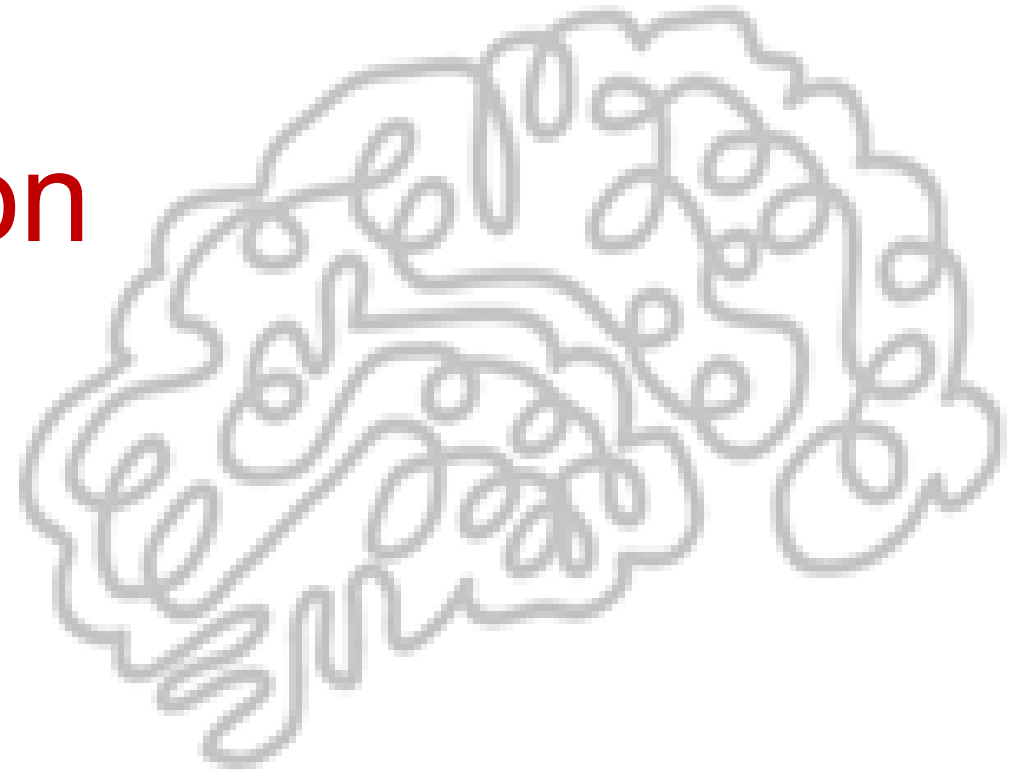
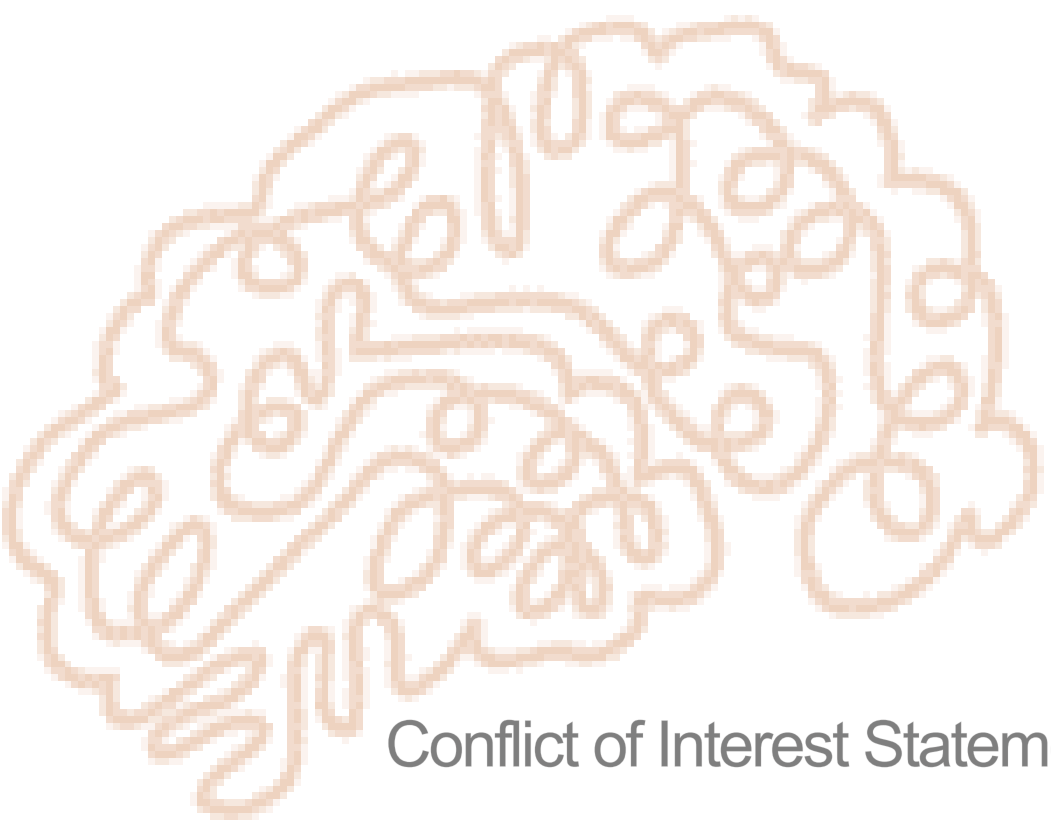


GABARs: Mechanisms of action for GABA-A modulators in depression

Jamie Maguire, PhD
Kenneth and JoAnn G. Wellner Professor
Tufts University School of Medicine



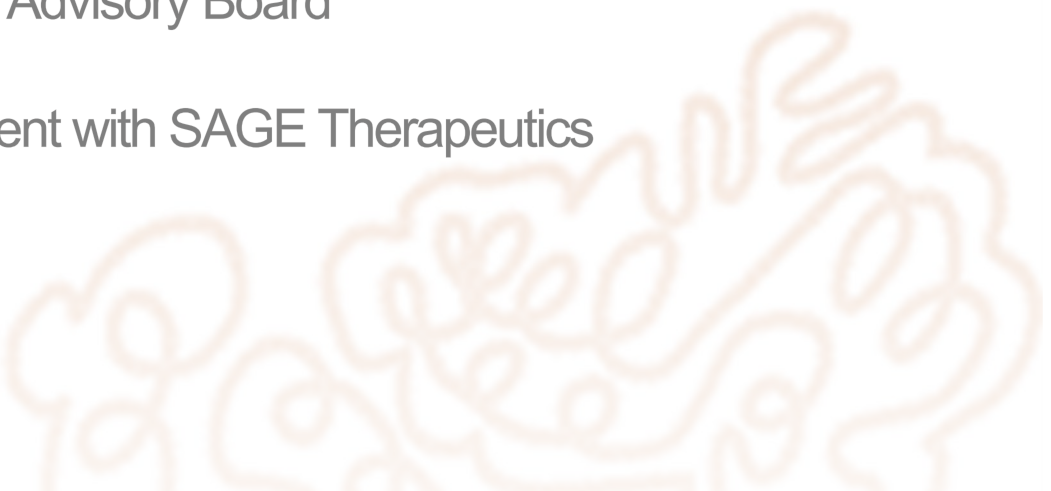
Novel Molecular Targets in Mood Disorders and Psychosis:
A Workshop



Conflict of Interest Statement

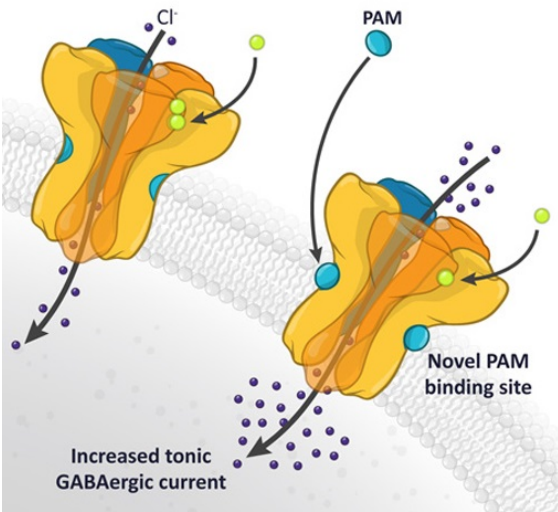
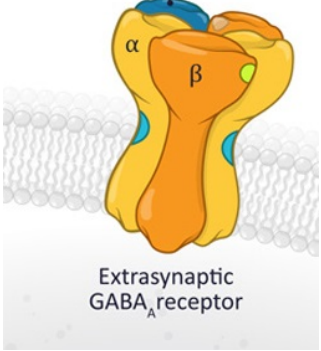
Serve on SAGE Therapeutics Scientific Advisory Board

Sponsored Research Agreement with SAGE Therapeutics

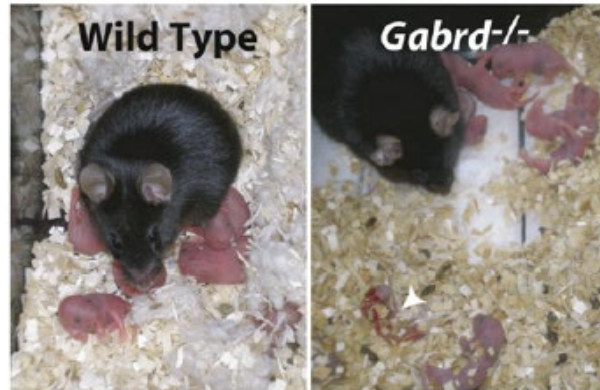


Abnormal postpartum behaviors in *Gabrd*^{-/-} mice

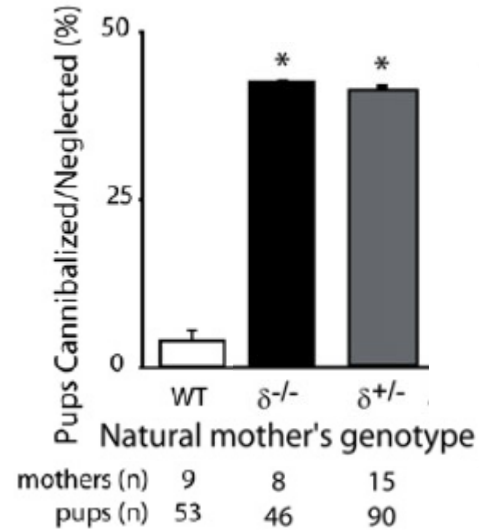
Extrasynaptic receptors contain a δ subunit



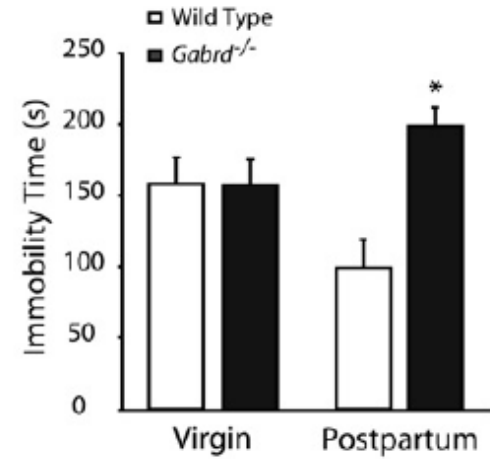
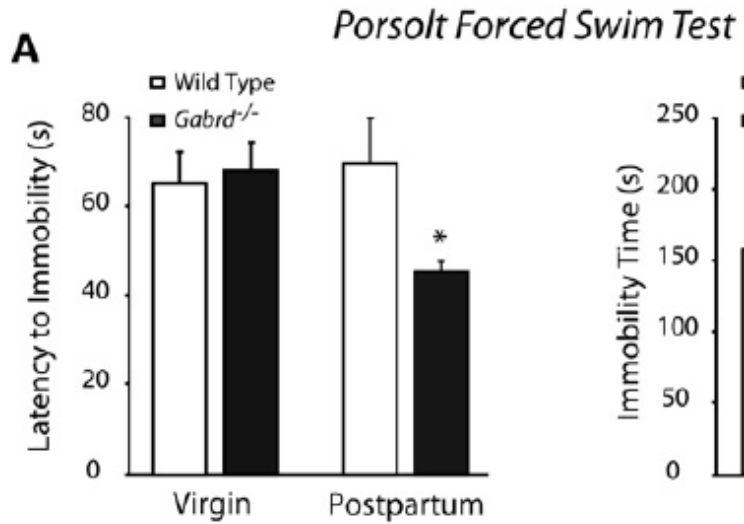
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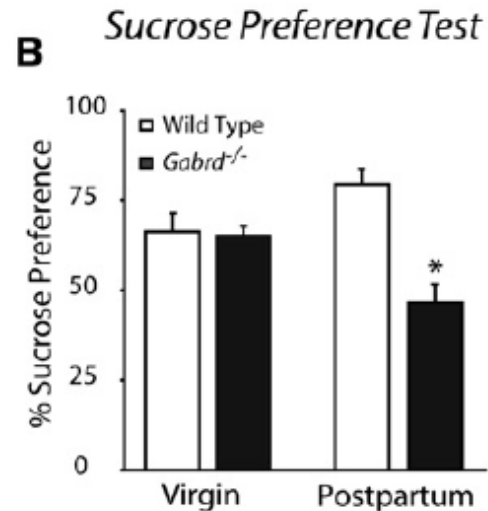
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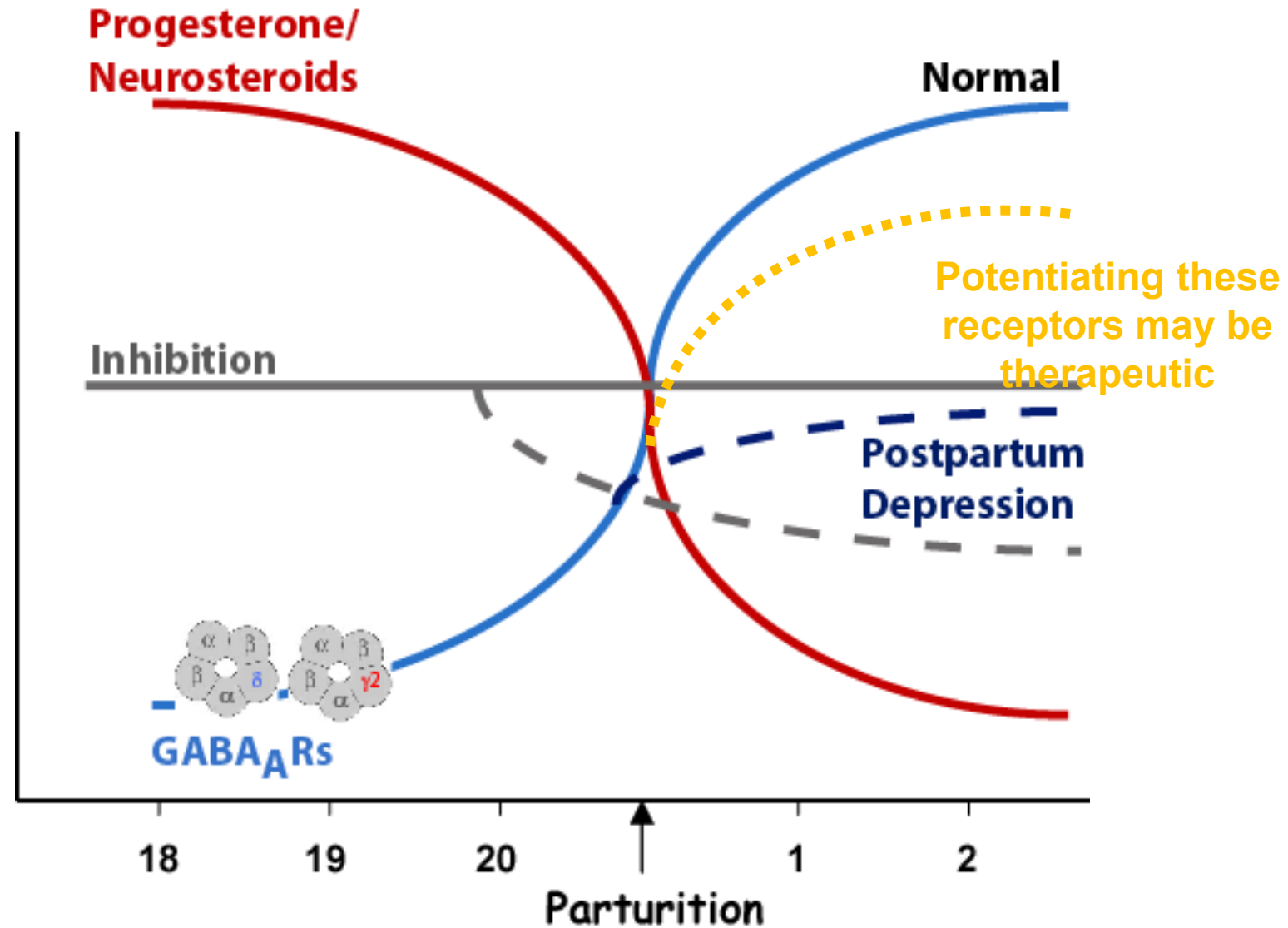
A



B



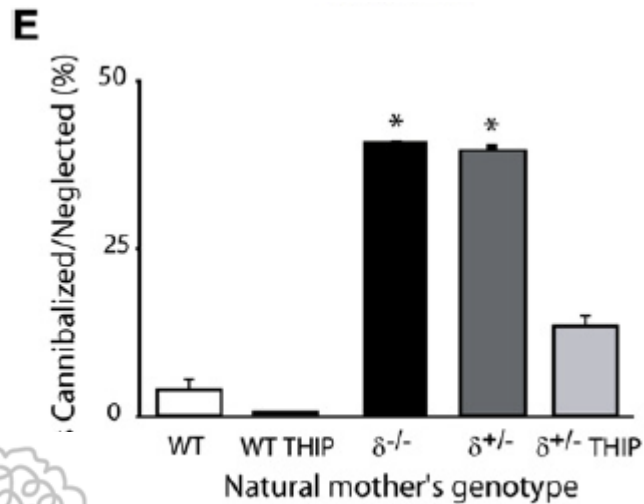
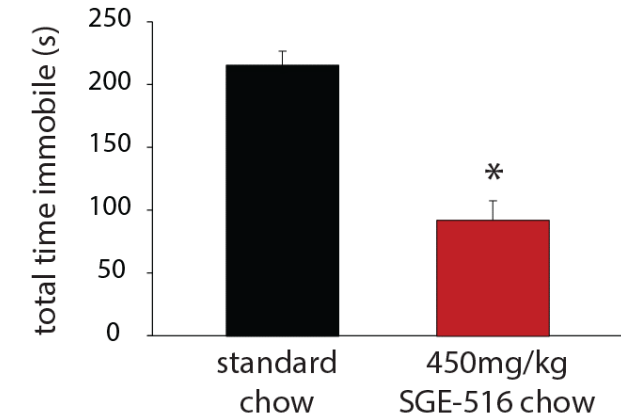
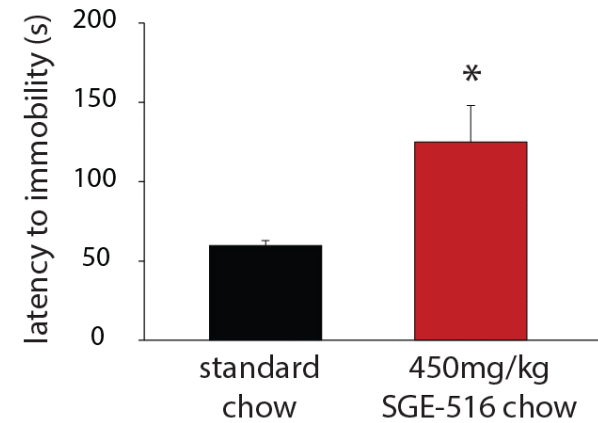
Therapeutic potential of GABA PAMs for postpartum depression



Therapeutic effects of GABA PAMs in preclinical PPD models

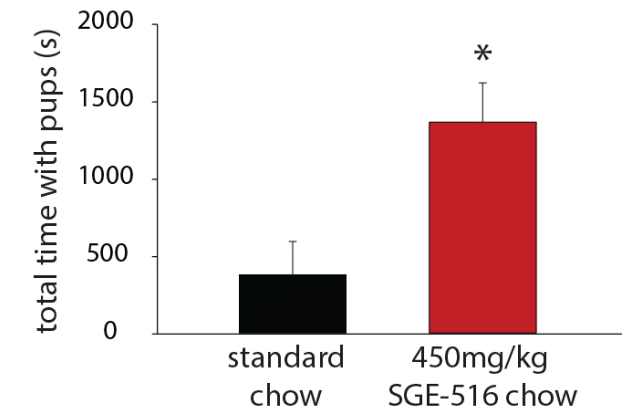
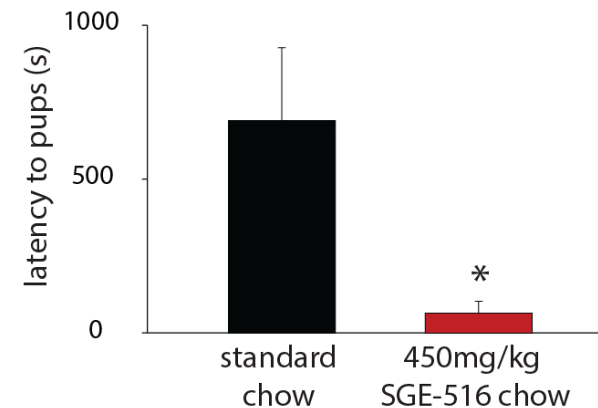
SGE-516 improves behavioral outcomes in preclinical PPD model(s)

$Gabrd^{-/-}$ mice



SGE-516 improves maternal behaviors in preclinical PPD model(s)

$Gabrd^{-/-}$ mice



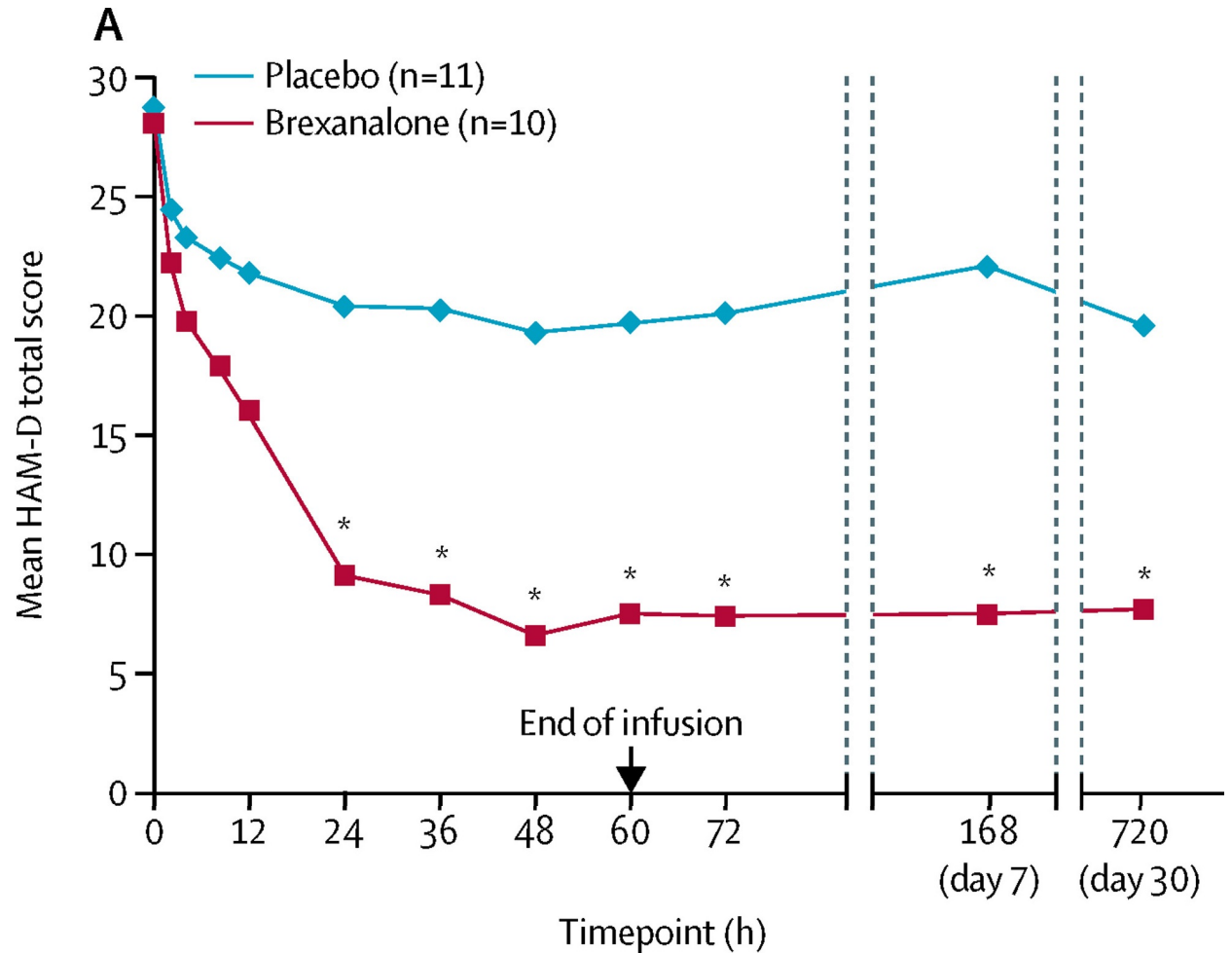
Maguire and Mody, 2008

Melón, 2018

Prolonged antidepressant effects of Brexanolone

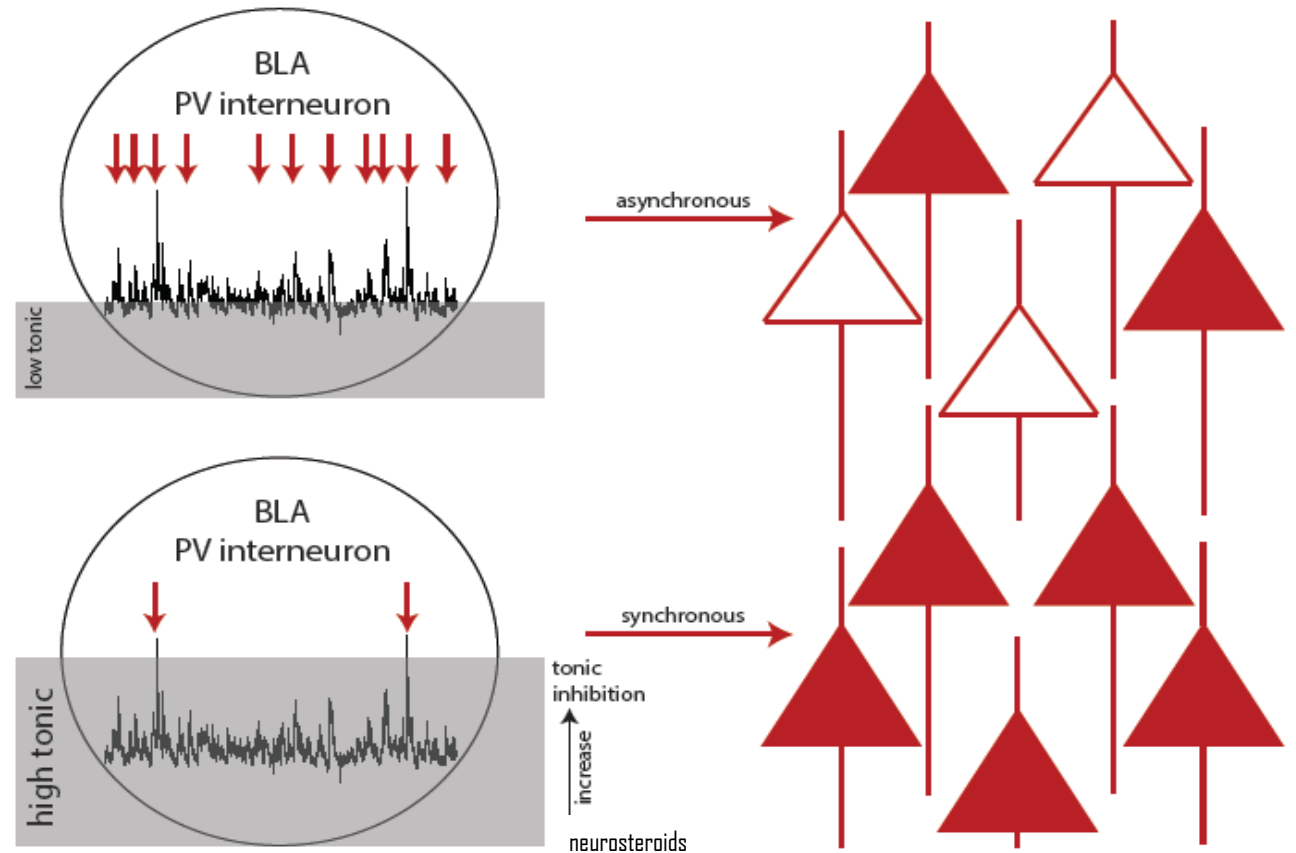
Brexanolone, ZULRESSO®:
a synthetic allopregnanolone
analog and an allosteric
modulator of GABAA
receptors

Kanes, 2017; Meltzer-Brody, 2018



Proposed role of tonic inhibition in oscillations

Tonic inhibition:
high pass filter, increases
network synchrony,
modulates neuronal gain,
and enhances the fidelity
of information processing.

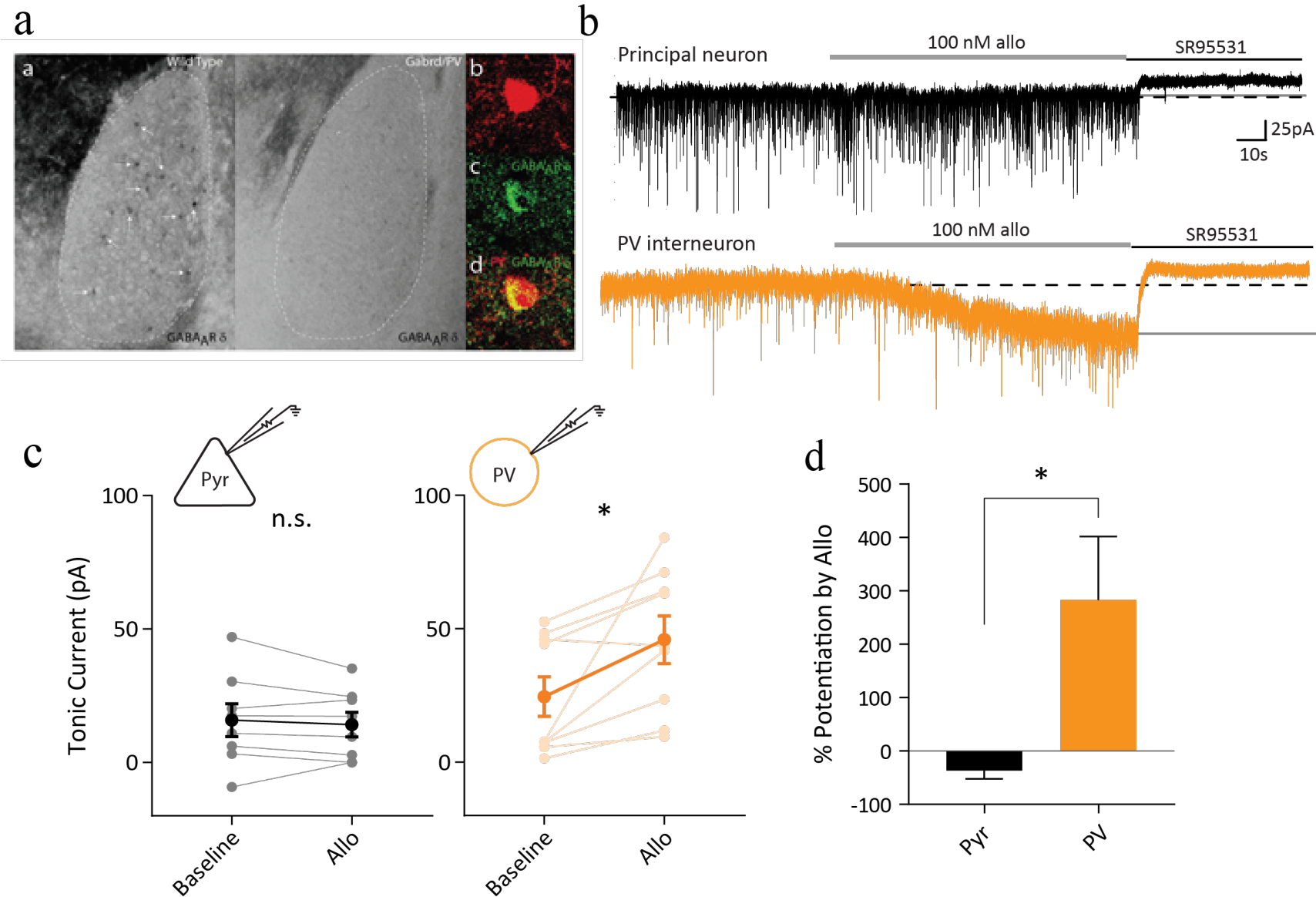


Tonic GABA_A conductance bidirectionally controls interneuron firing pattern and synchronization in the CA3 hippocampal network

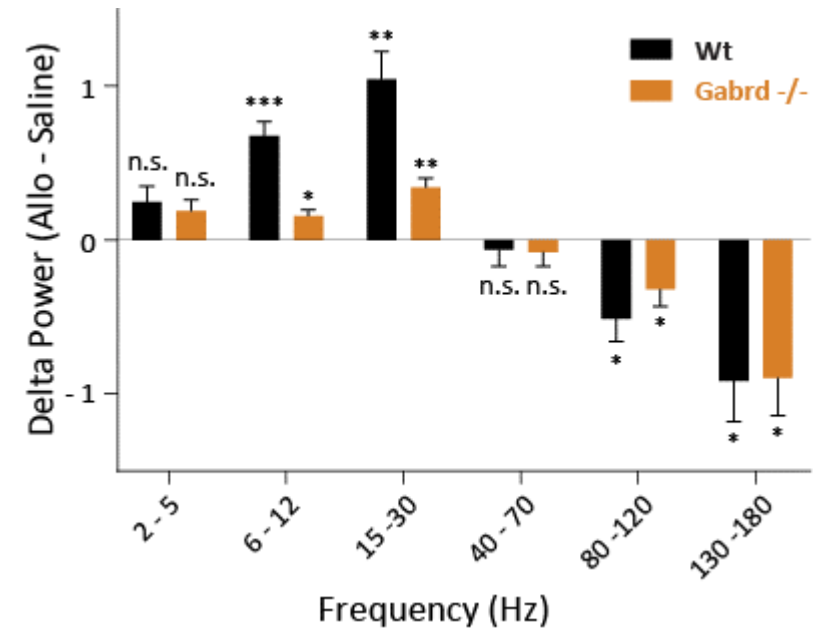
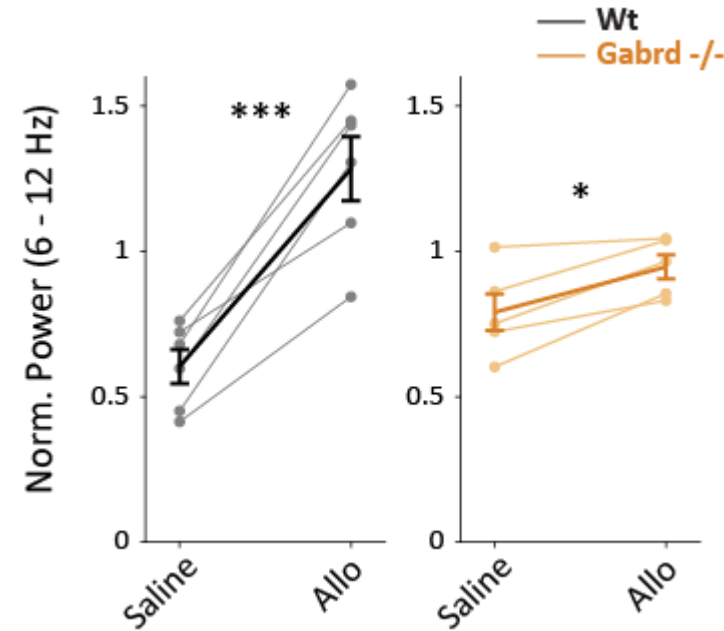
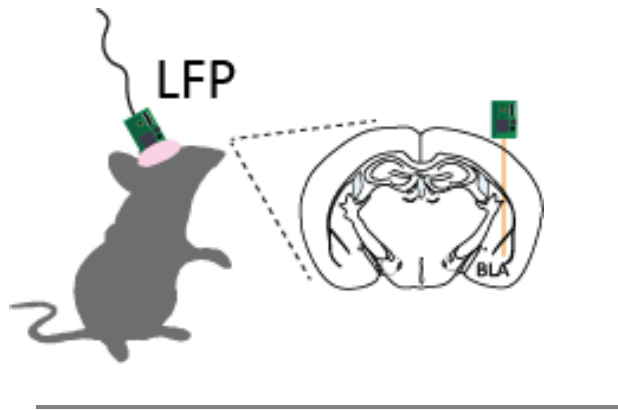
Ivan Pavlov^{a,1,2}, Leonid P. Savtchenko^{a,b,1}, Inseon Song^{b,1}, Jaeyeon Koo^b, Alexey Pimashkin^c, Dmitri A. Rusakov^{a,2}, and Alexey Semyanov^{b,c,2}



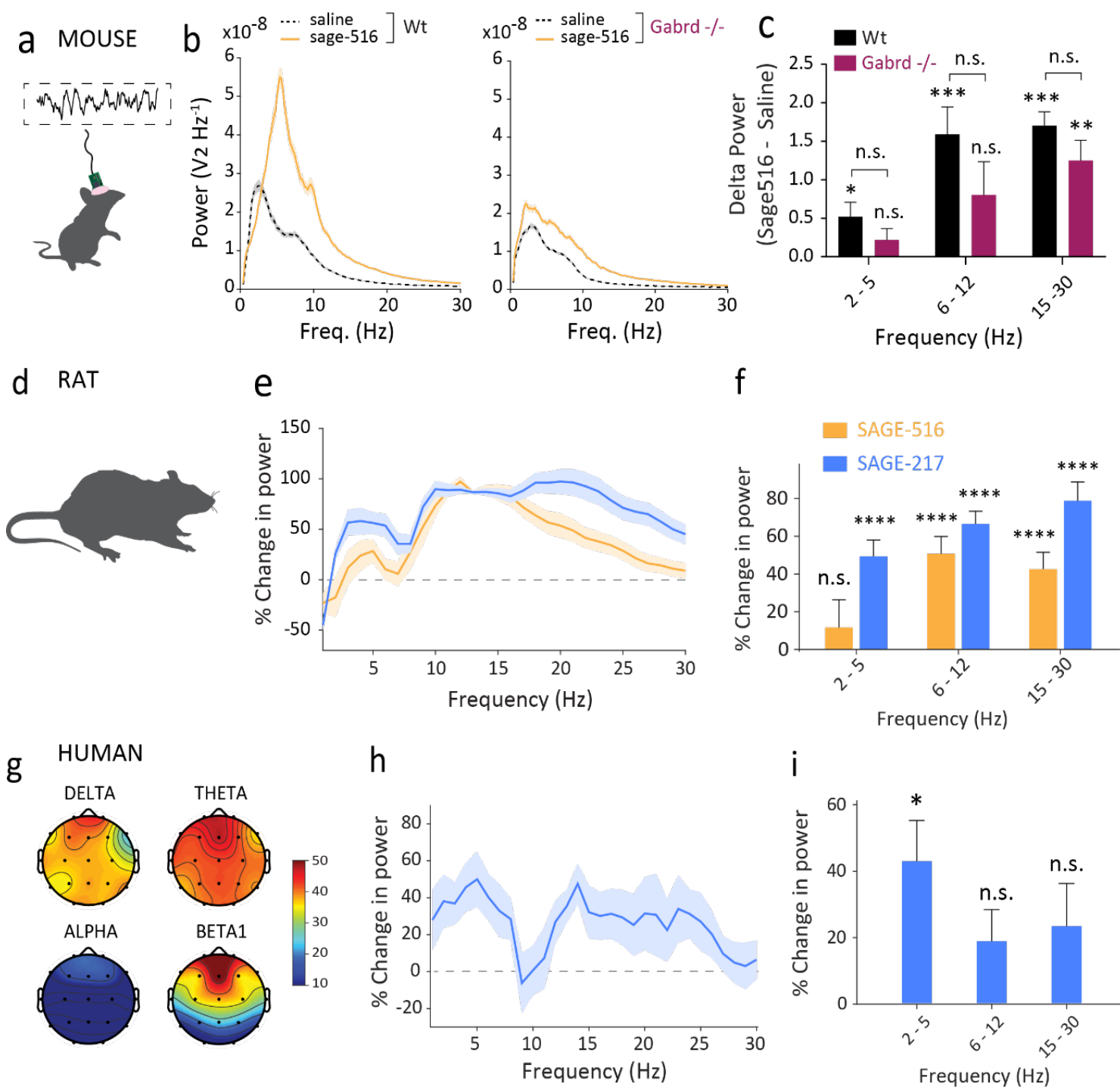
δ GABA_ARs are uniquely expressed on PV interneurons in the BLA, which are critical for orchestrating oscillatory states



Allopregnanolone alters network activity in part through GABA_A δ subunit-containing receptors



Allopregnanolone has the ability to alter network activity across species

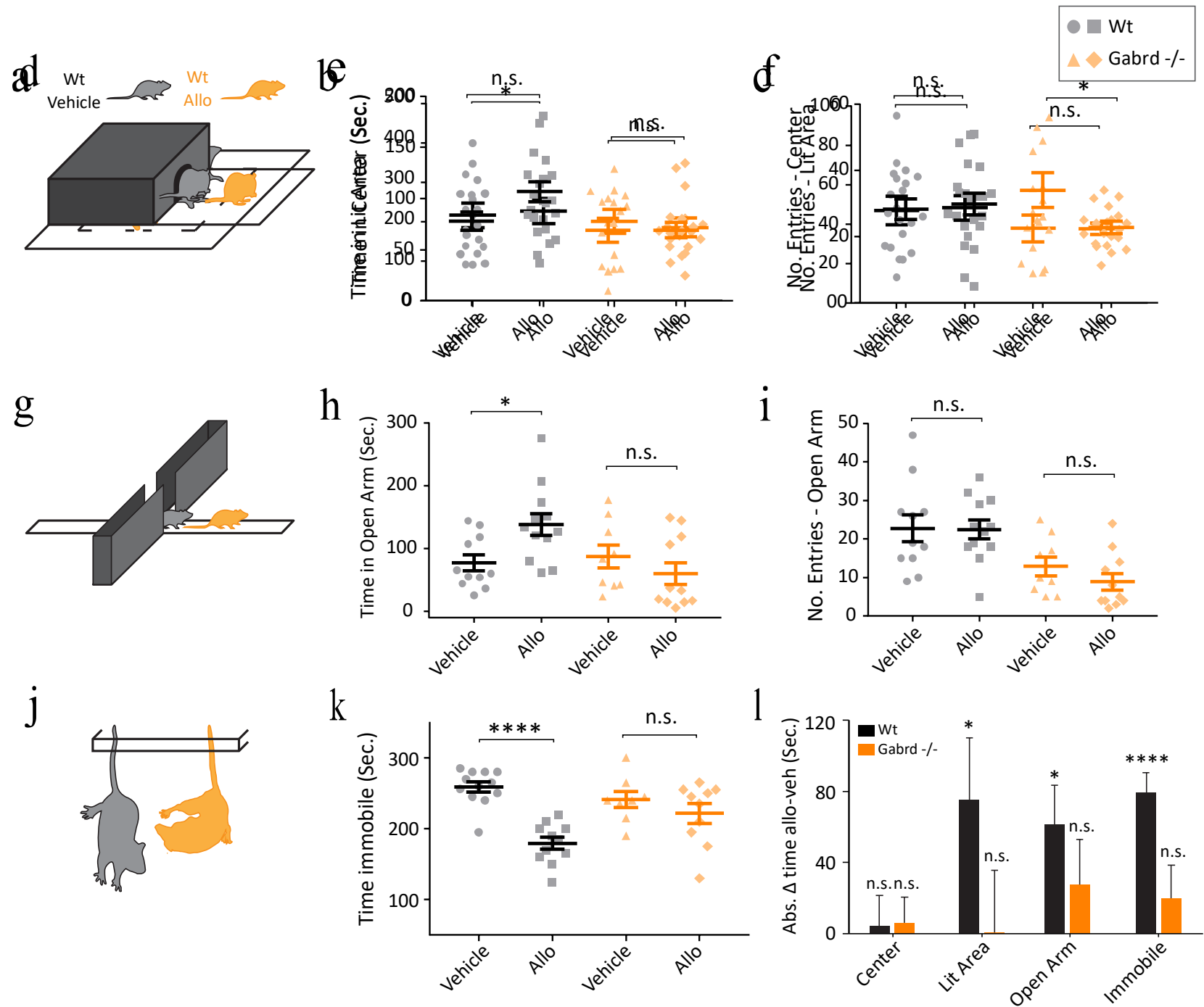


in submission at *Biological Psychiatry*

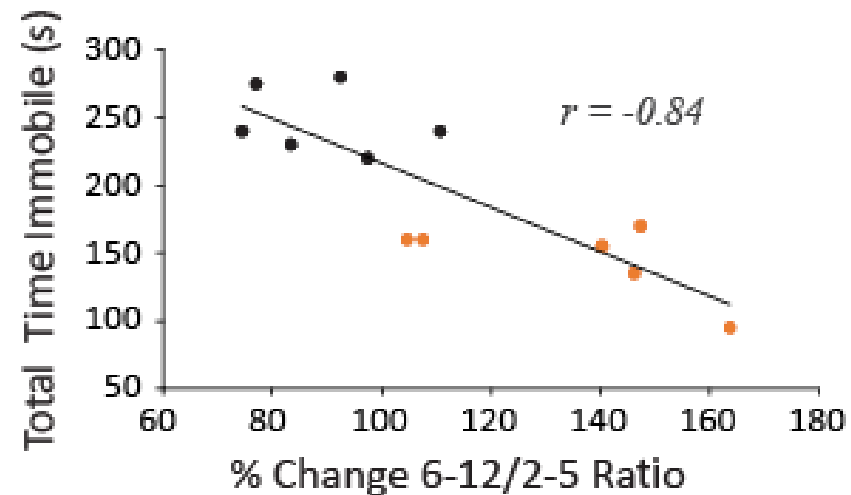
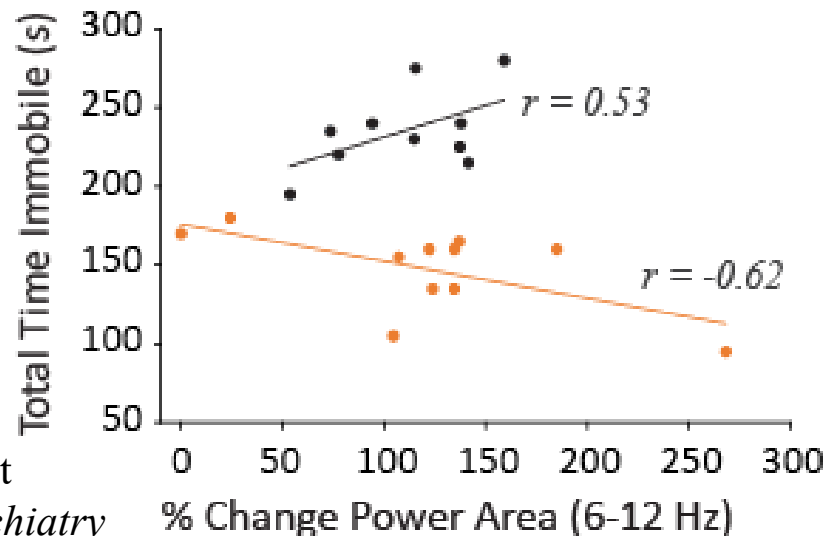
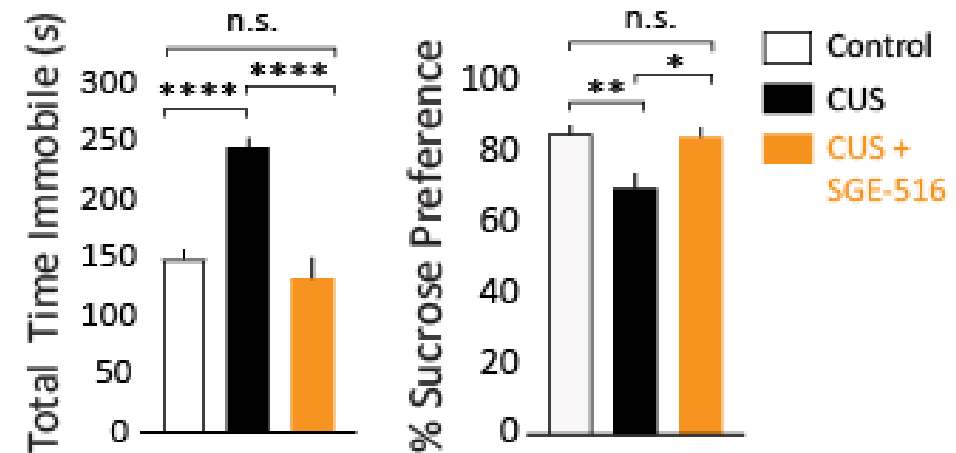
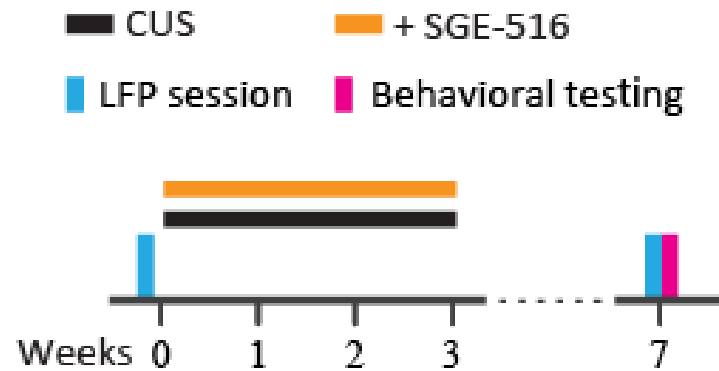
Allopregnanolone infusion into the BLA exerts anxiolytic and antidepressant effects



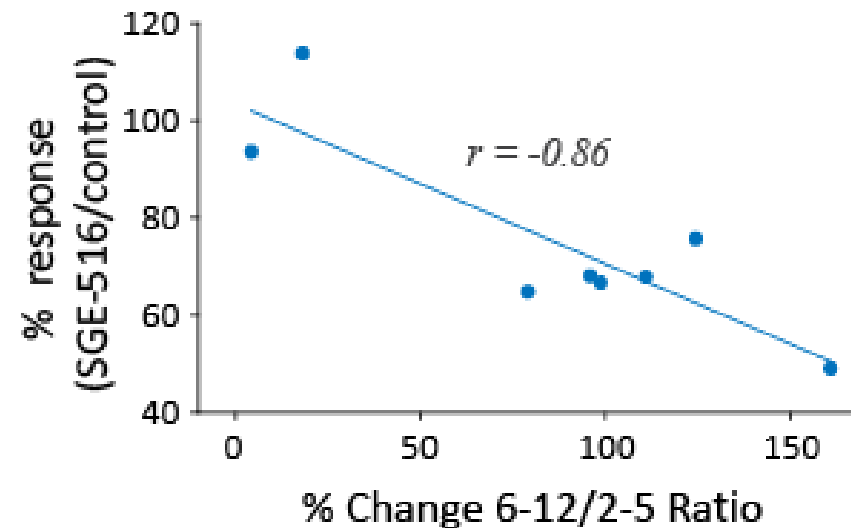
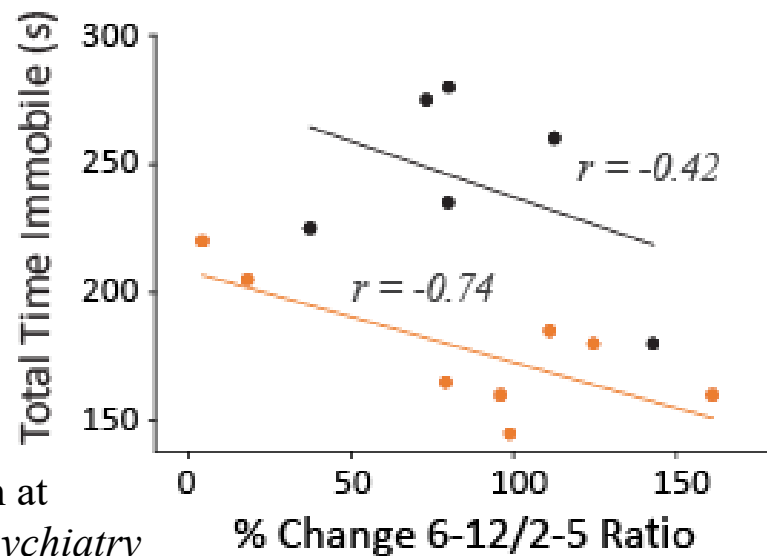
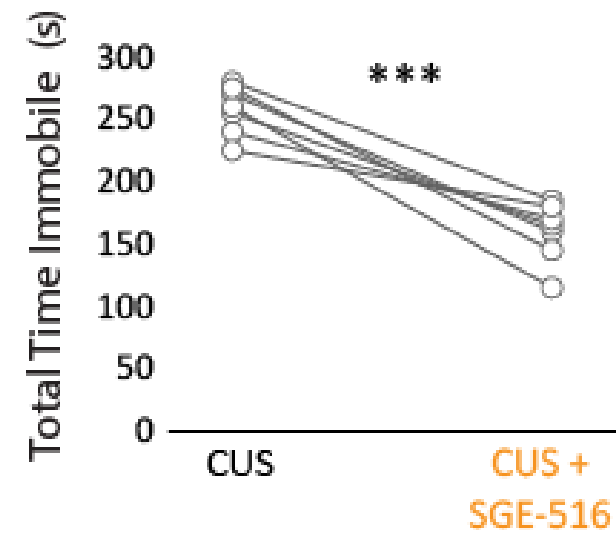
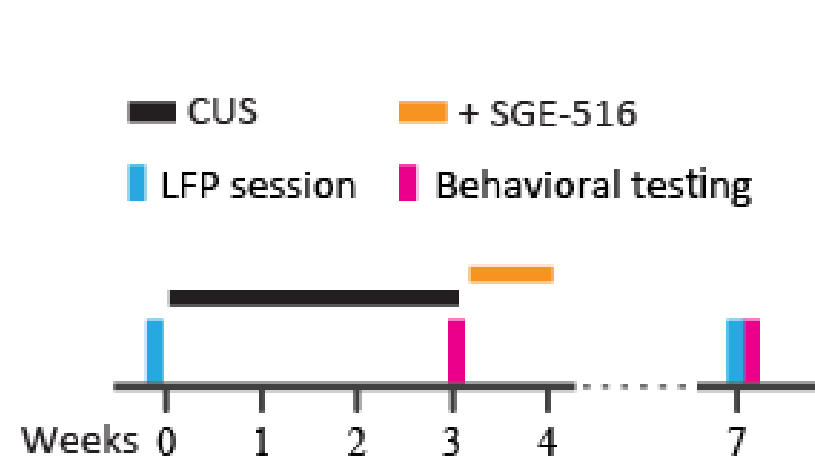
in submission at *Biological Psychiatry*



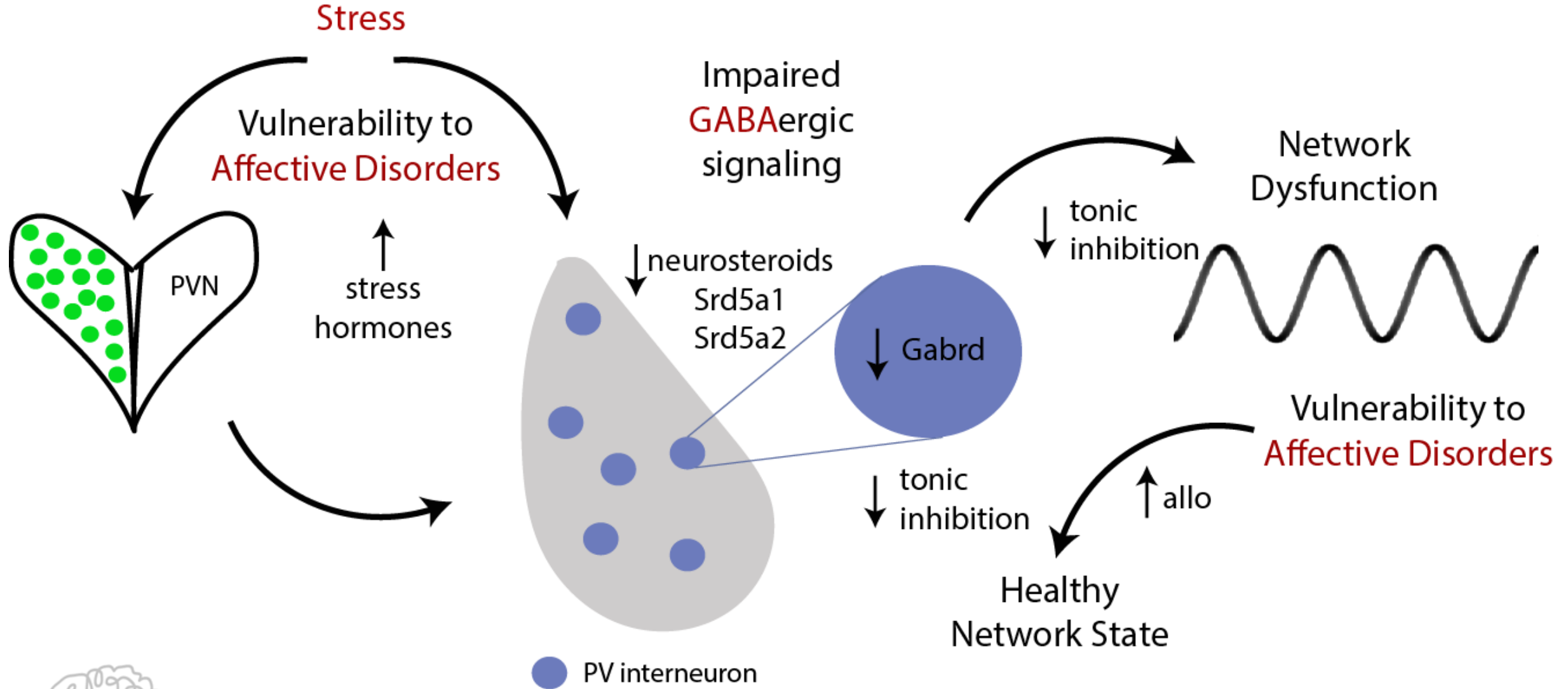
SGE-516 is capable of preventing the chronic stress-induced deficits in network and behavioral states



SGE-516 is capable of restoring the chronic stress-induced deficits in network and behavioral states



Working Model



“There are multiple ways to perturb the network in the same way”

– Eve Marder



Summary



Mice lacking δ subunit-containing GABA_ARs exhibit abnormal postpartum behaviors



Demonstrated therapeutic potential of PAMs of GABA_AR for postpartum depression in preclinical models



Allopregnanolone is capable of modulating BLA network states in part through δ subunit-containing GABA_ARs, which are uniquely expressed on PV interneurons in the BLA



Allopregnanolone exerts unique effects on BLA network activity compared to other GABA agonists, such as diazepam.



SGE-516 exerts prolonged effects on chronic stress-induced impairments in network and behavioral states.



NINDS: R01NS105628
NINDS: R01NS102937
NIAAA: R01AA026256
SRA SAGE Therapeutics



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