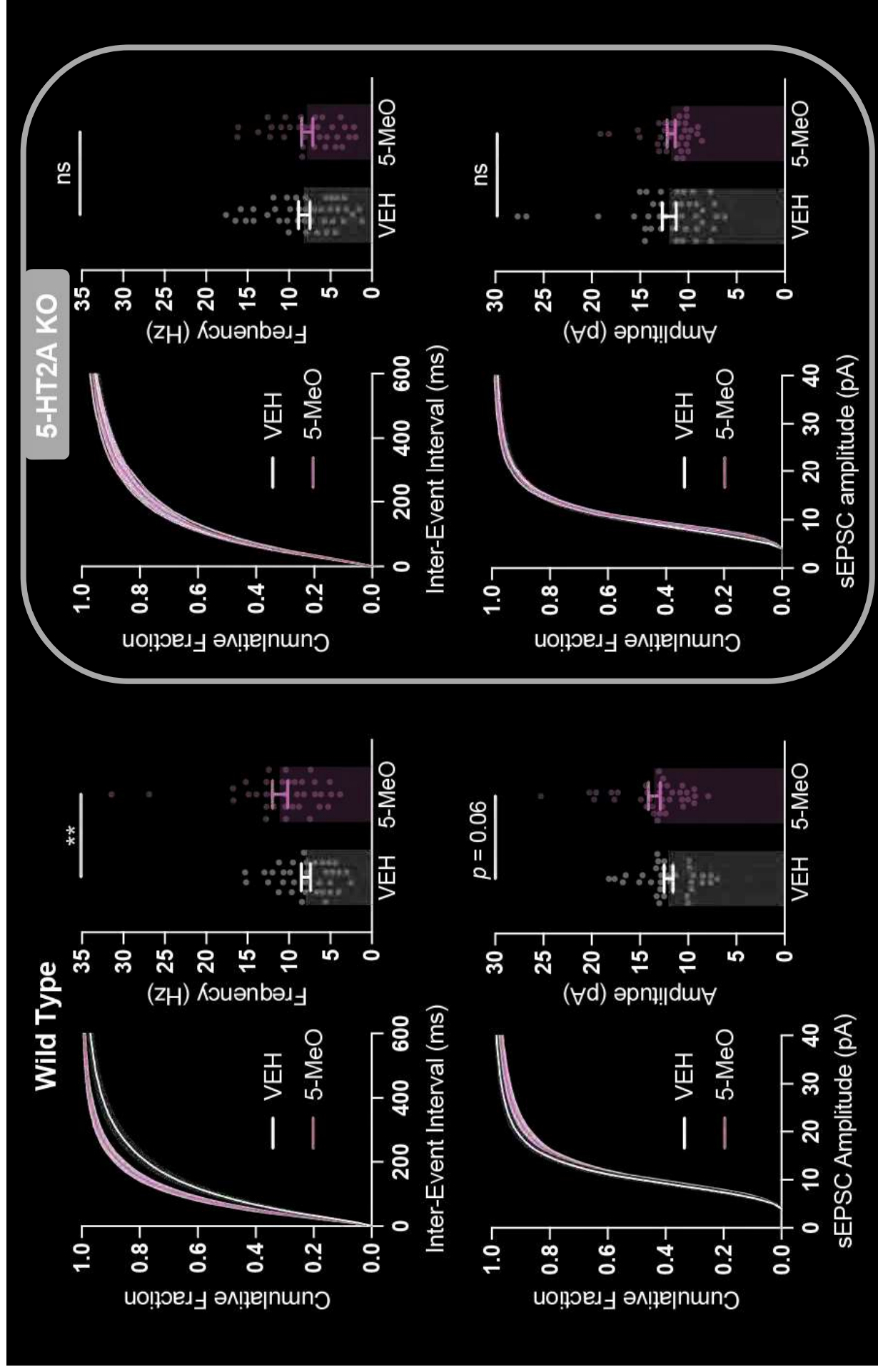
# Psilocybin Increases Dendritic Spine Density



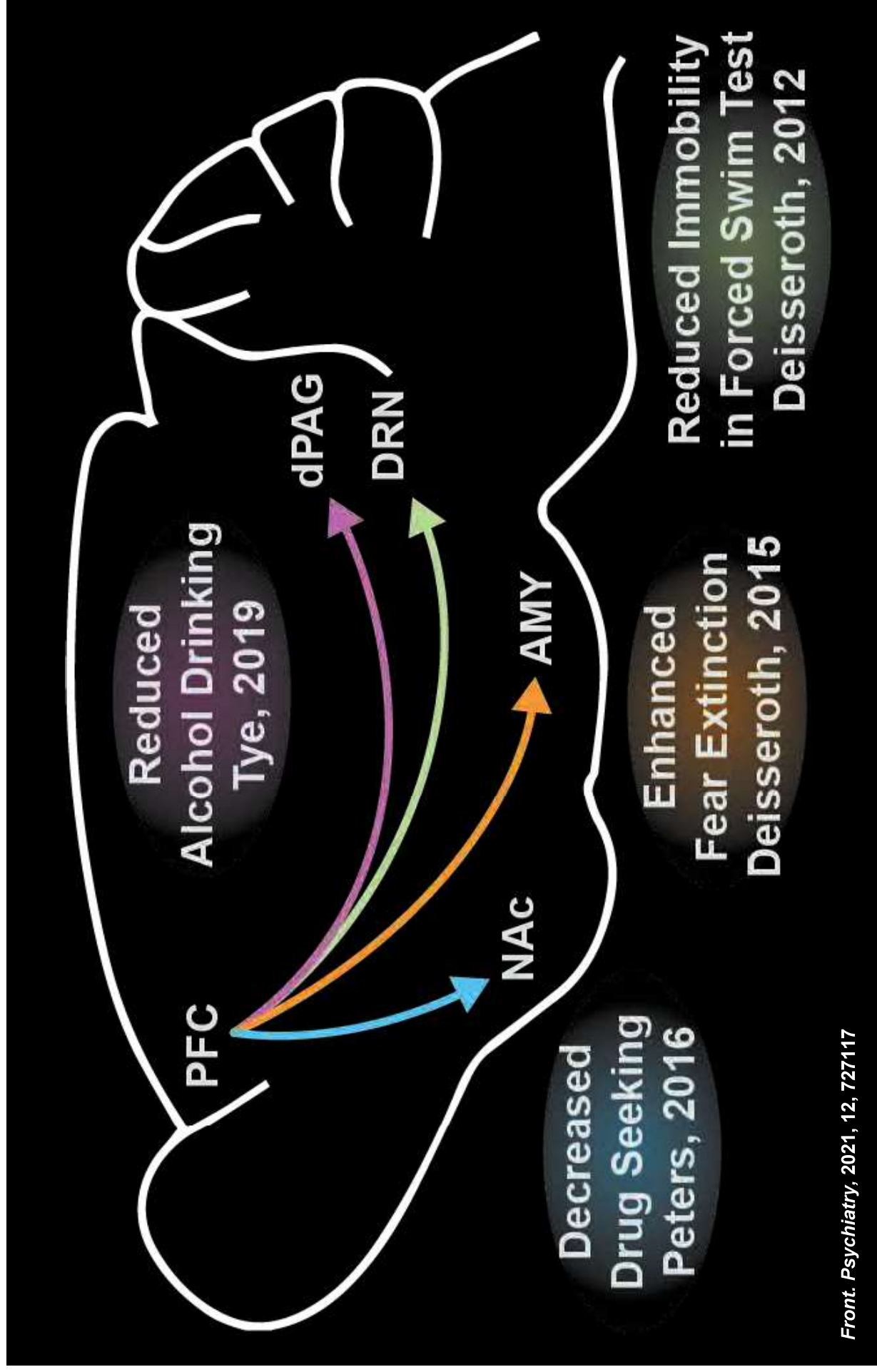
# Structural Plasticity is Mediated by 5-HT<sub>2</sub>ARs



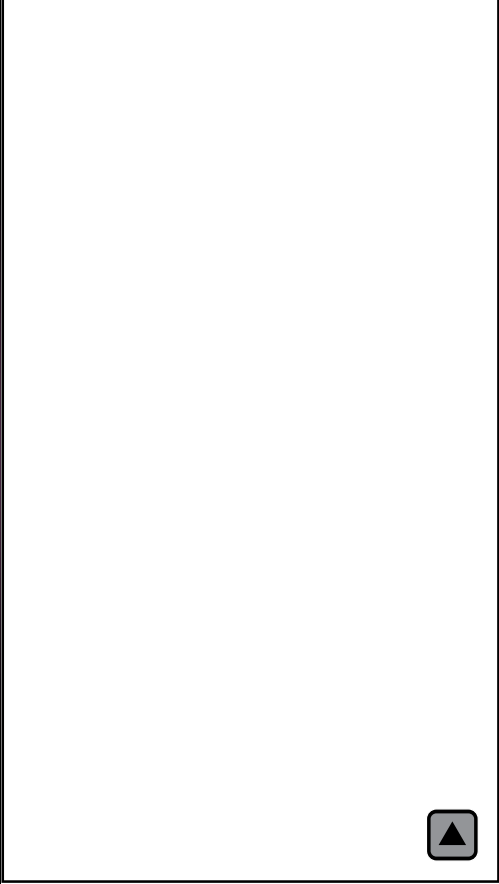
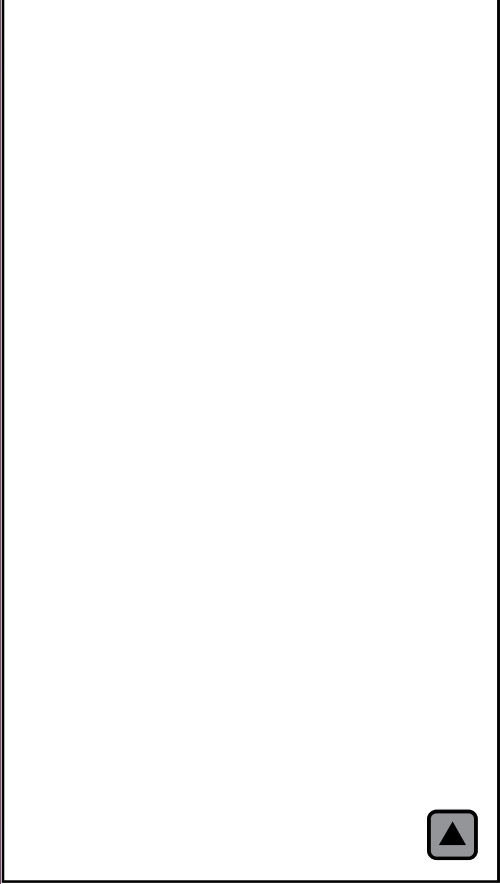
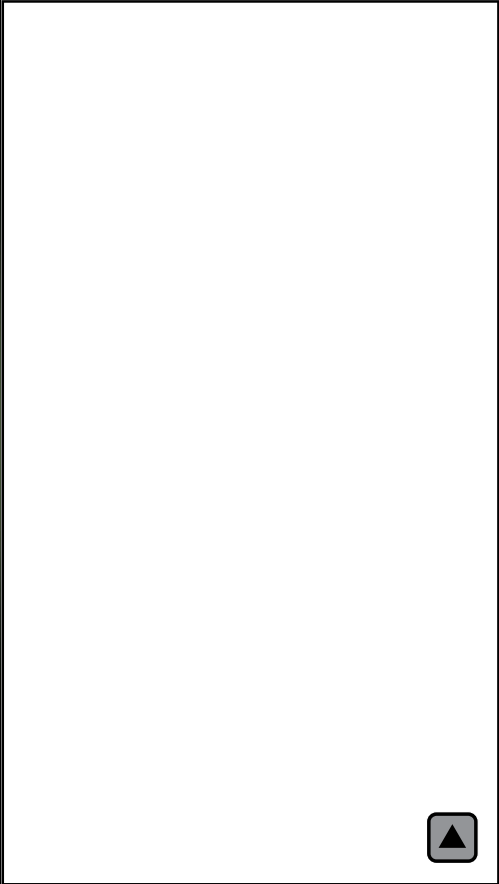
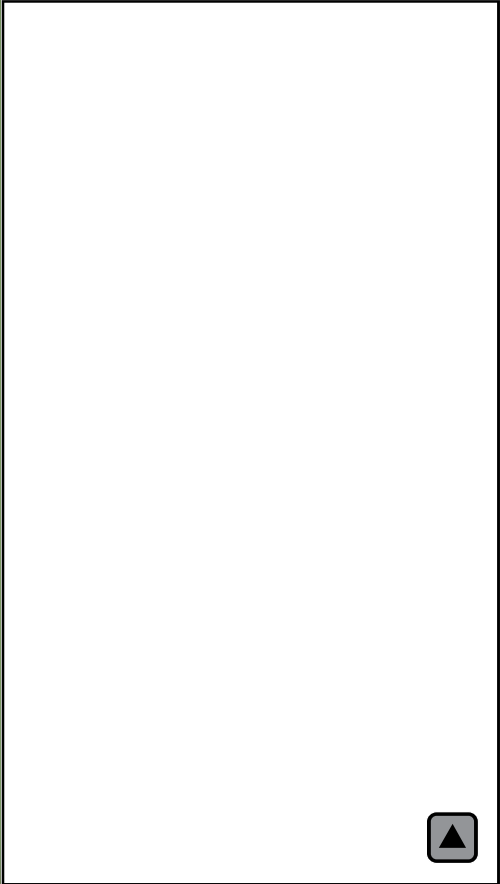
# Functional Plasticity is Mediated by 5-HT<sub>2A</sub>Rs



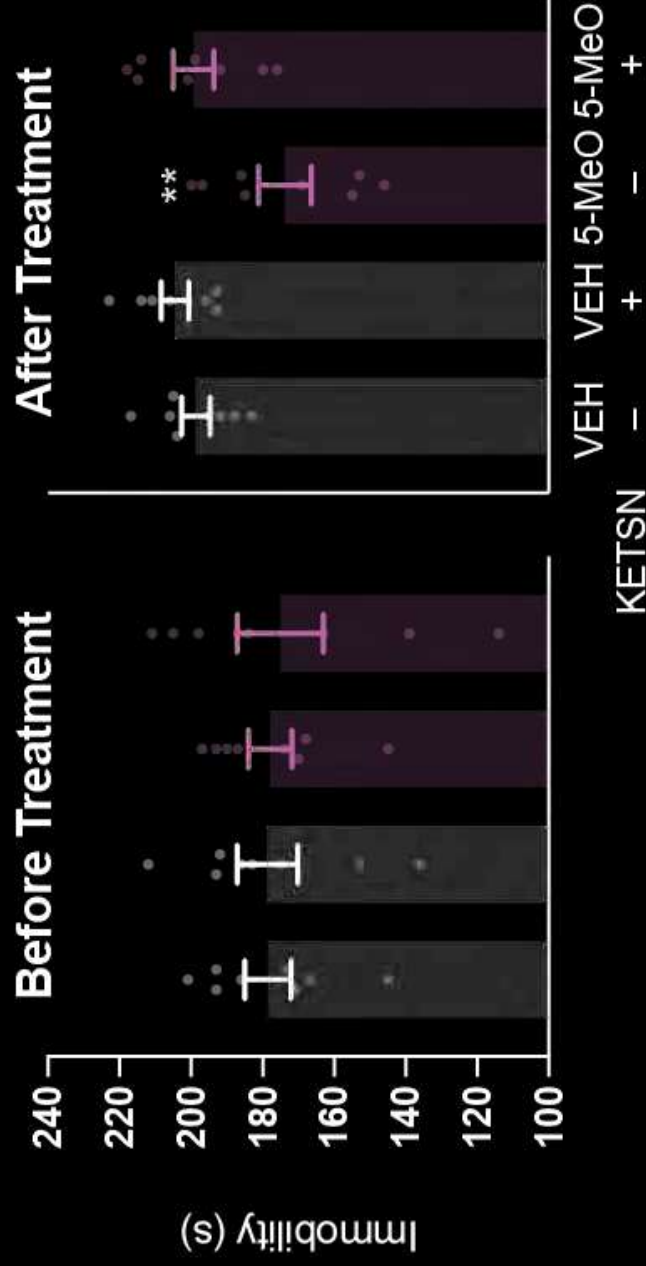
# Potential Circuits Mediating Therapeutic Effects



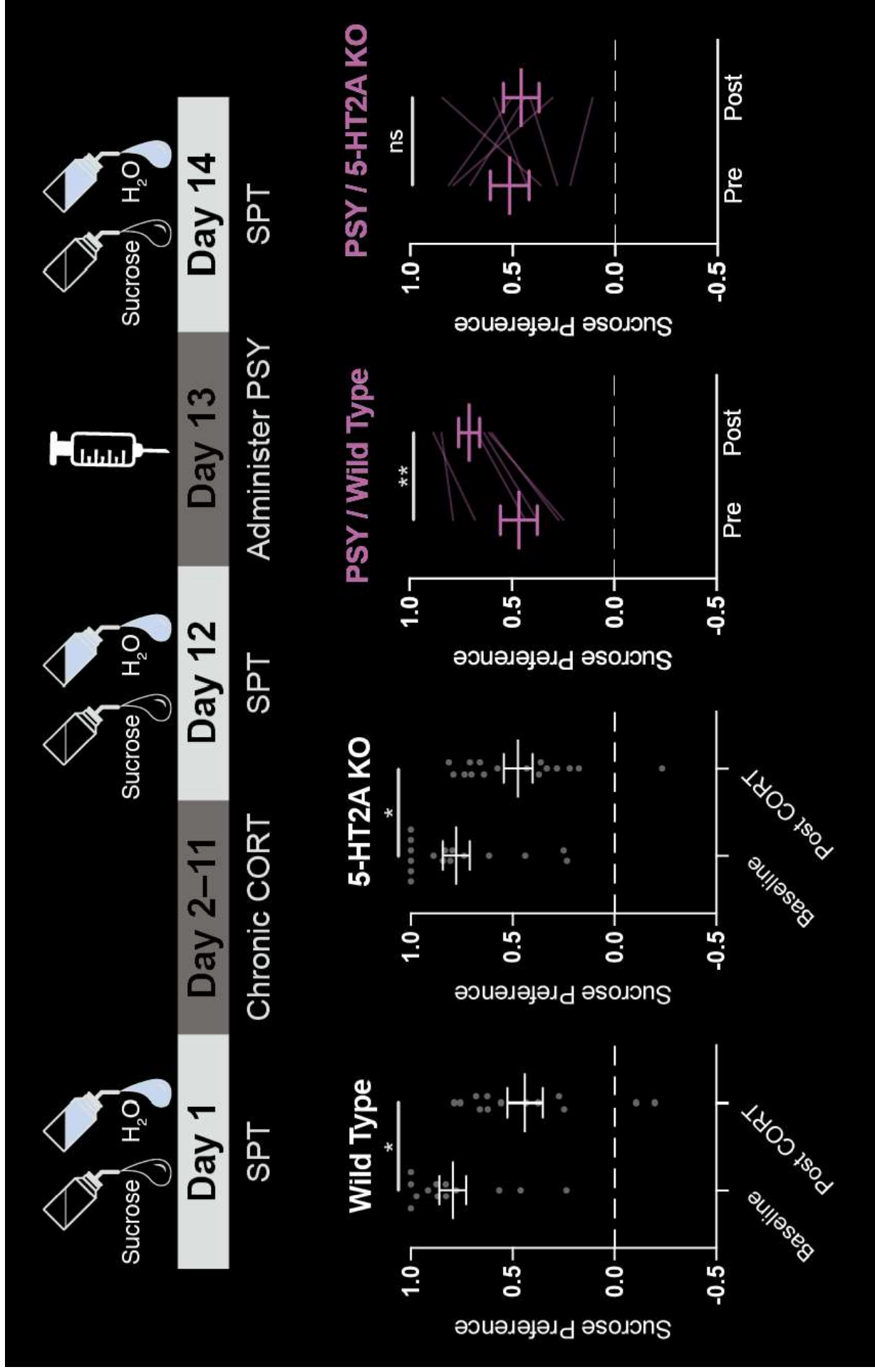
# ***Psychoplastogens Produce Therapeutic Effects***

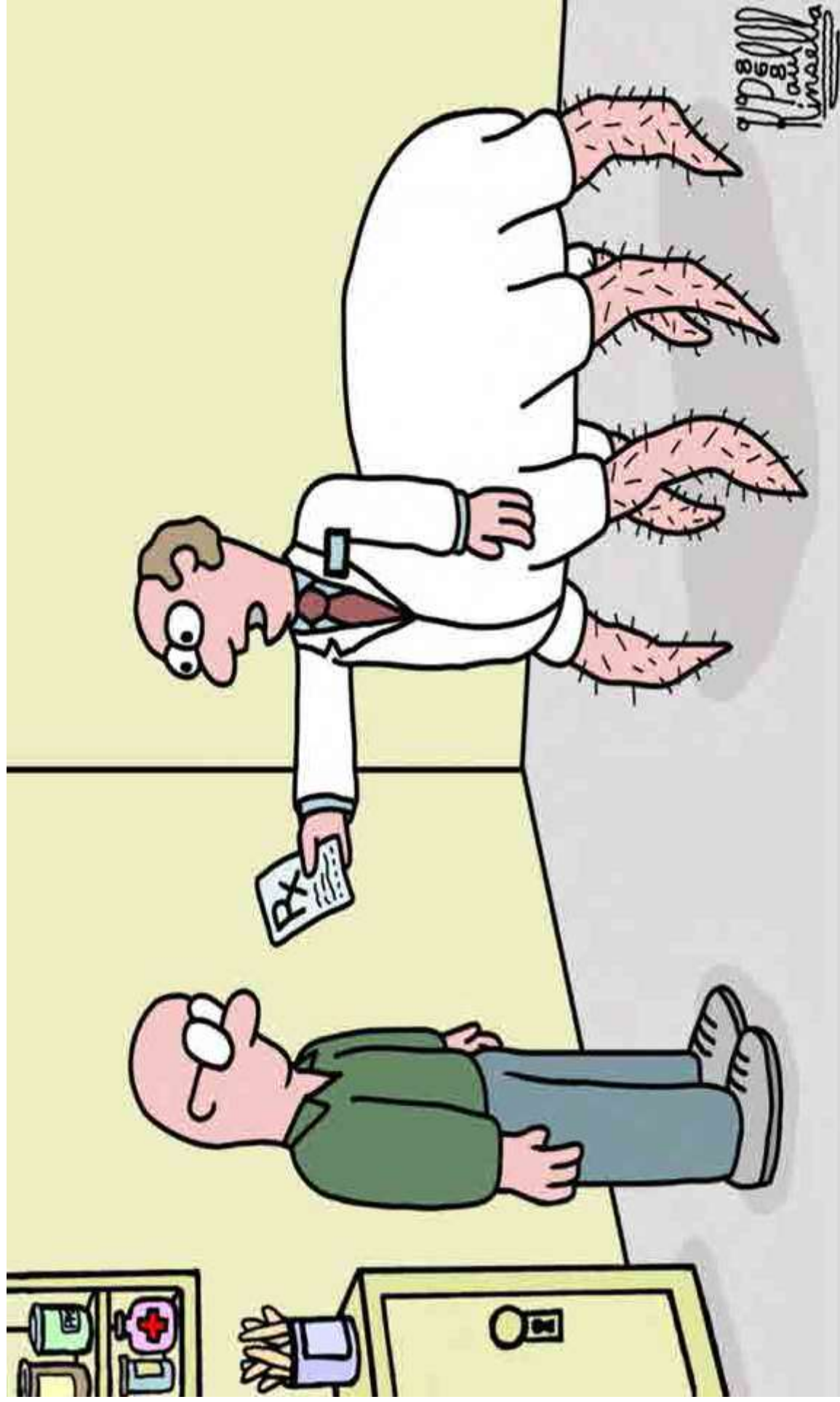
| Vehicle Control                                                                     |                                                                                      | Psychoplastogen                                                                    |                                                                                     |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|  |  |  |  |

# 5-HT<sub>2A</sub> Antagonist Blocks Antidepressant Effects



# 5-HT2AR is Necessary to Rescue Anhedonia

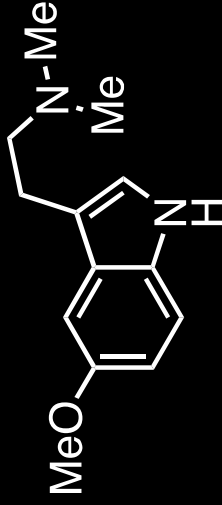




**"Call me immediately if this prescription causes any headaches or hallucinations."**

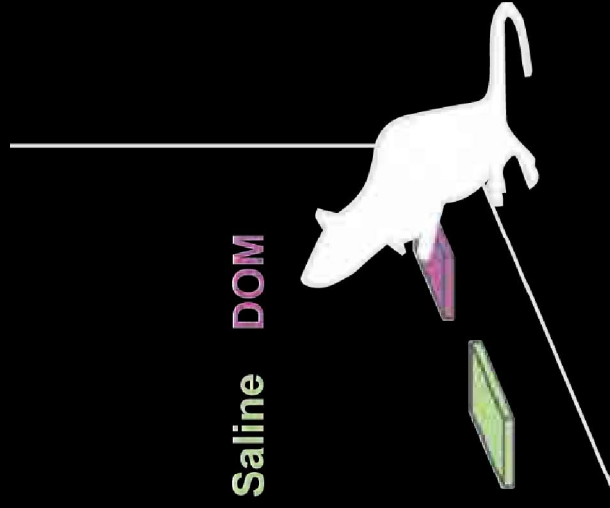
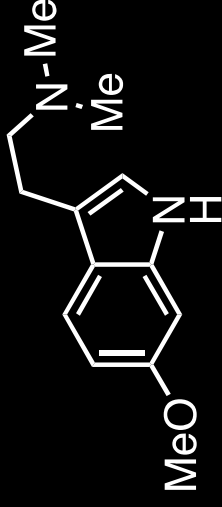
# Non-Hallucinogenic Psychoplastogens

5-MeO-DMT

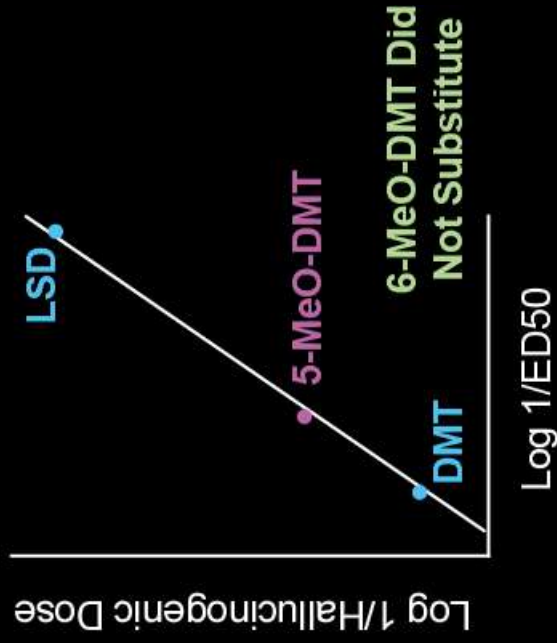


VS

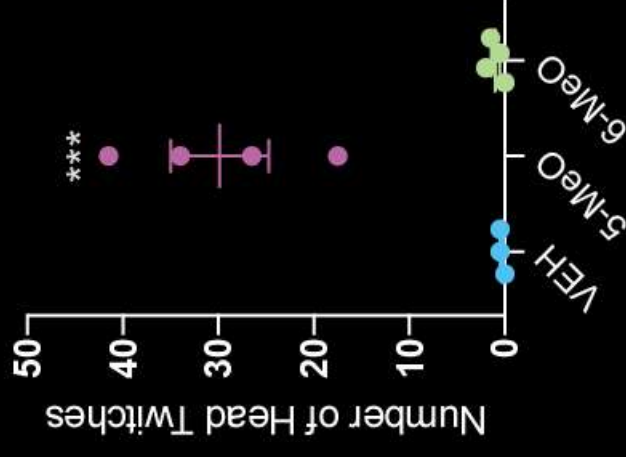
6-MeO-DMT



DOM Drug Discrimination



Head-Twitch Response



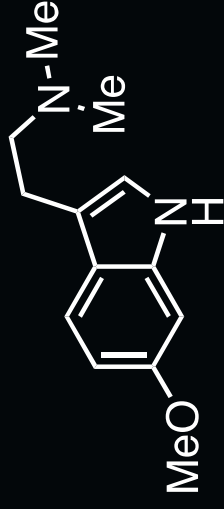
# Non-Hallucinogenic Psychoplastogens

5-MeO-DMT



VS

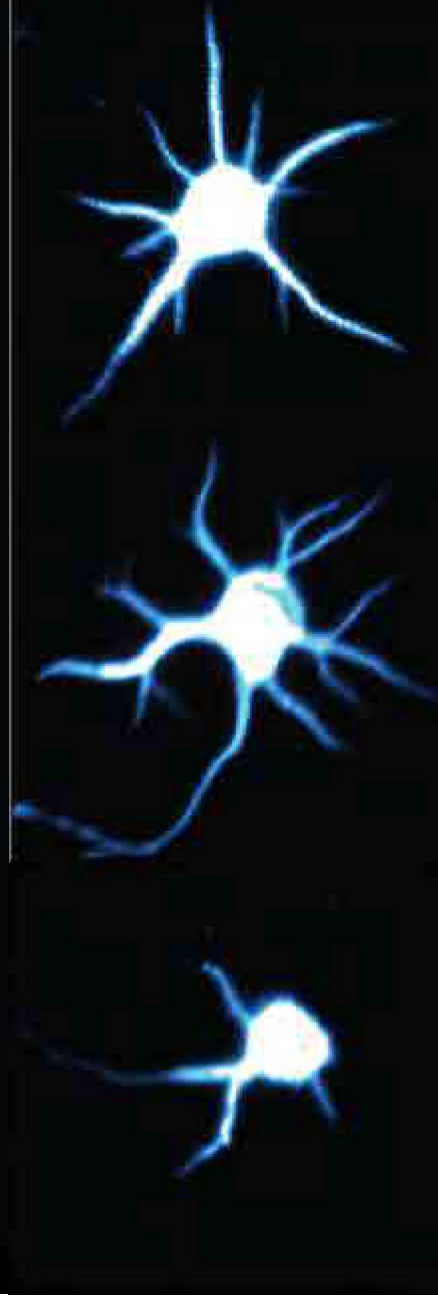
6-MeO-DMT



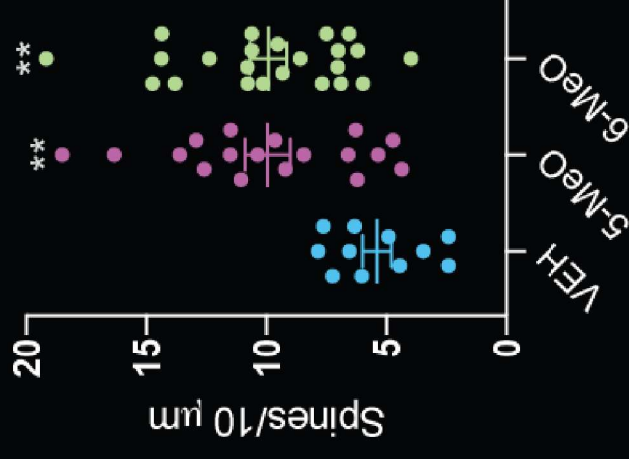
VEH

5-MeO-DMT

6-MeO-DMT

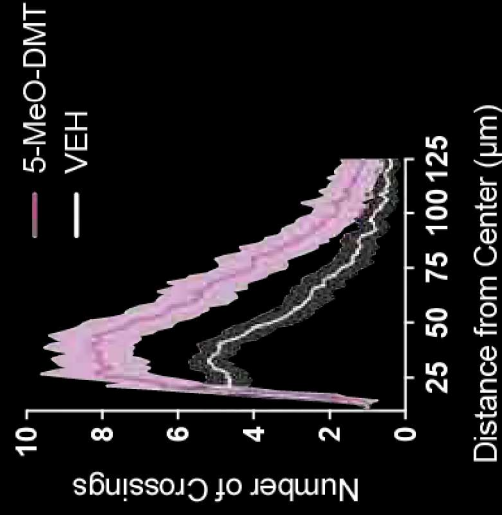


Dendritic Spine Density

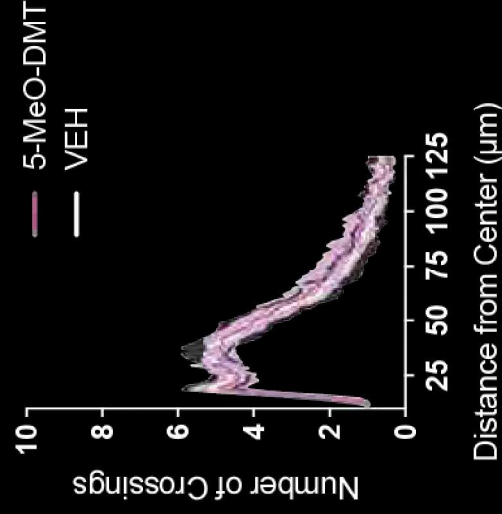


# Non-Hallucinogenic Psychoplastogens

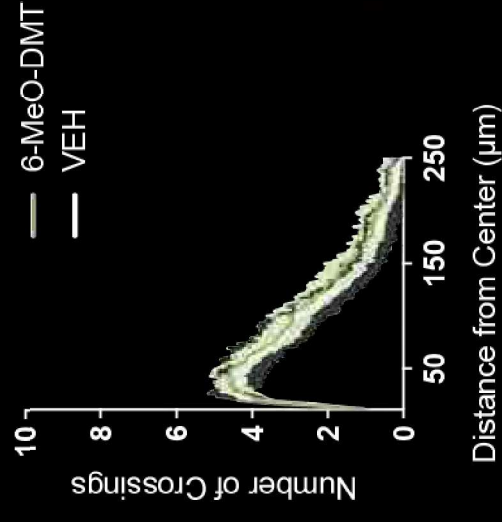
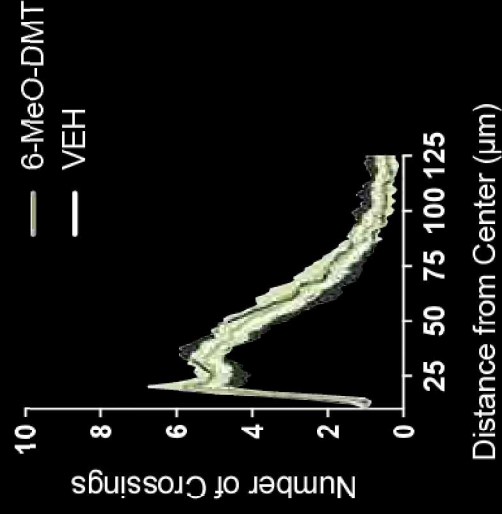
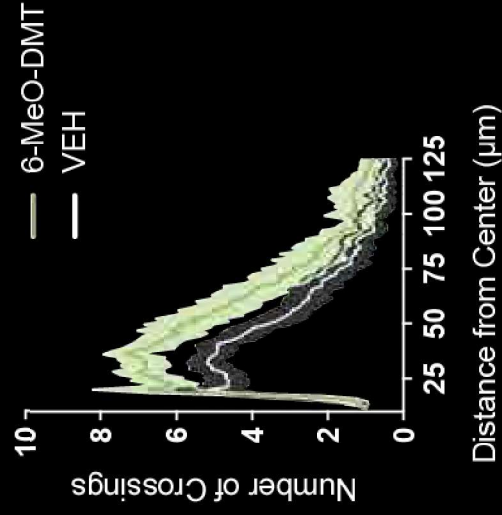
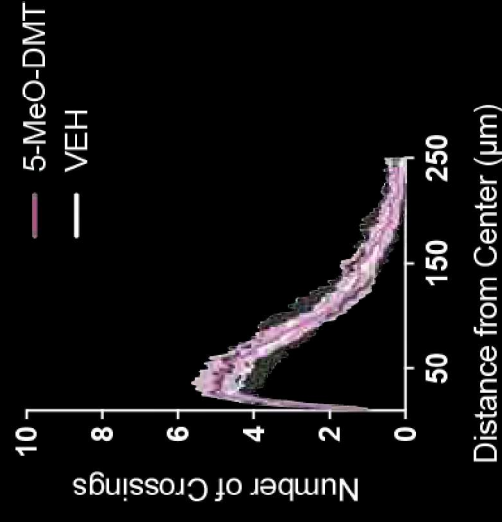
## Wild Type



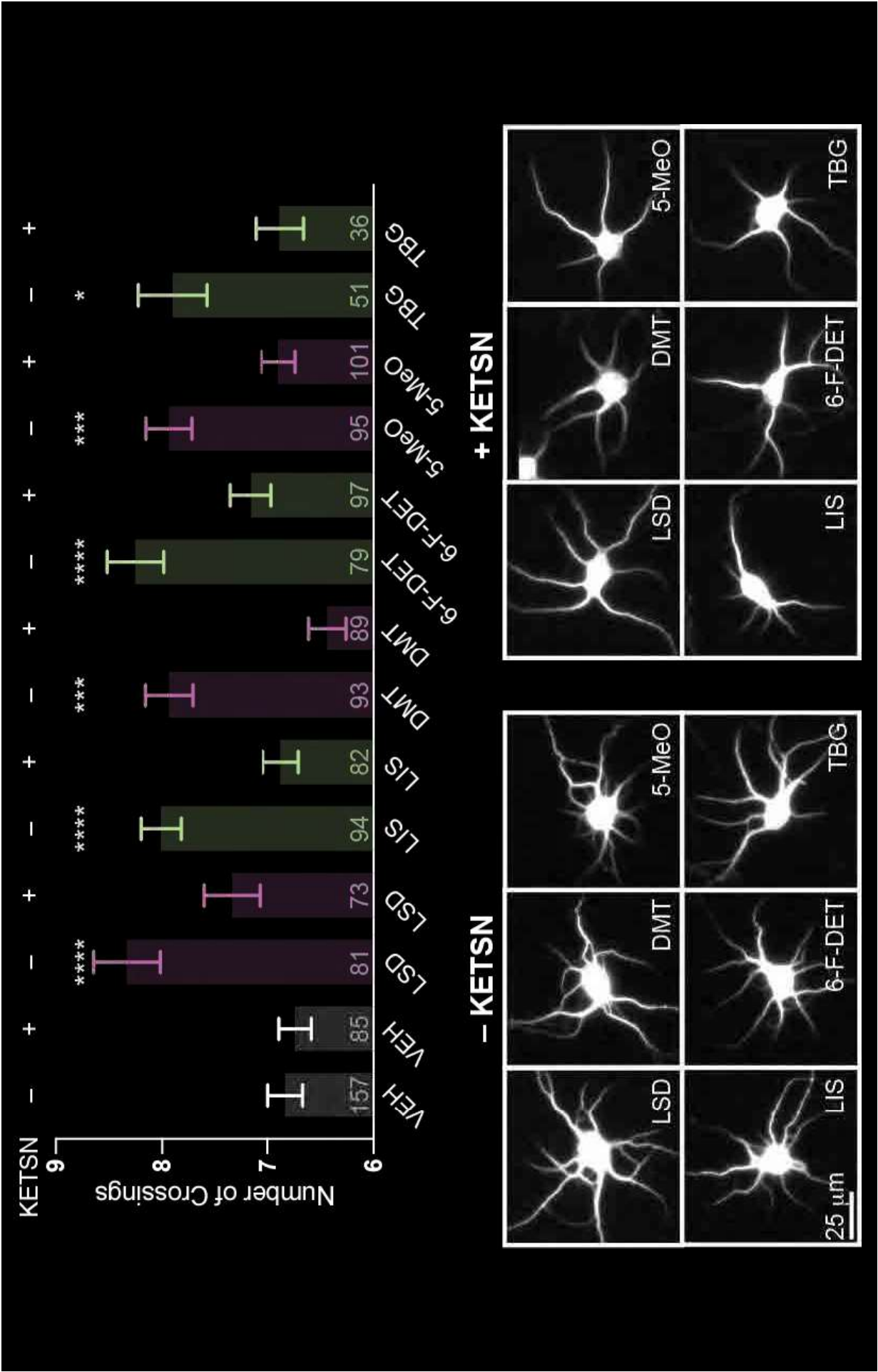
## + Ketanserin



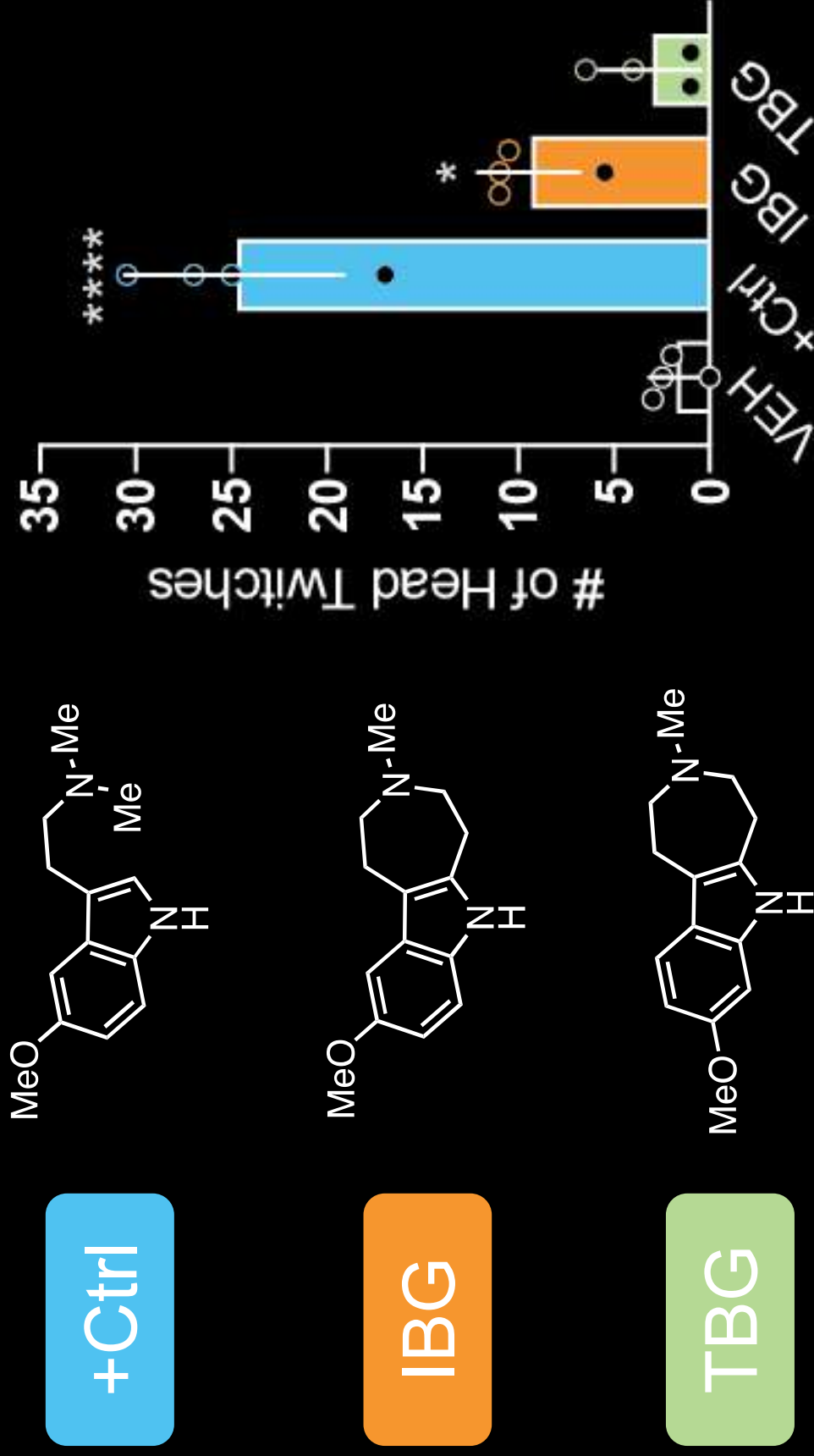
## 5-HT2A KO



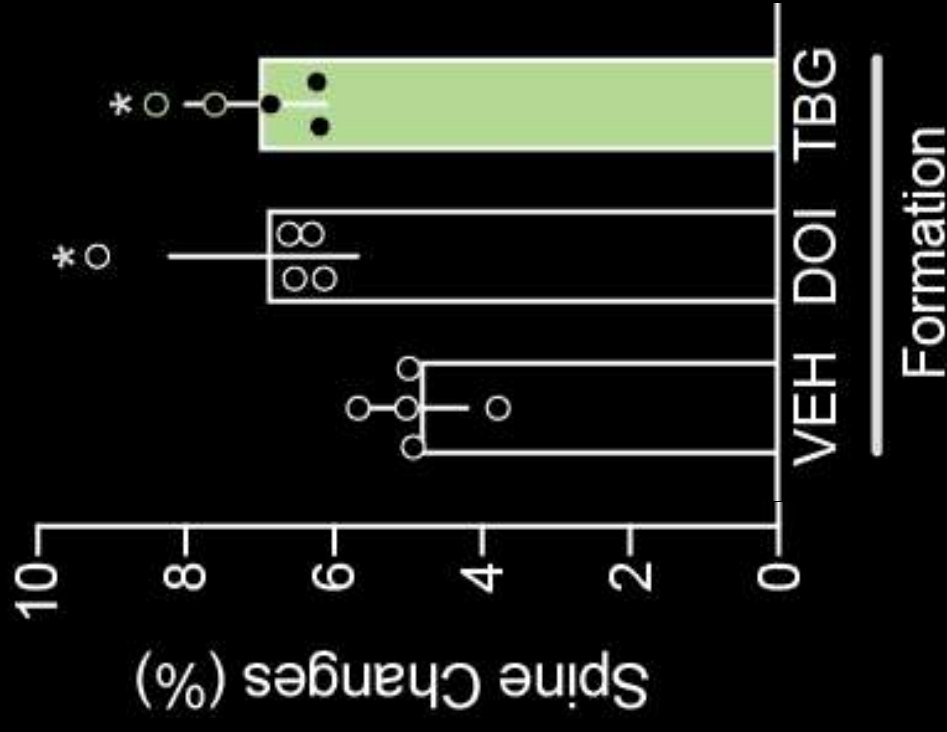
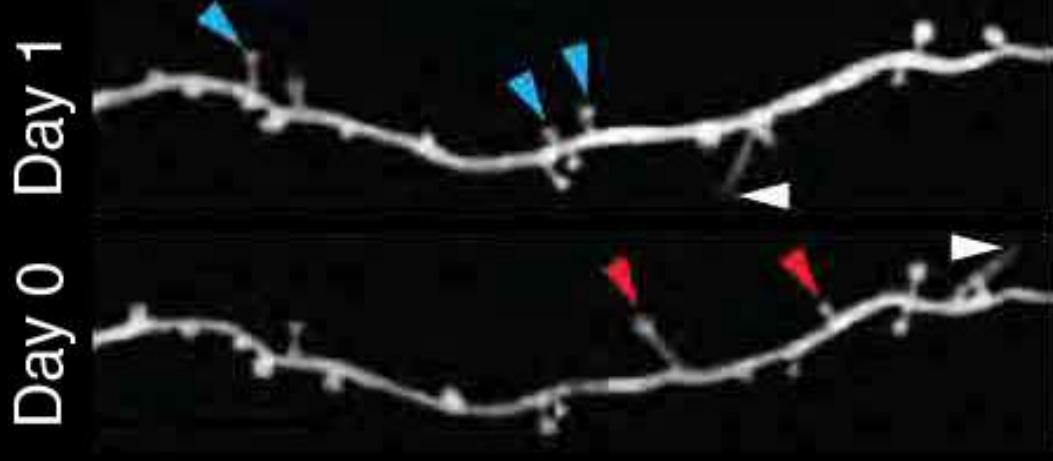
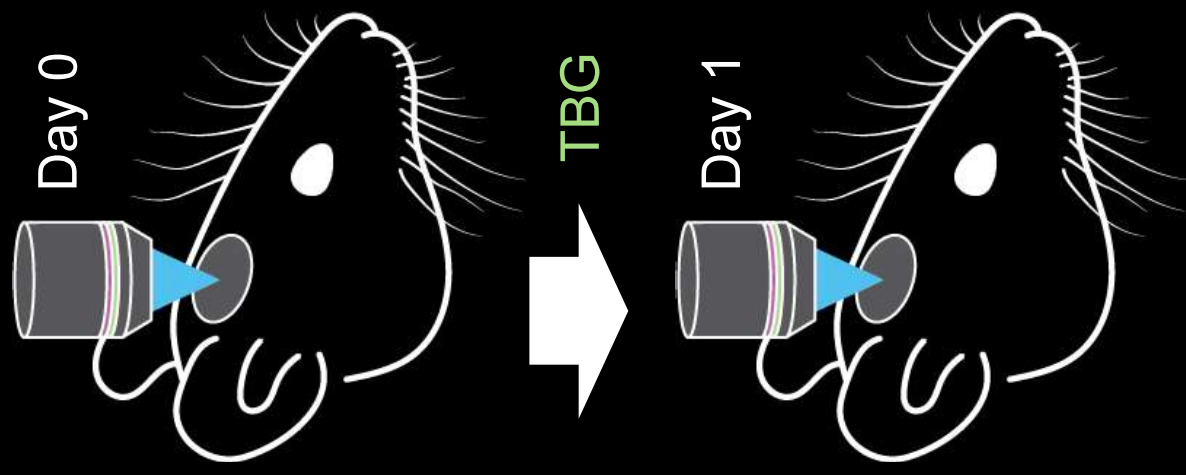
# Bona Fide Non-Hallucinogenic Psychoplastogens



# *Tabernanthalog (TBG) is Not Hallucinogenic*

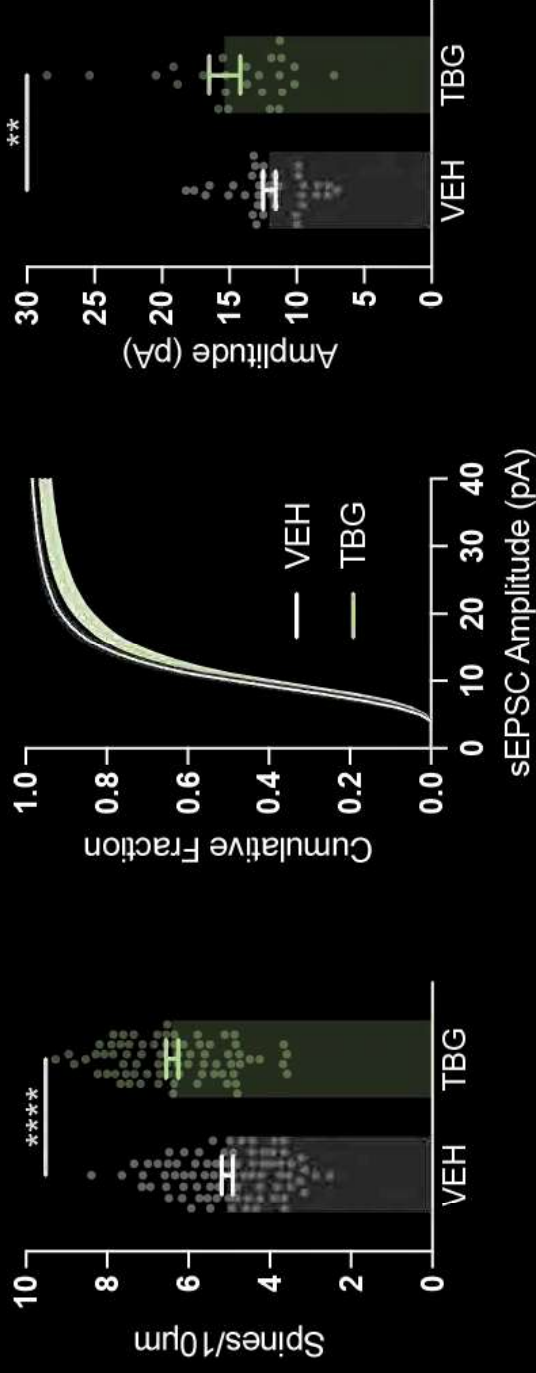


# *Tabernanthalog (TBG) is Psychoplastogenic*

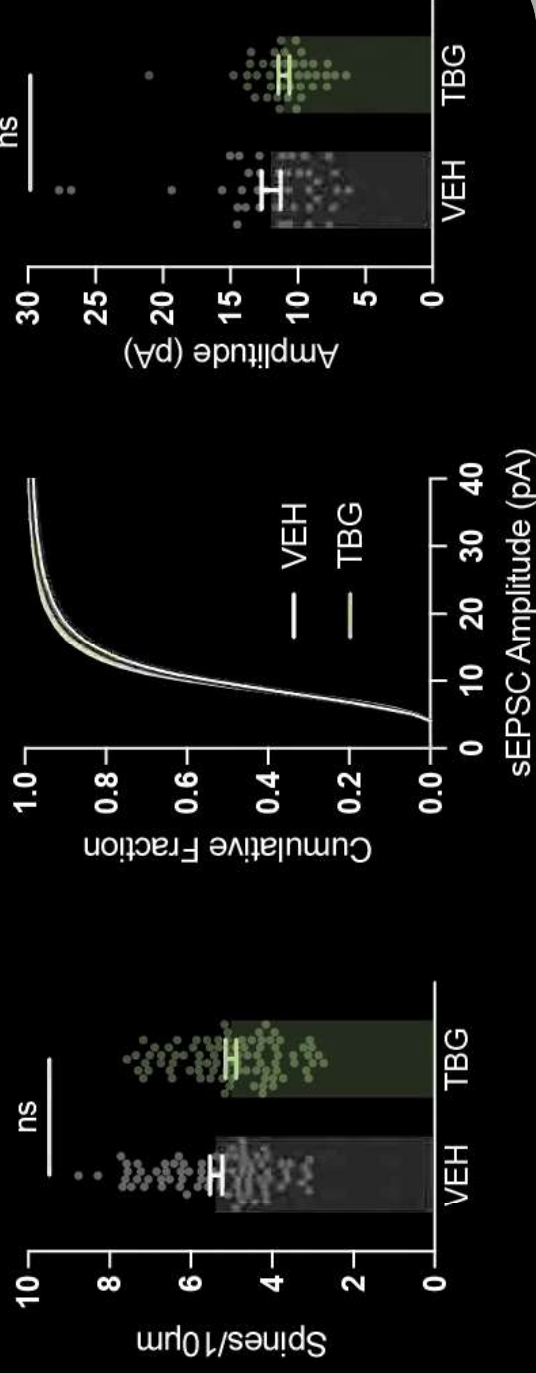


# TBP Promotes Plasticity Through 5-HT<sub>2</sub>ARs

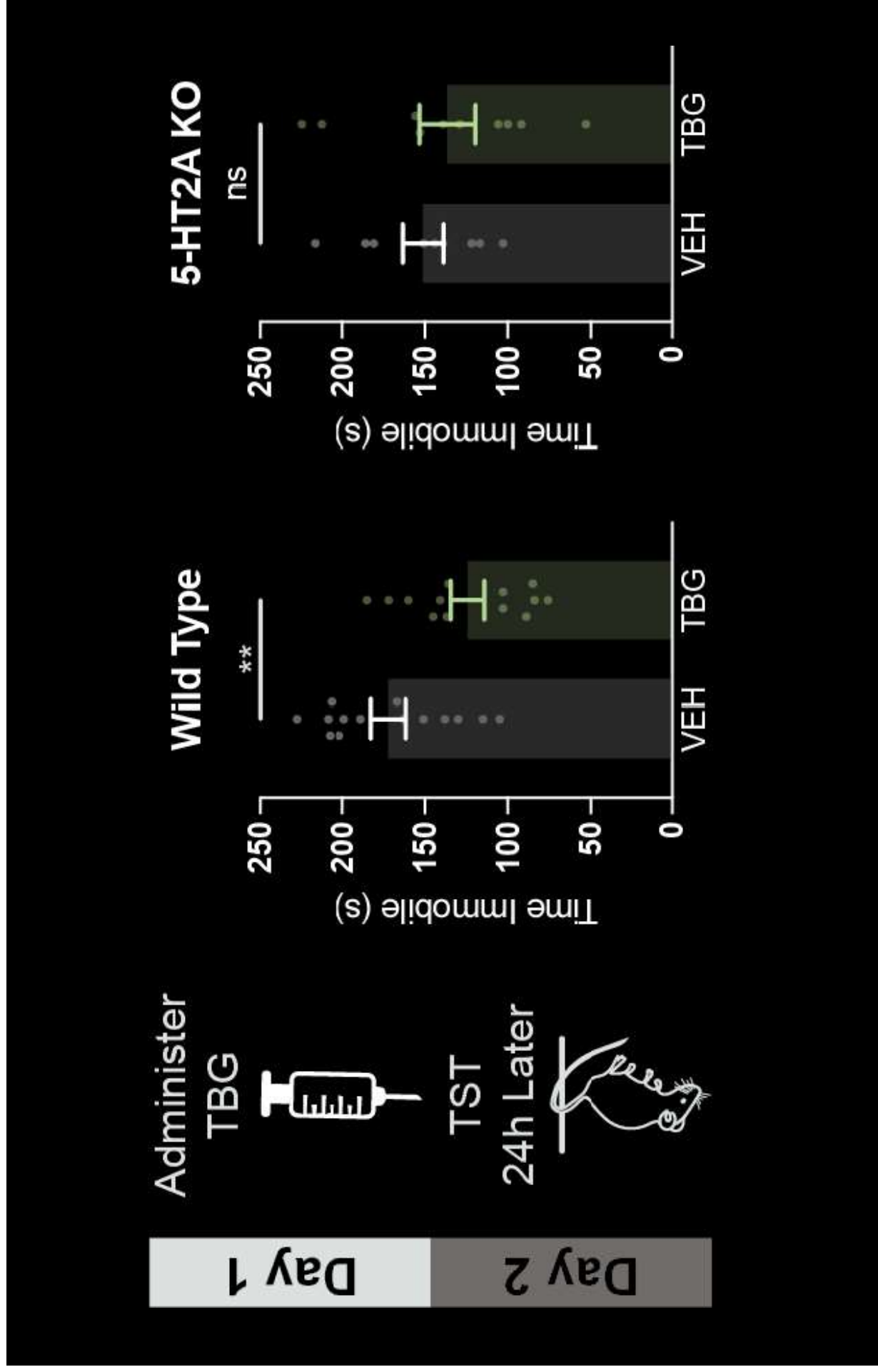
Wild  
Type



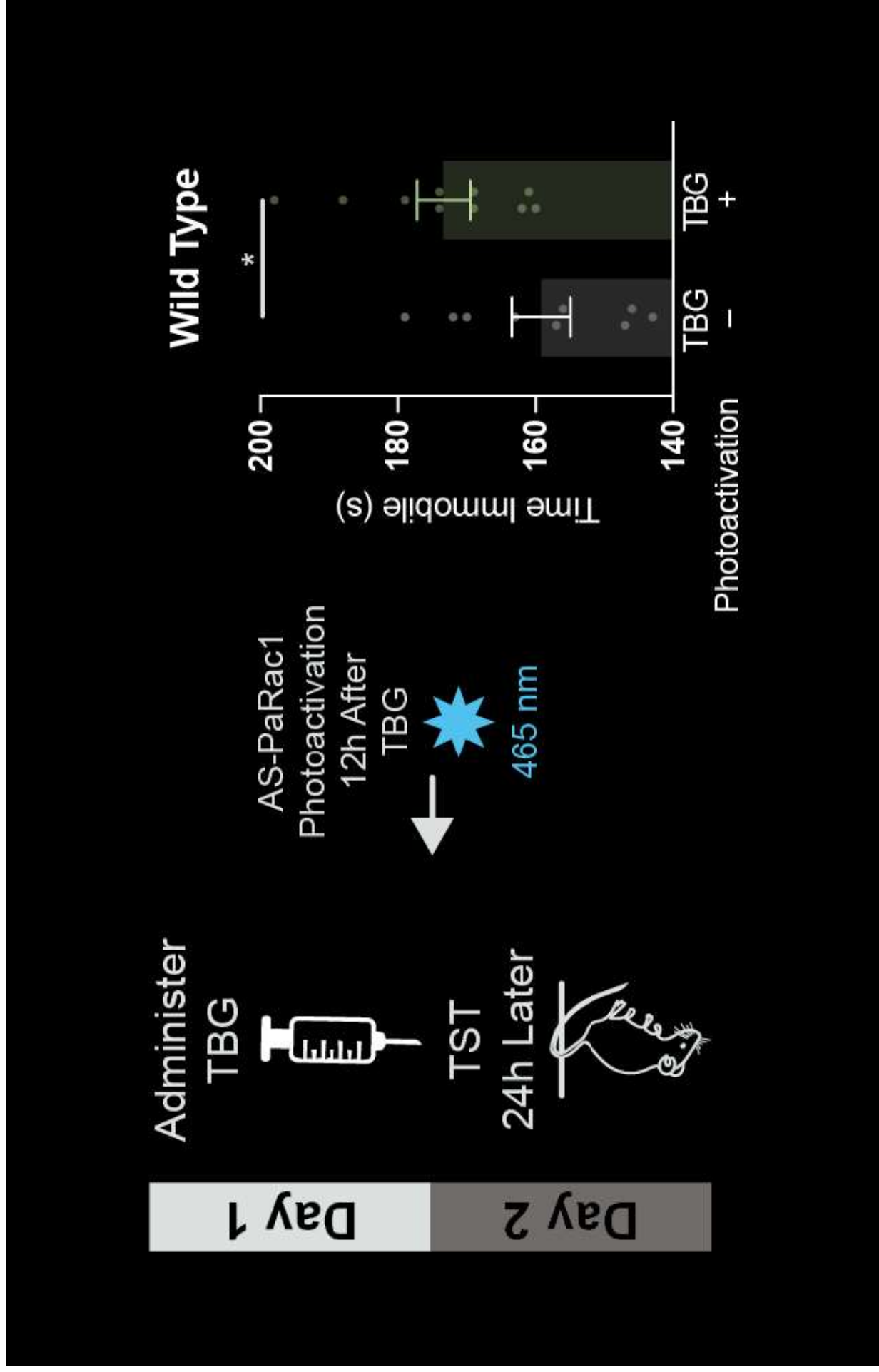
5-HT<sub>2</sub>A  
KO



# 5-HT2ARs are Required for Therapeutic Effects

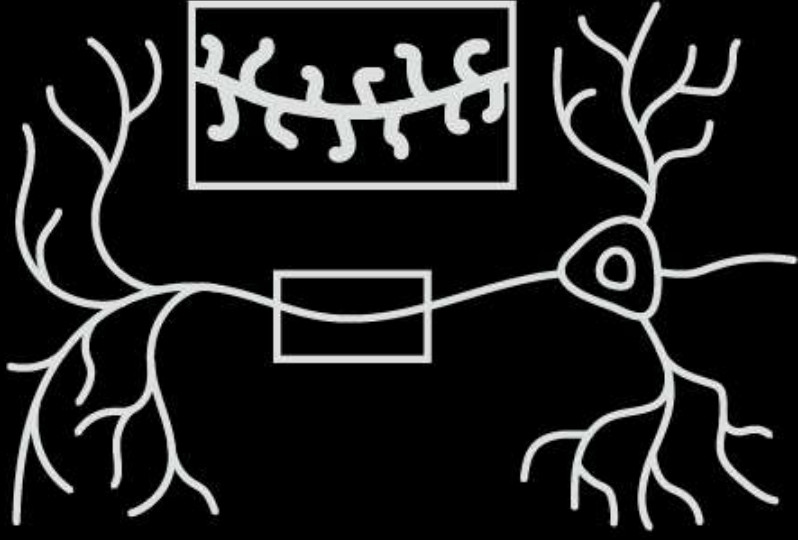


# Spinogenesis is Required for *Therapeutic Effects*

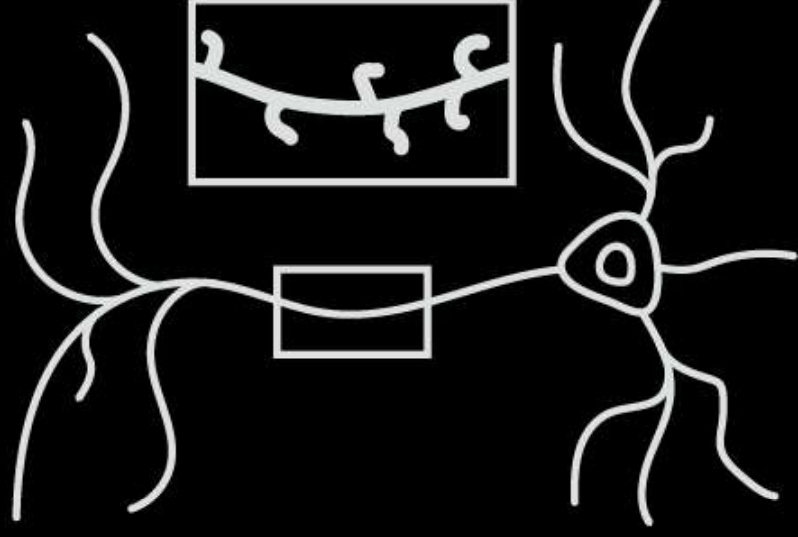


# ***Psychoplastogens Heal Damaged Neurocircuitry***

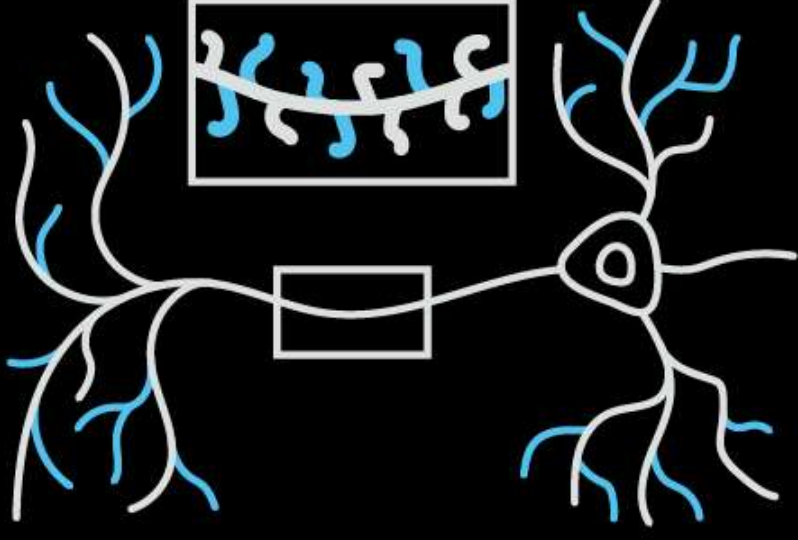
**Healthy Brain**



**Brain Disorder**



**Psychoplastogen**



# *Unanswered Questions*

*How long do the effects last for?*

*What role does polypharmacology play?*

*Can we develop translatable biomarkers?*

# Acknowledgements



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Yi Zuo  
UCSC



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*Hellman*  
Fellows Fund

**UCDAVIS**  
ALZHEIMER'S DISEASE  
CENTER



National Institutes  
of Health  
R01GM128997

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THE CAMILLE  
& HENRY DREYFUS  
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