A fluorescence micrograph of a neuron, likely a pyramidal neuron, showing its cell body (soma) and extensive dendritic tree. The neuron is stained with multiple fluorescent dyes, appearing in shades of cyan, magenta, and blue against a black background. The dendrites are densely covered with small, protruding structures called dendritic spines, which are characteristic of the brain's cortex and hippocampus. The overall appearance is that of a complex, branching network of neural processes.

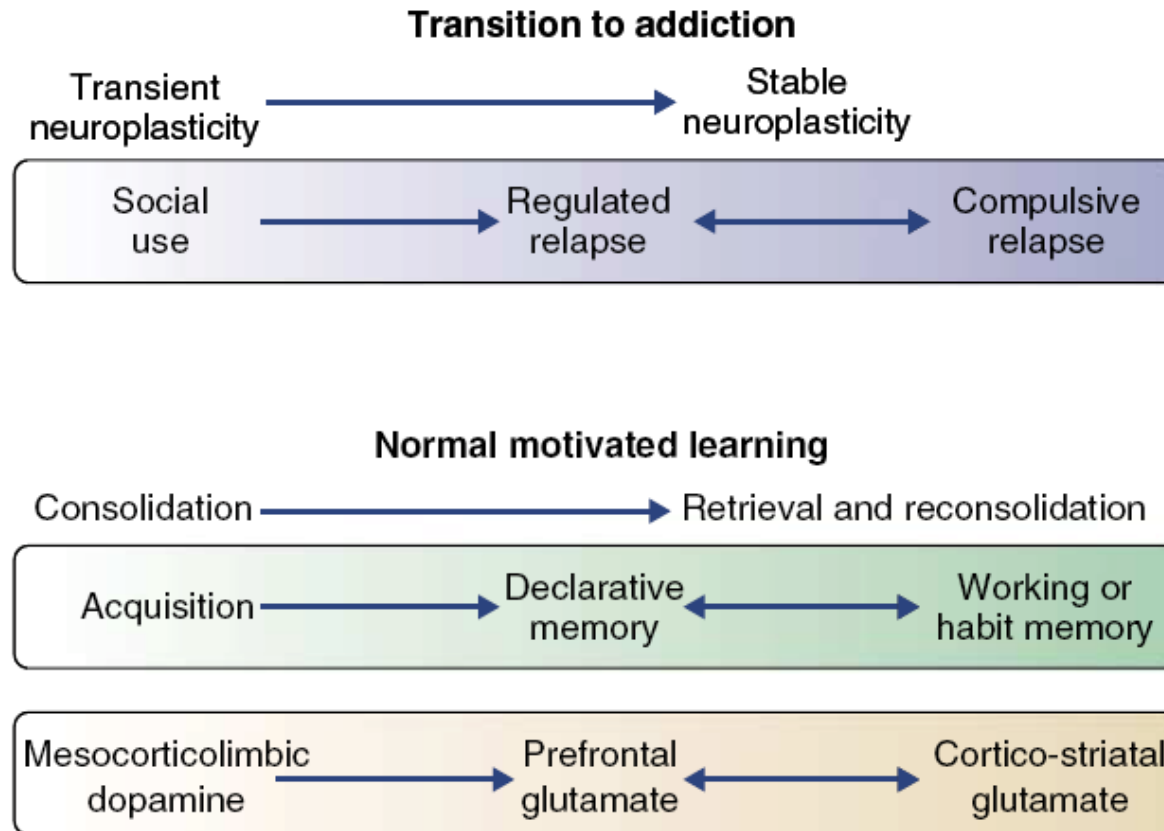
The Thorny Side of Addiction: Adaptive Plasticity and Dendritic Spines

Judson Chandler

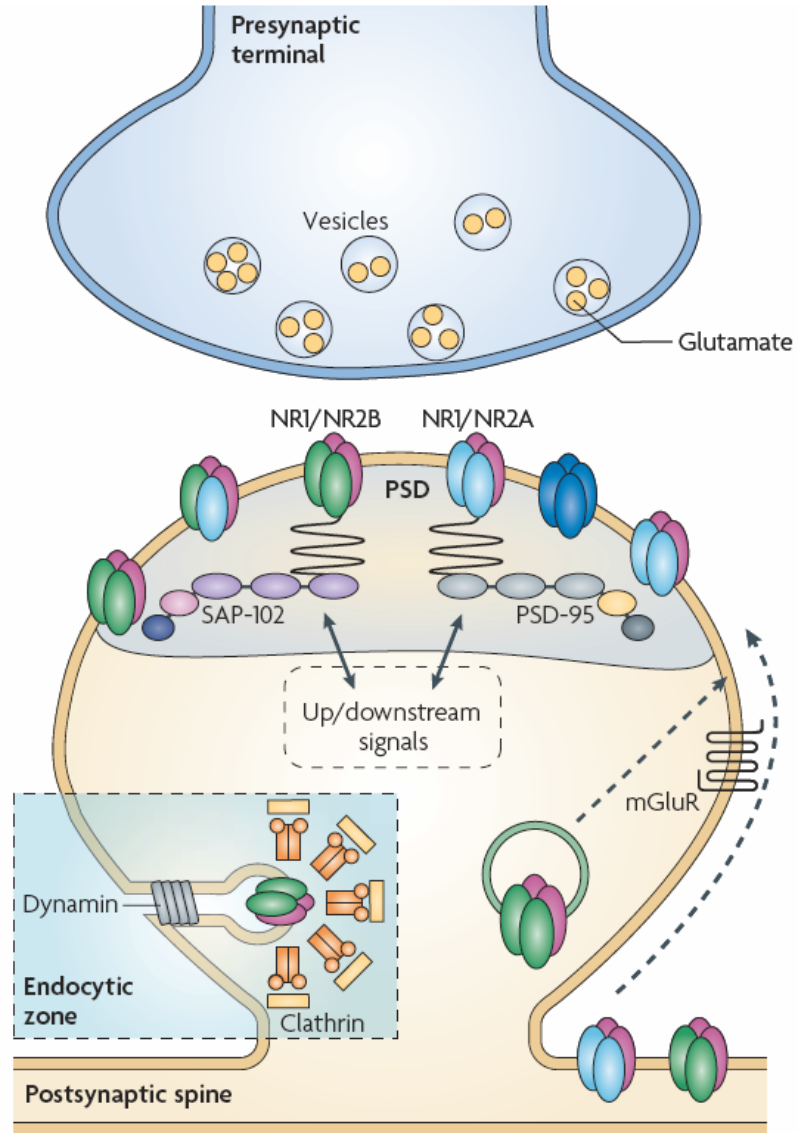
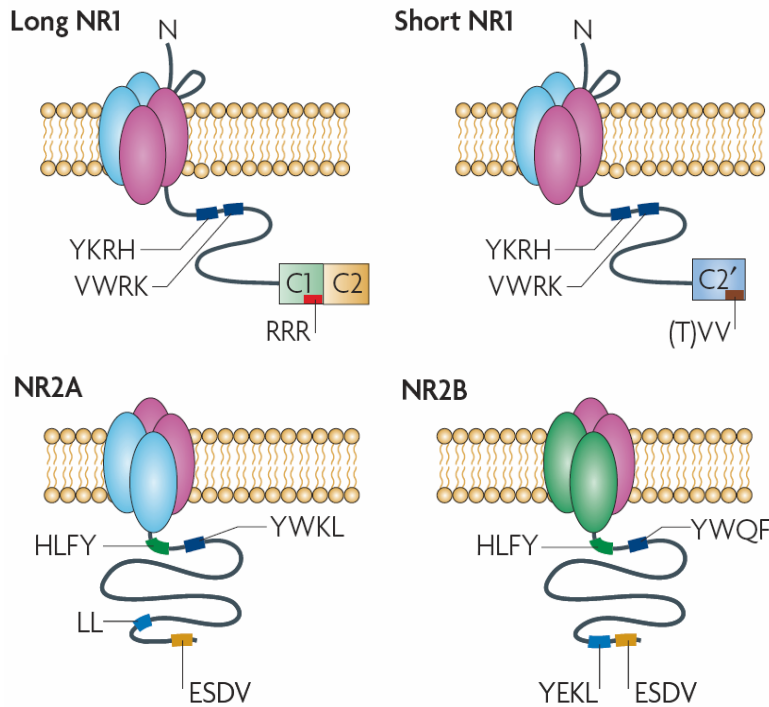
Department of Neurosciences
Medical University of South Carolina

Drug Addiction as a Pathology of Staged Neuroplasticity

Peter W Kalivas and Charles O'Brien



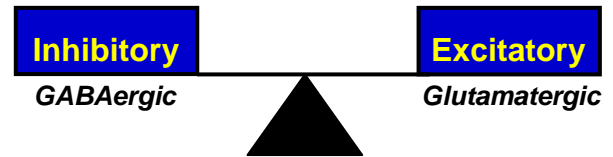
NMDA Receptors: Subunits and membrane trafficking



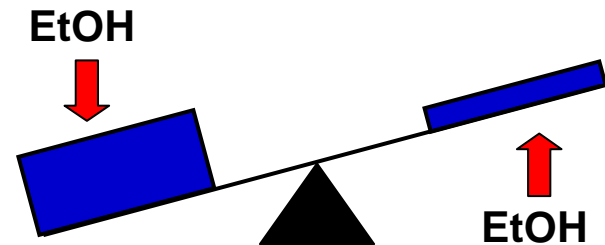
Nature Reviews Neuroscience **8**, 413–426 (2007)
 C. Geoffrey Lau and R. Suzanne Zukin

Alcohol Tolerance and Homeostatic Plasticity

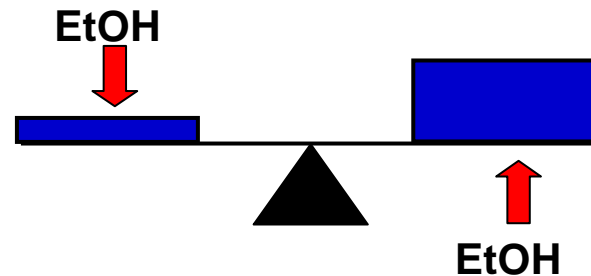
Normal balance



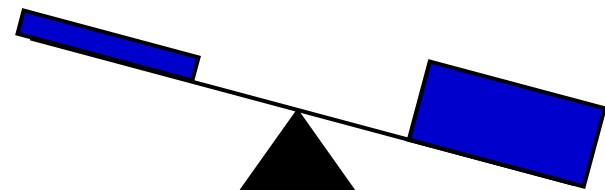
Acute ethanol
(Instability of neuronal circuits)



Prolonged ethanol
(Homeostatic plasticity restores stability to neuronal circuits; underlies tolerance development)



Ethanol withdrawal
(Hyper-excitability; promotes aberrant plasticity)



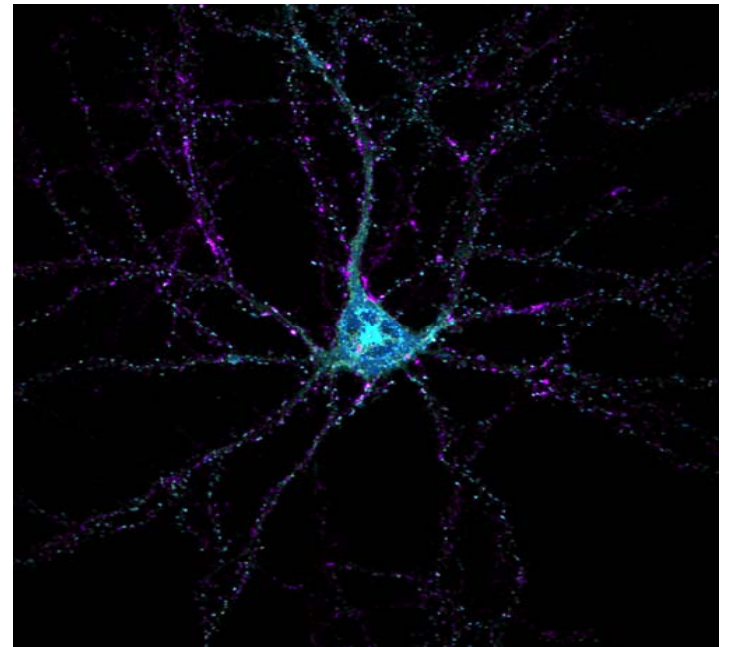
In Vitro Model of Chronic Alcohol Exposure

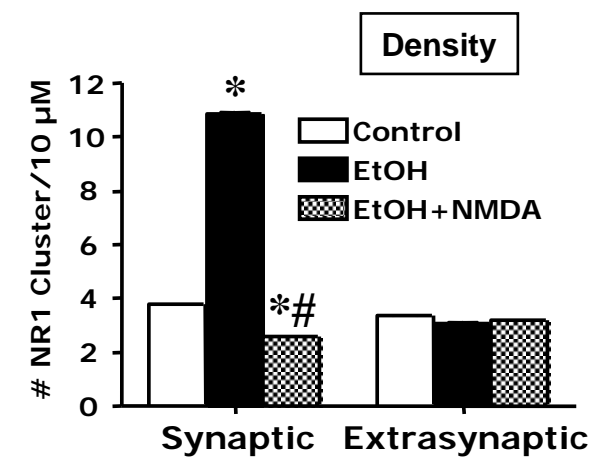
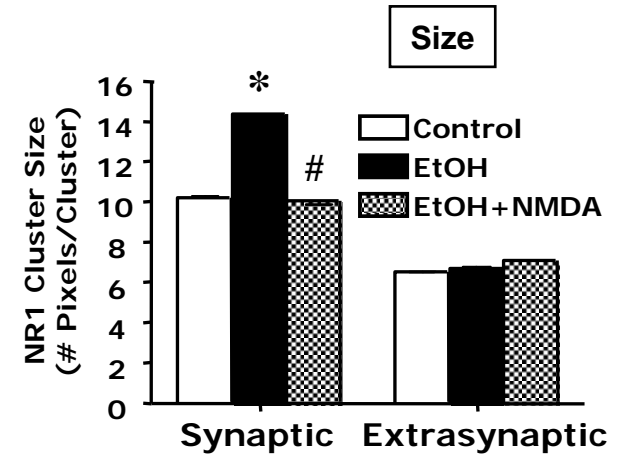
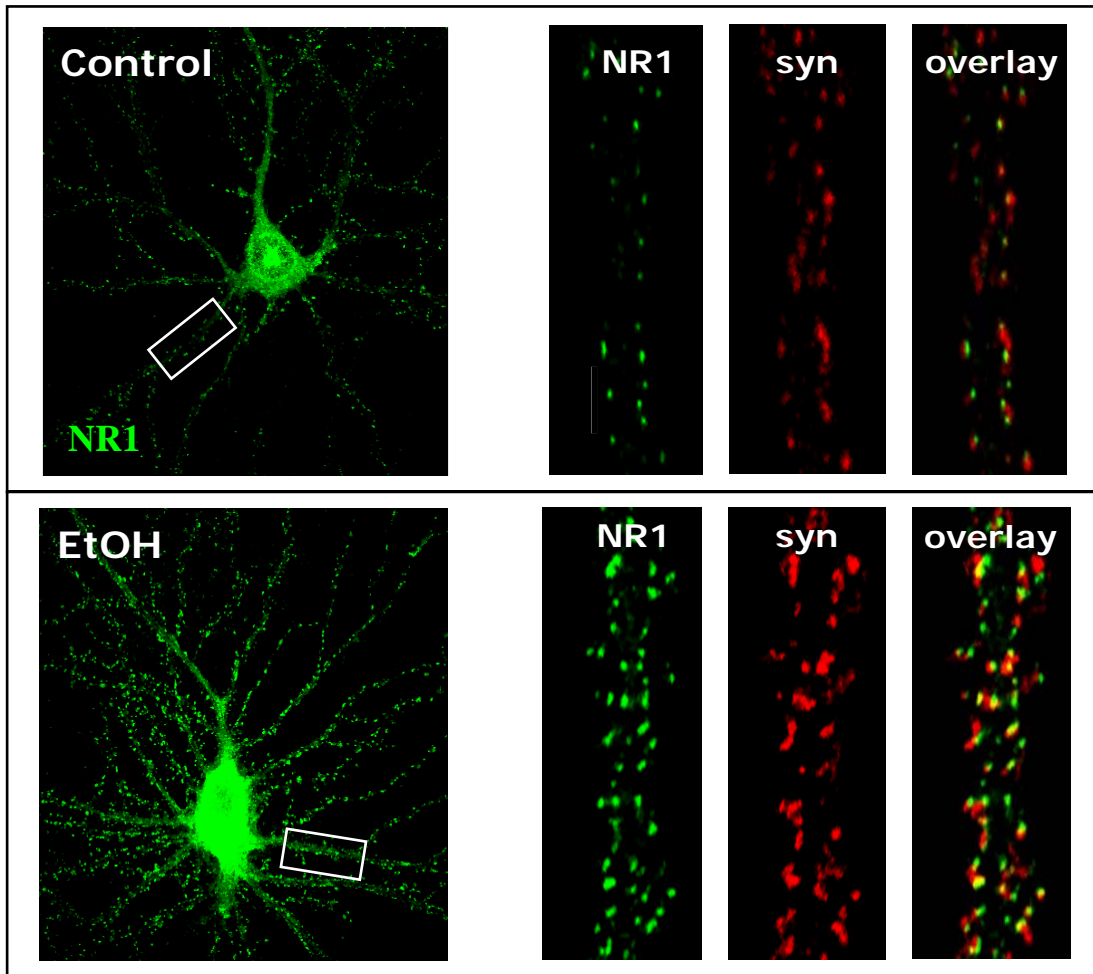
Primary rat hippocampal neurons

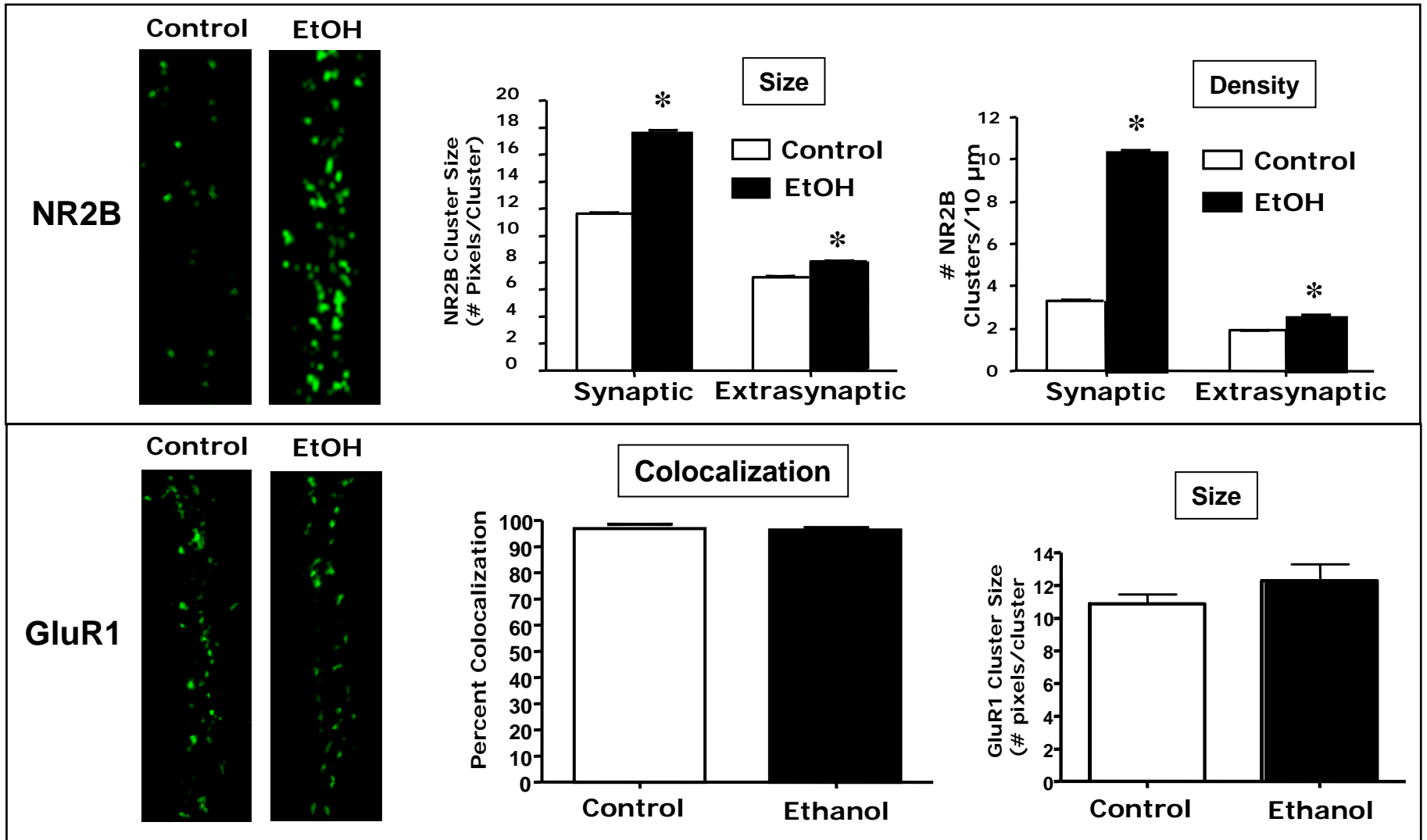
Used for experimentation when fully mature (2-3 weeks *in vitro*)

Chronic ethanol exposure in sealed vapor chambers

Evaluated by IHC/confocal imaging & electrophysiology

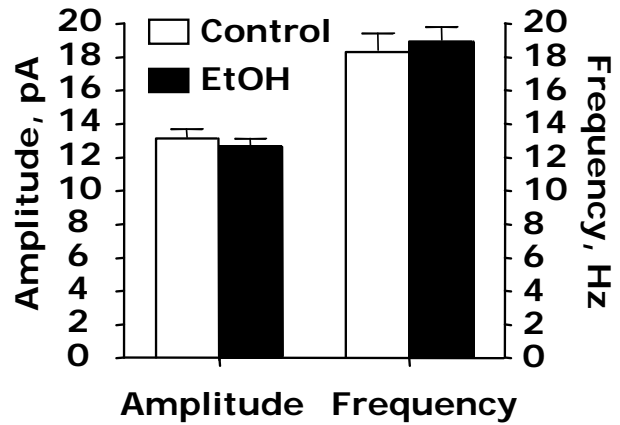




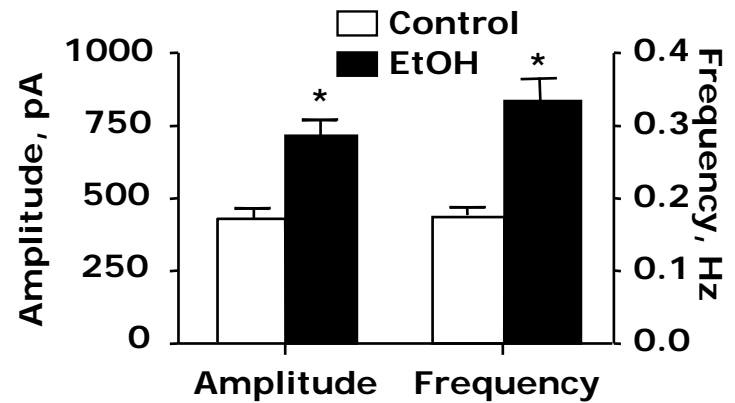




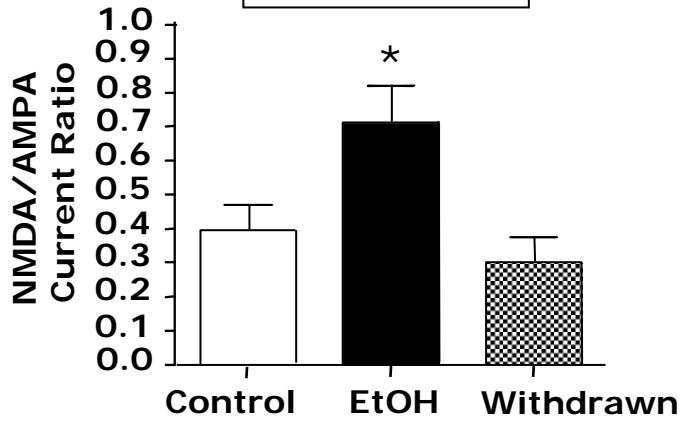
AMPA mEPSC



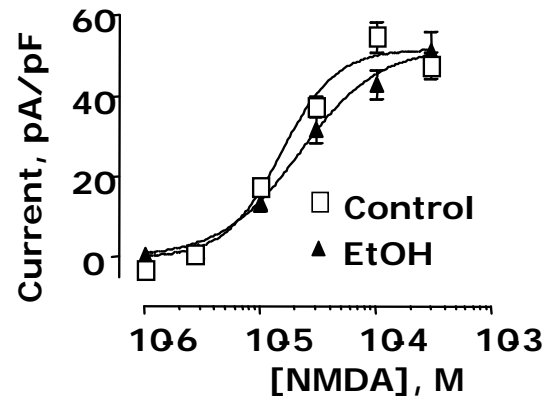
Spontaneous NMDA EPSC



NMDA mEPSC



Extrasynaptic NMDA Currents



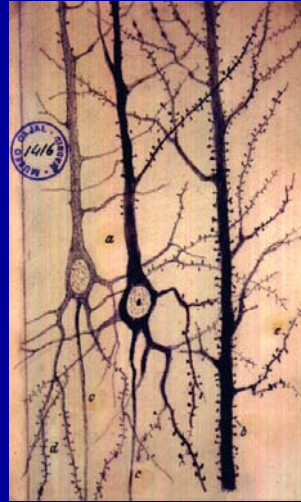
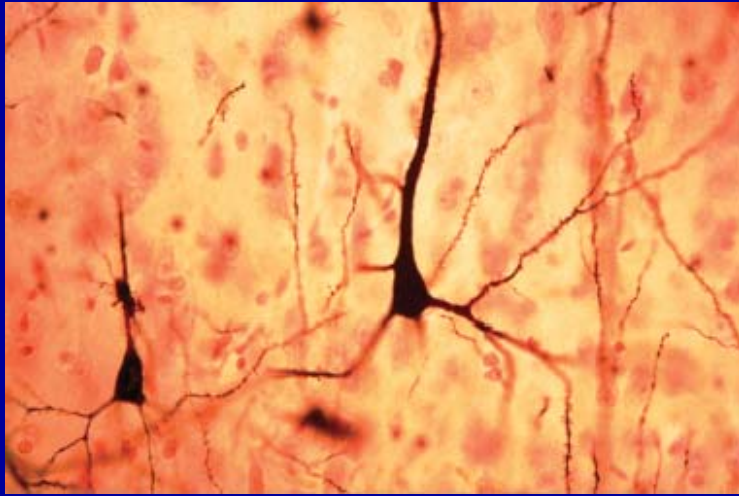


Summary of findings

- Prolonged ethanol exposure results in the enhancement of NR2B-containing NMDA receptors selectively at the synapse.
- No changes in AMPA receptors.
- Activity and PKA-dependent.
- Slowly reverses upon ethanol removal.
- Electrophysiological observations correlated with confocal image analysis confirming functional plasticity.

Is there a corresponding structural component of this homeostatic response to chronic alcohol exposure?

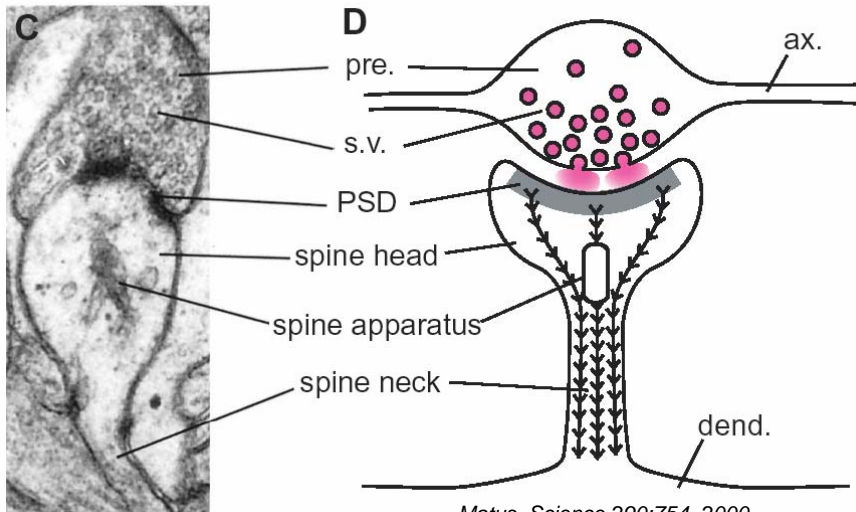
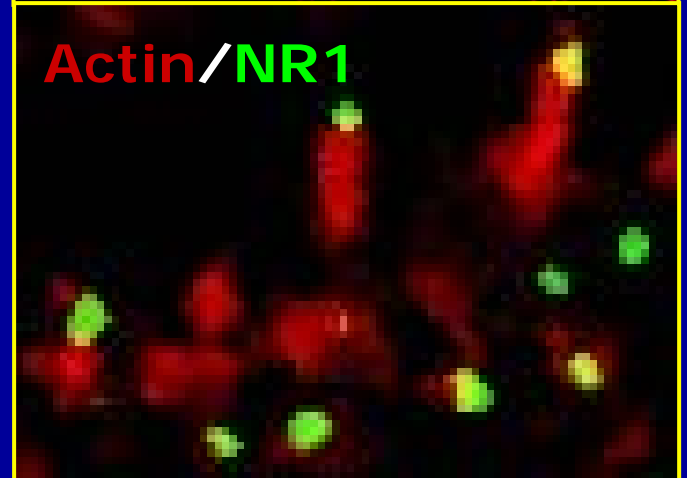
Dendritic Spines and Structural Plasticity



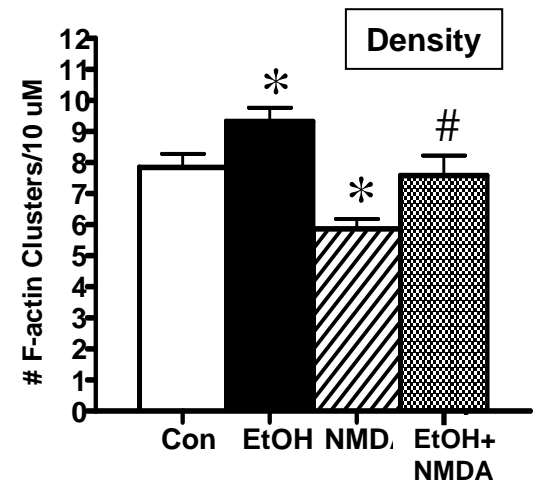
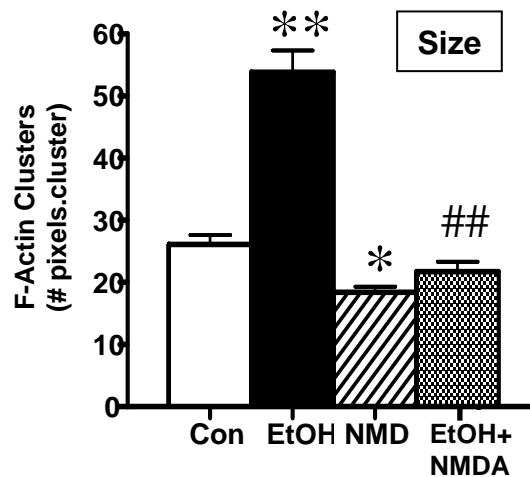
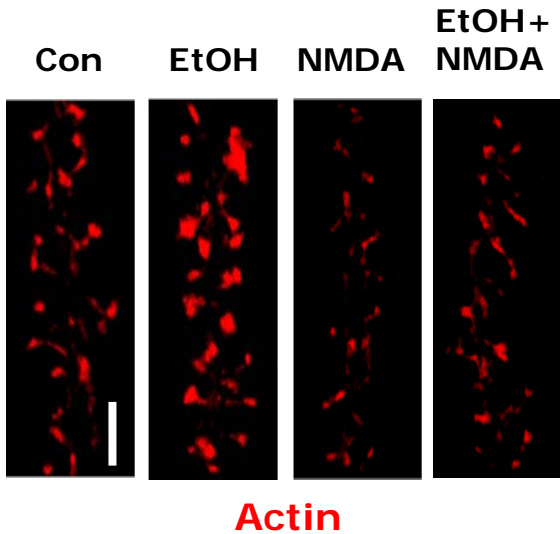
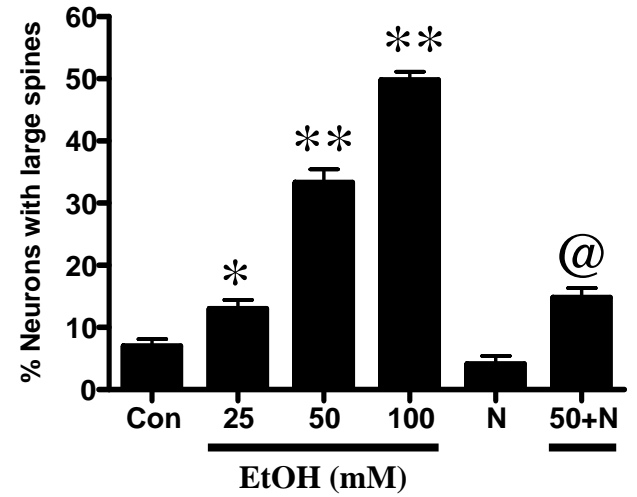
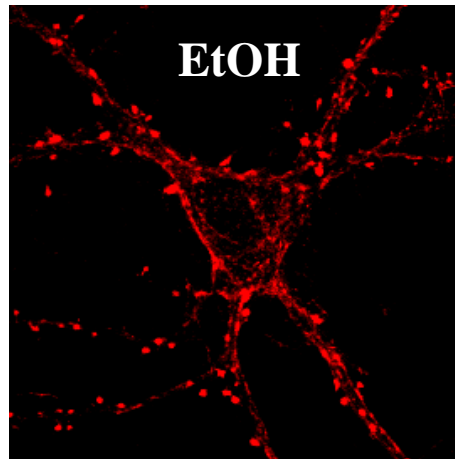
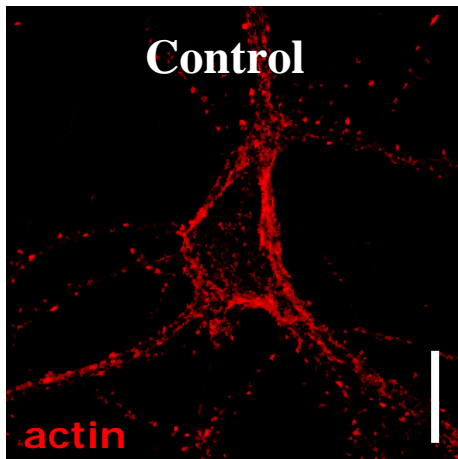
Phalloidin stained
F-actin

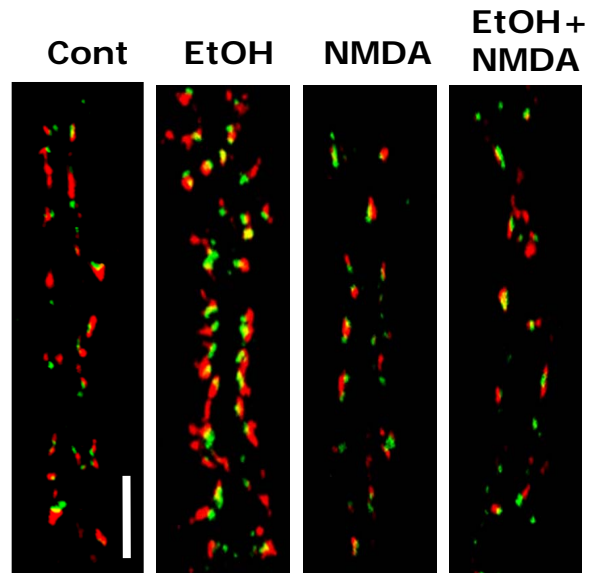
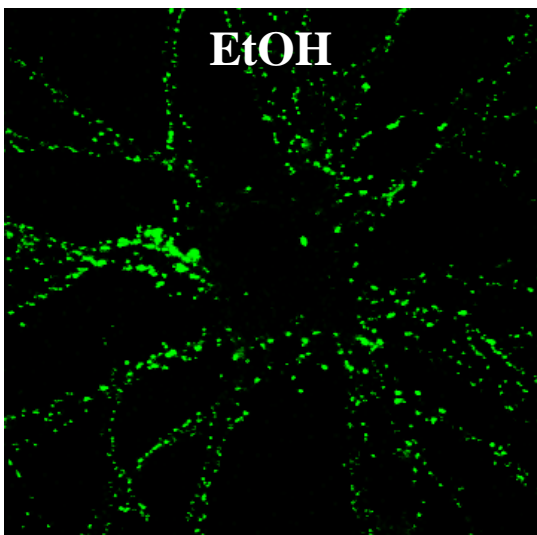
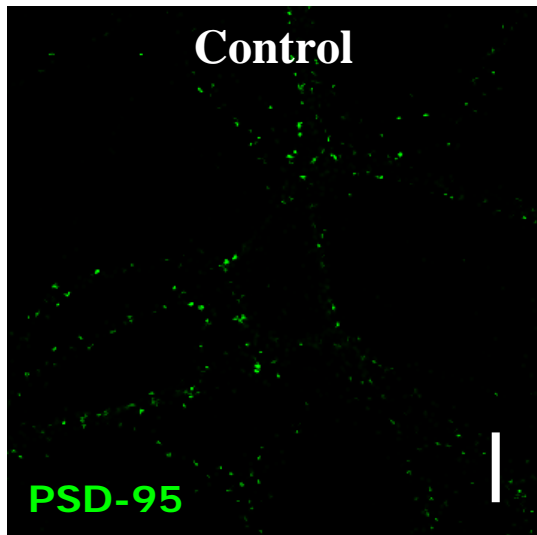


Actin/NR1

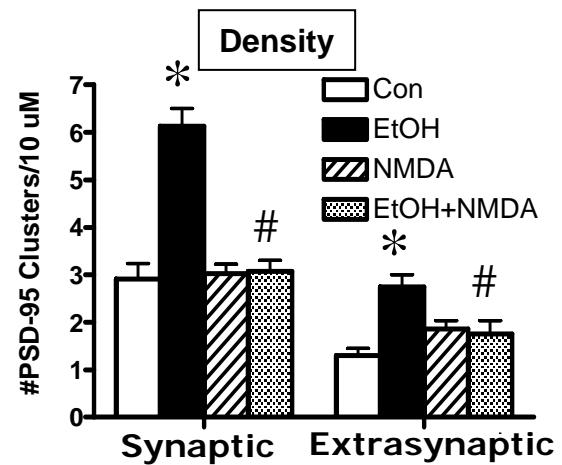
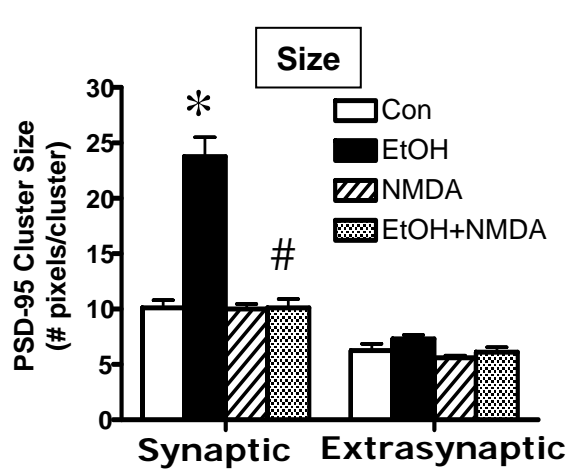


Matus, Science 290:754, 2000





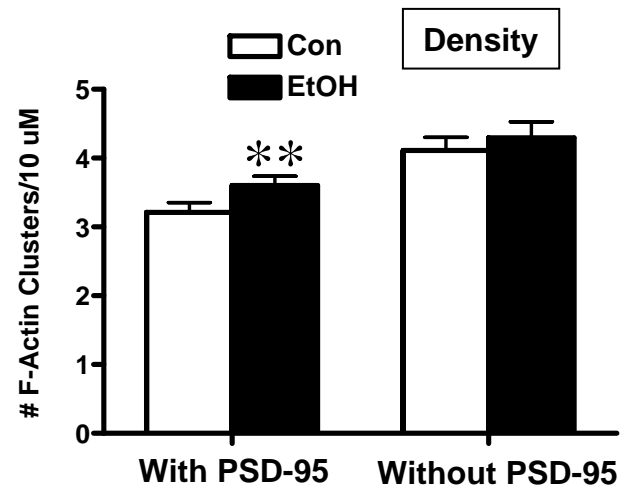
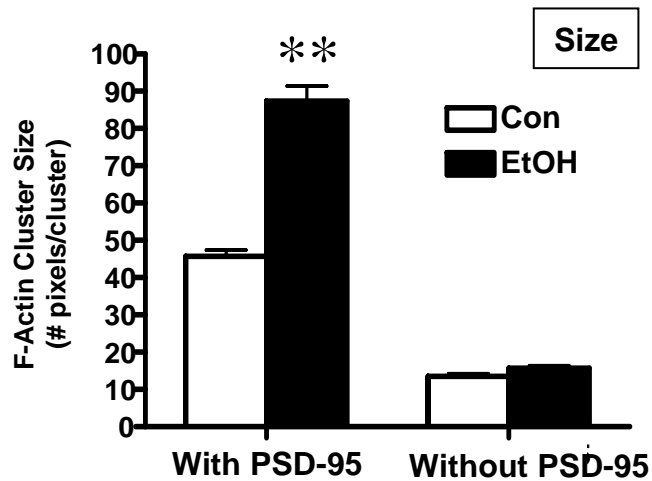
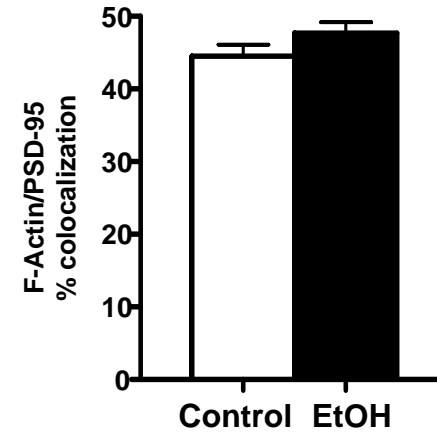
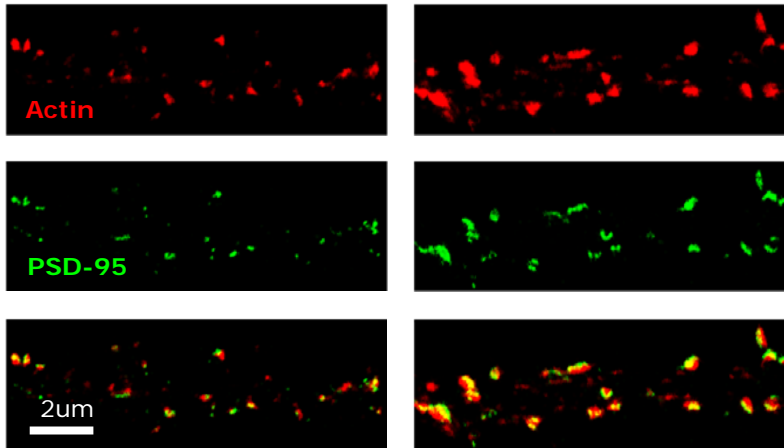
PSD-95/synapsin



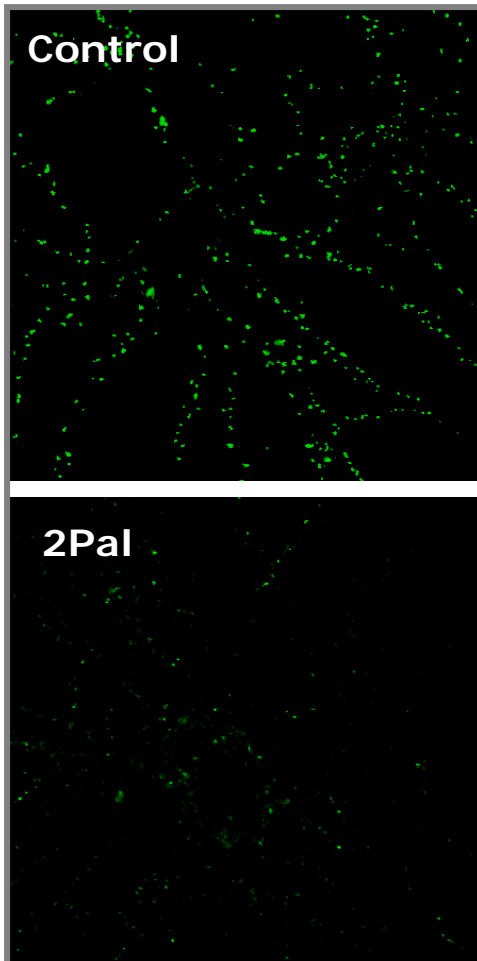


Control

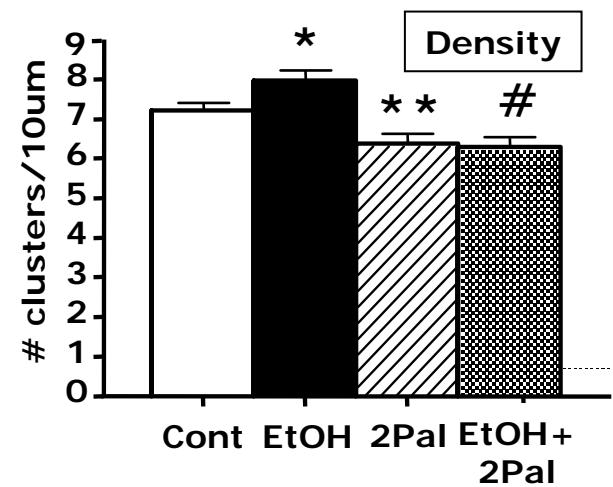
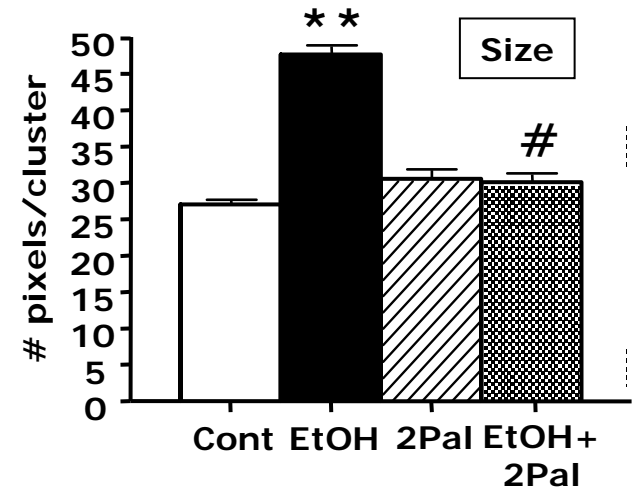
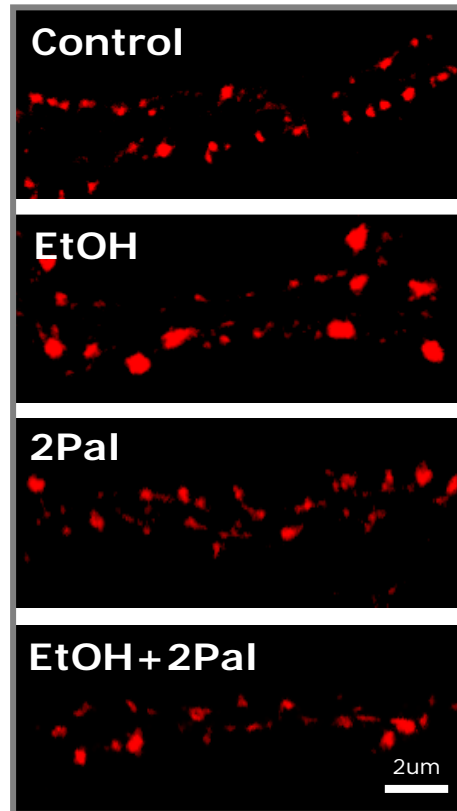
EtOH

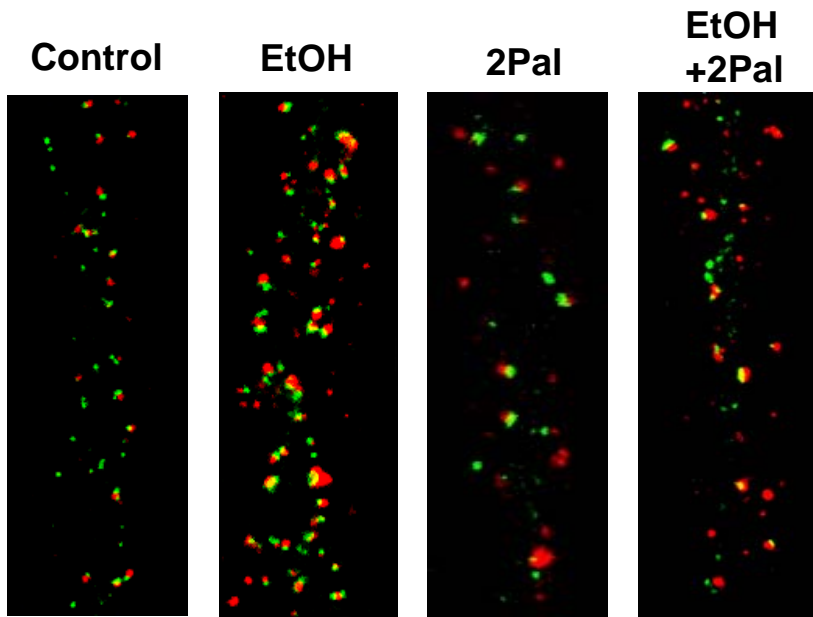
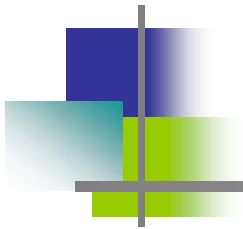


PSD-95

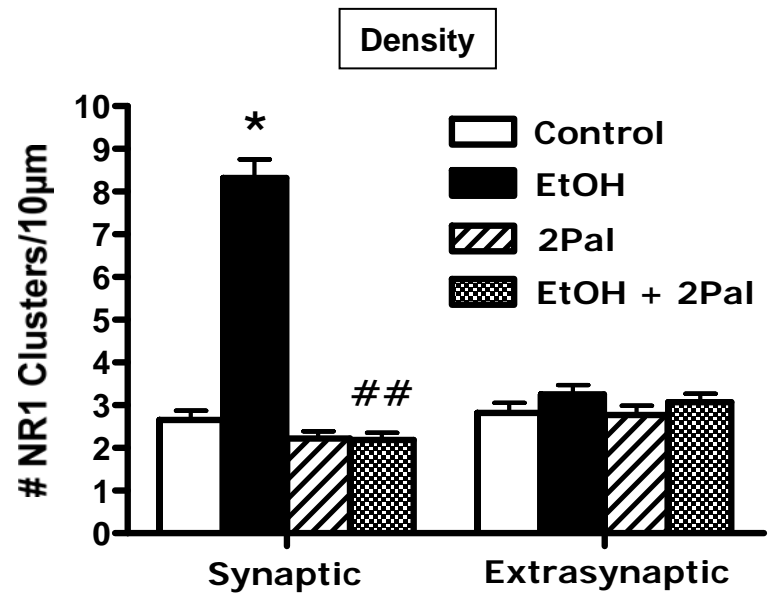


Actin

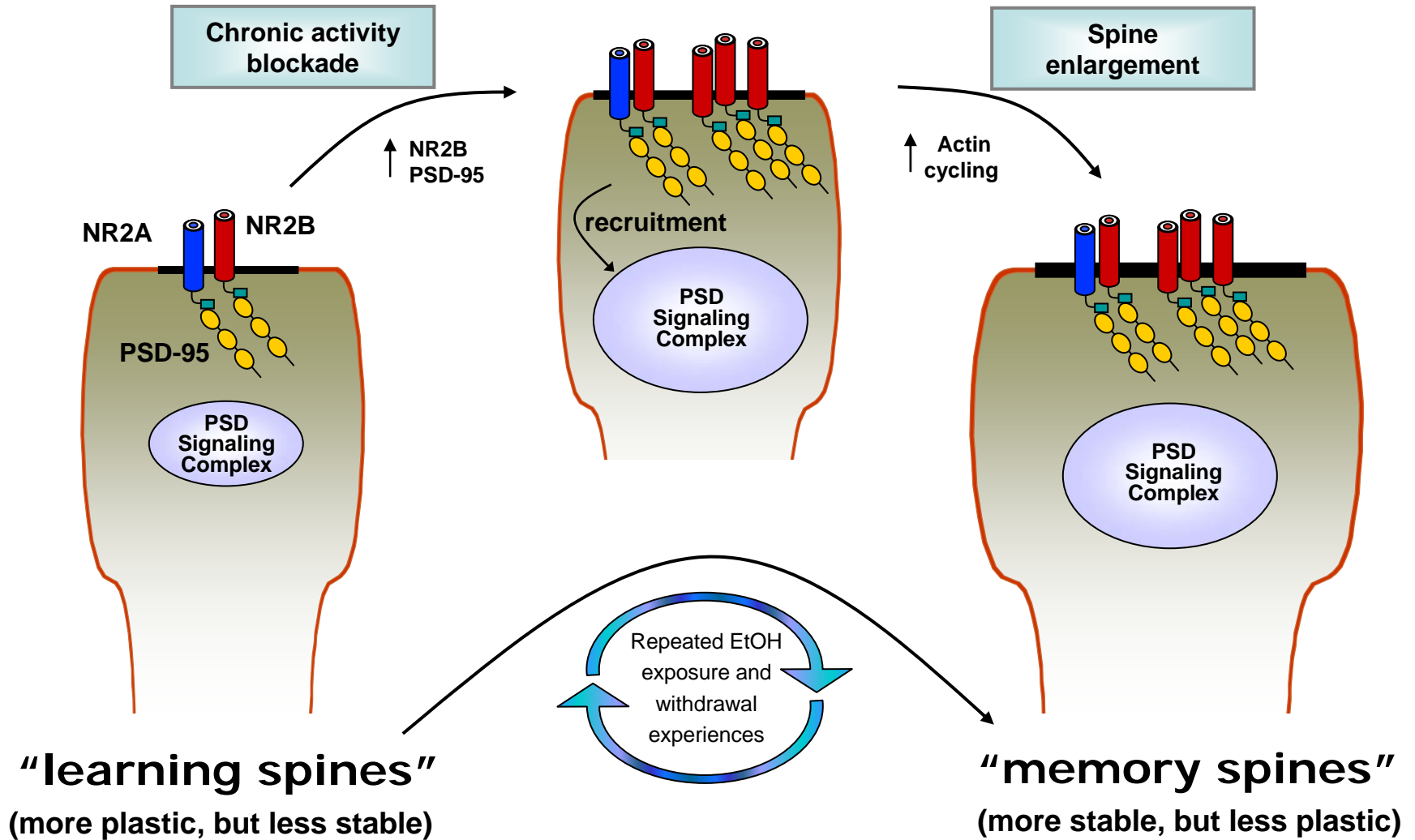


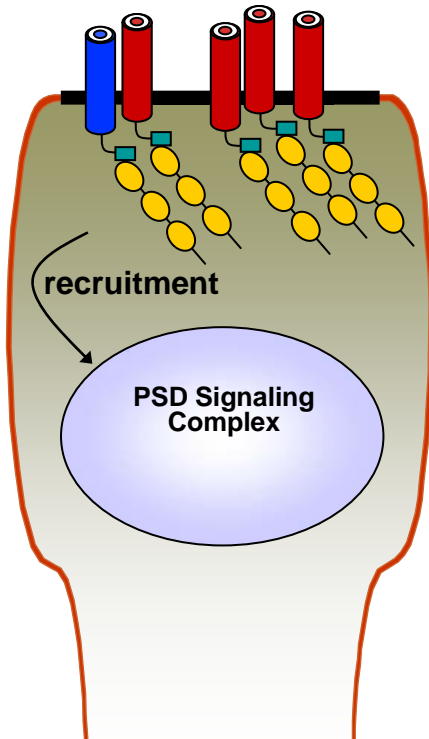


NR1/synapsin

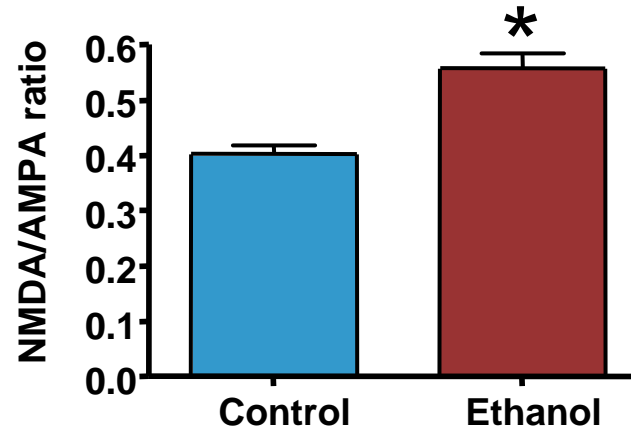


Molecular model of ethanol-induce plasticity

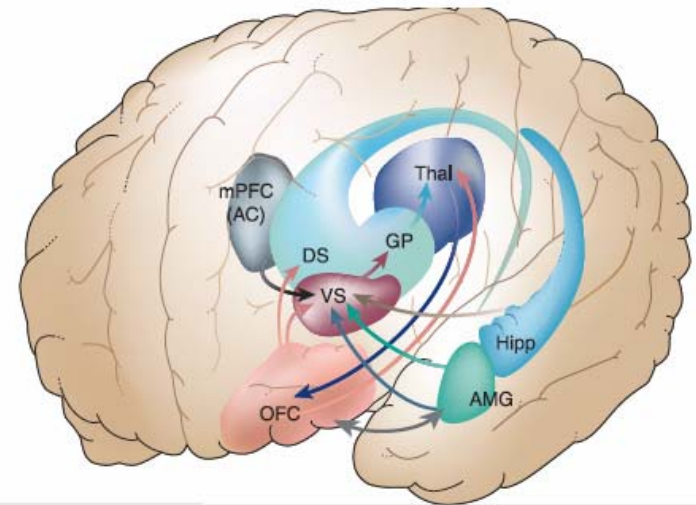




• Does this model have in vivo validity?



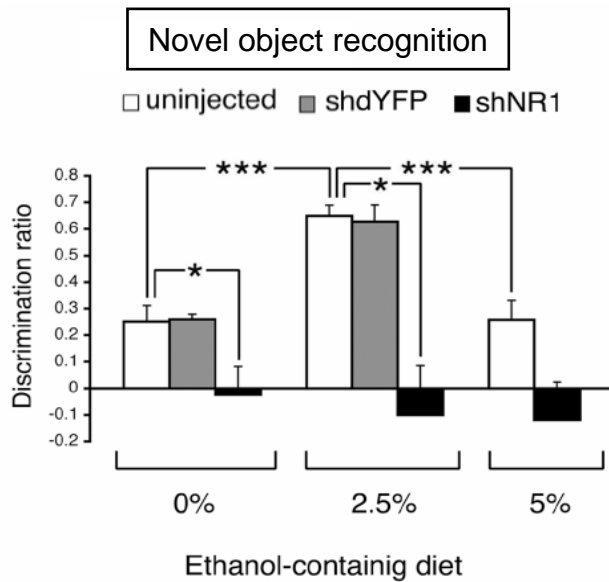
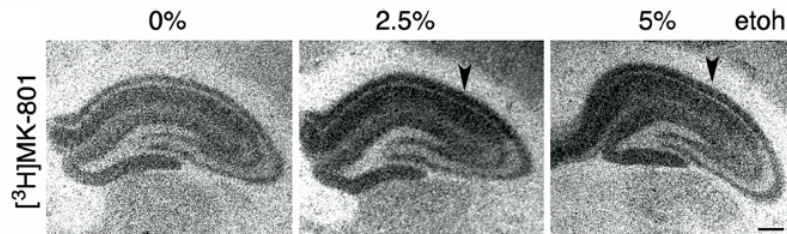
• How do these homeostatic changes impact synaptic plasticity in the context of the addiction neurocircuitry?



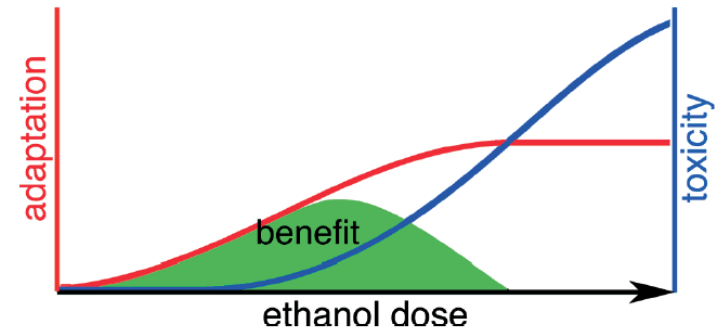
Everitt and Robbins, 2005

Paradoxical Facilitatory Effect of Low-Dose Alcohol Consumption on Memory Mediated by NMDA Receptors

Maggie L. Kaley-Zylinska¹ and Matthew J. During^{1,2}



Chronic Ethanol-induced Plasticity versus Toxicity



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**NIAAA
NIH
ABMRF**