



Kennedy Krieger Institute

Low-dose Perampanel rescues sleep deprivation-induced gamma dysregulation in juvenile Syngap1^{+/-} mice

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PNC Seminar Series



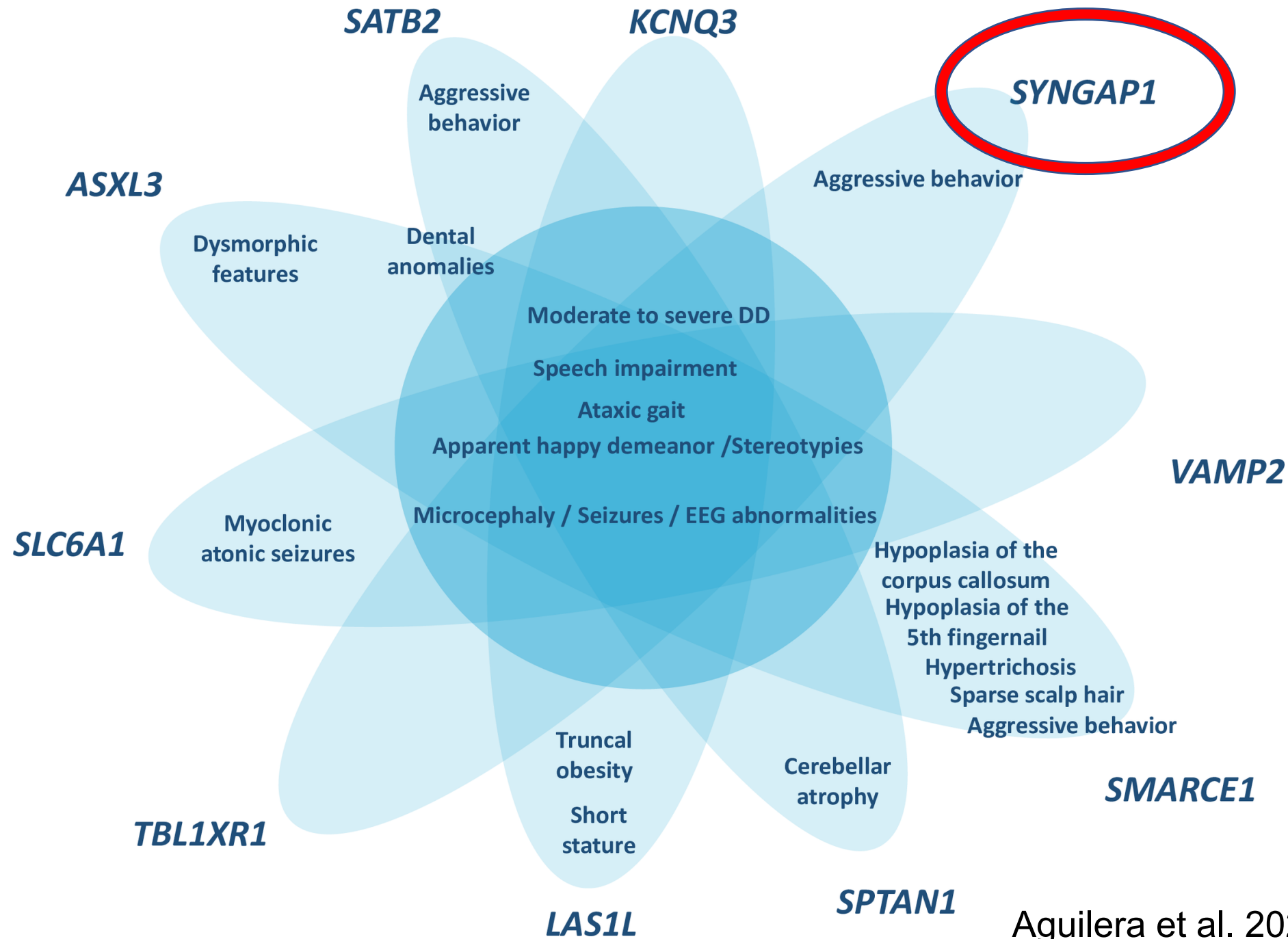
@KadamLab

<http://kadamlab.org>

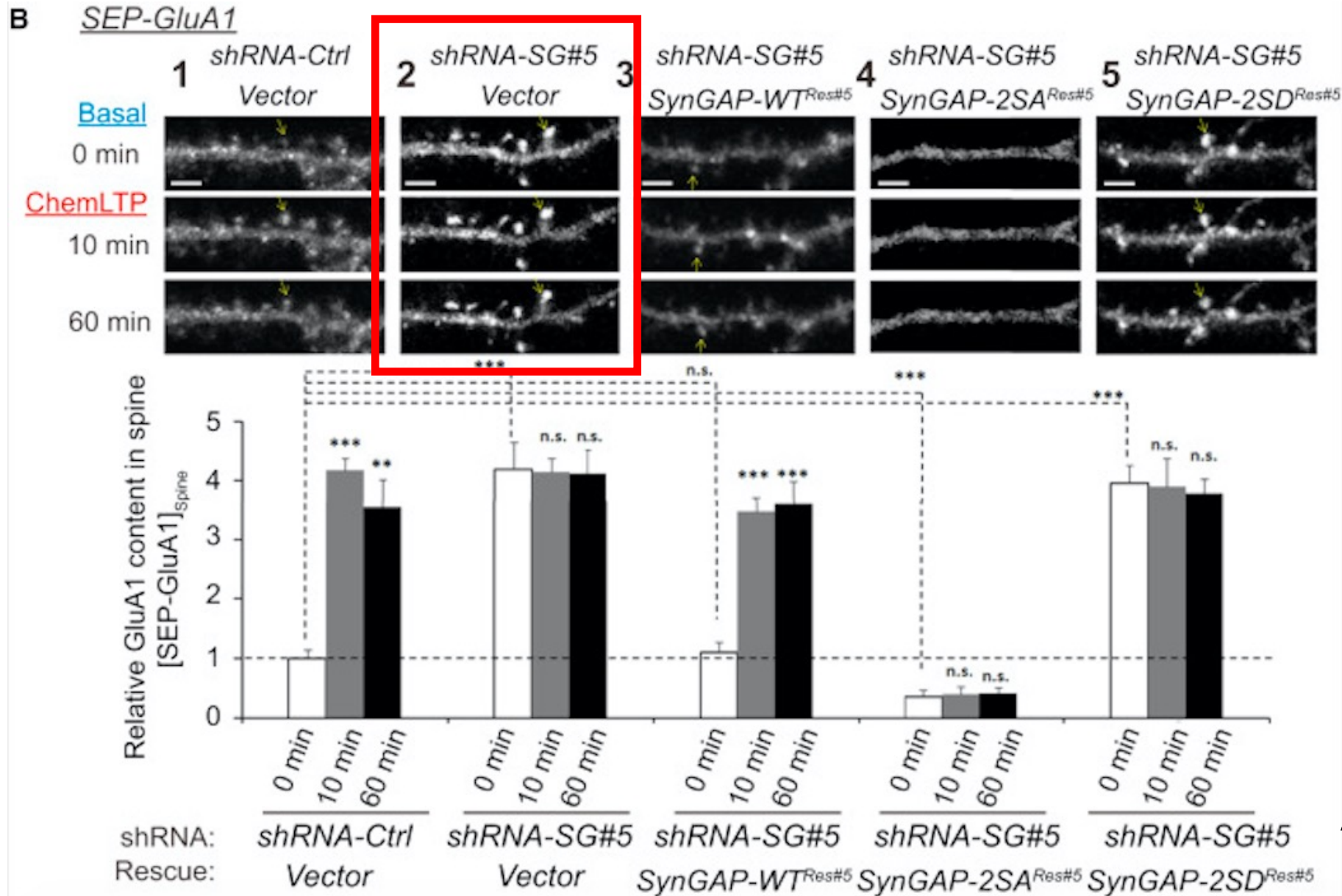


JOHNS HOPKINS
MEDICINE

SCHOOL OF MEDICINE

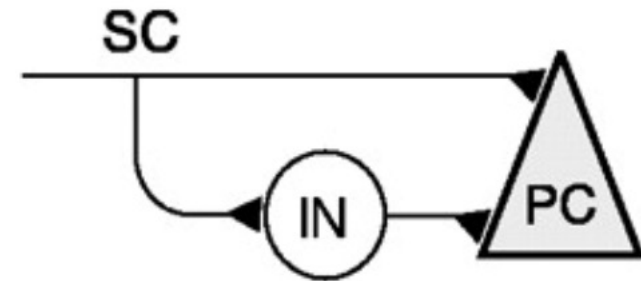
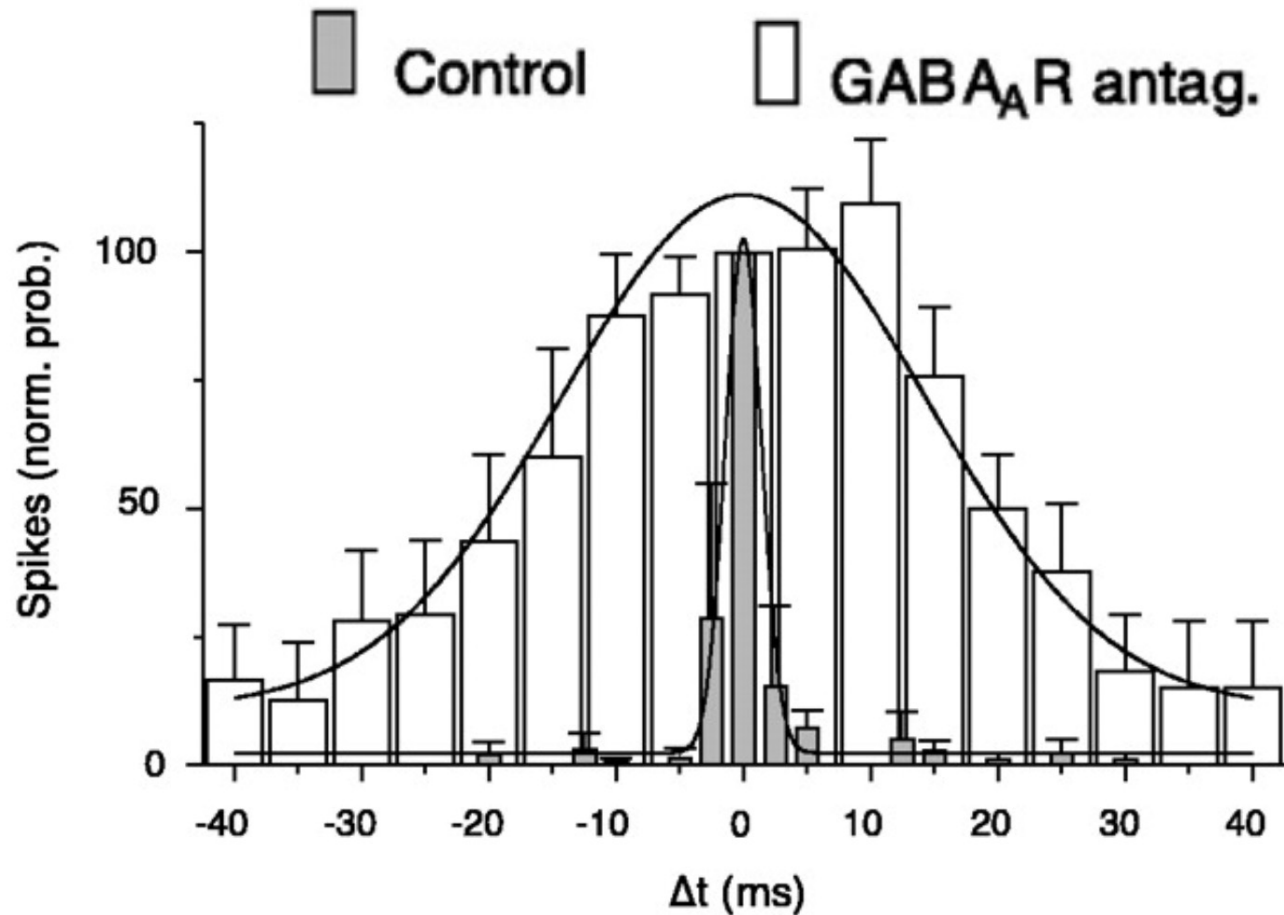


SynGAP regulates AMPAR trafficking



Araki et al., 2015,
Neuron

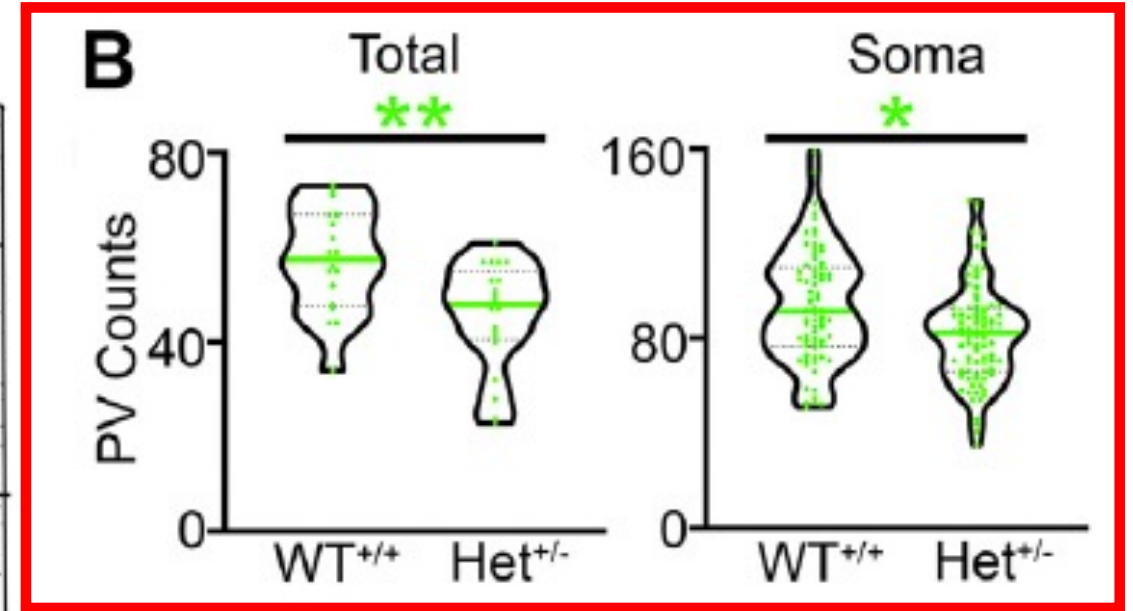
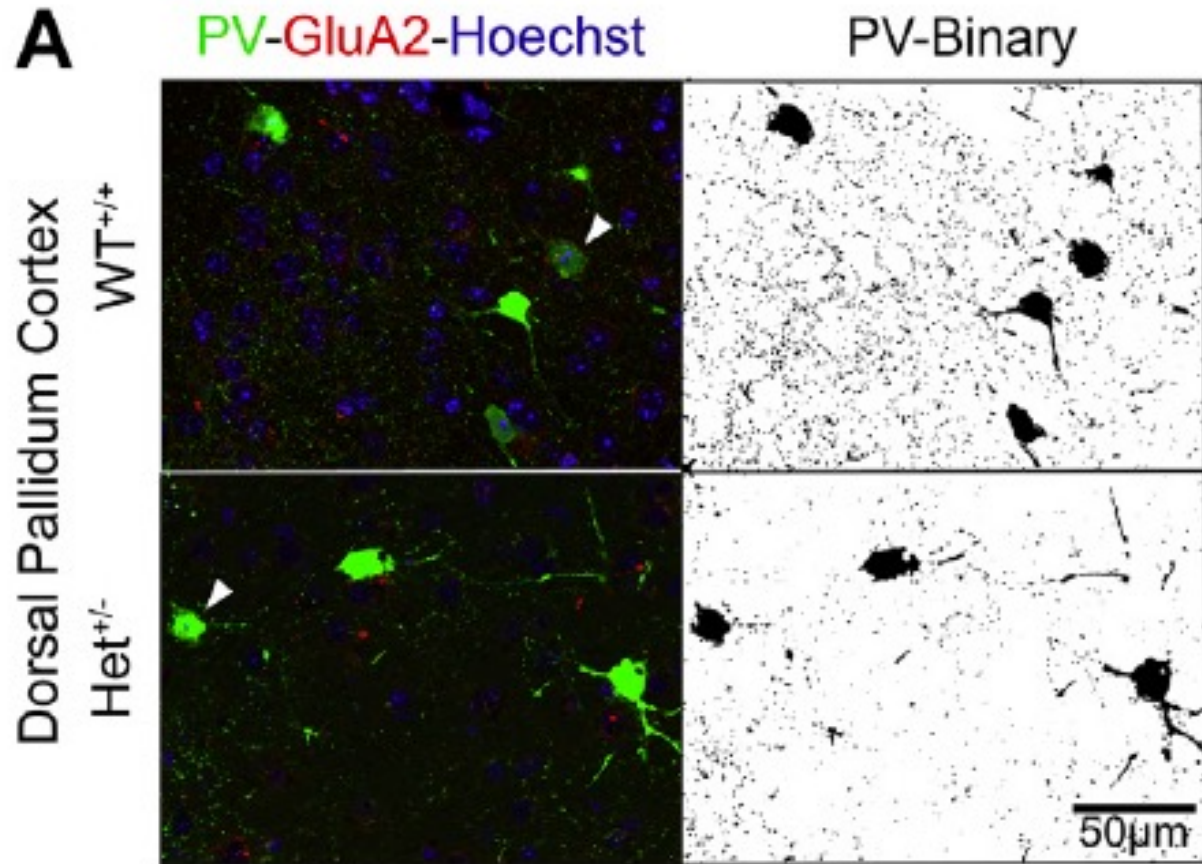
GABAergic cells for accurate information encoding



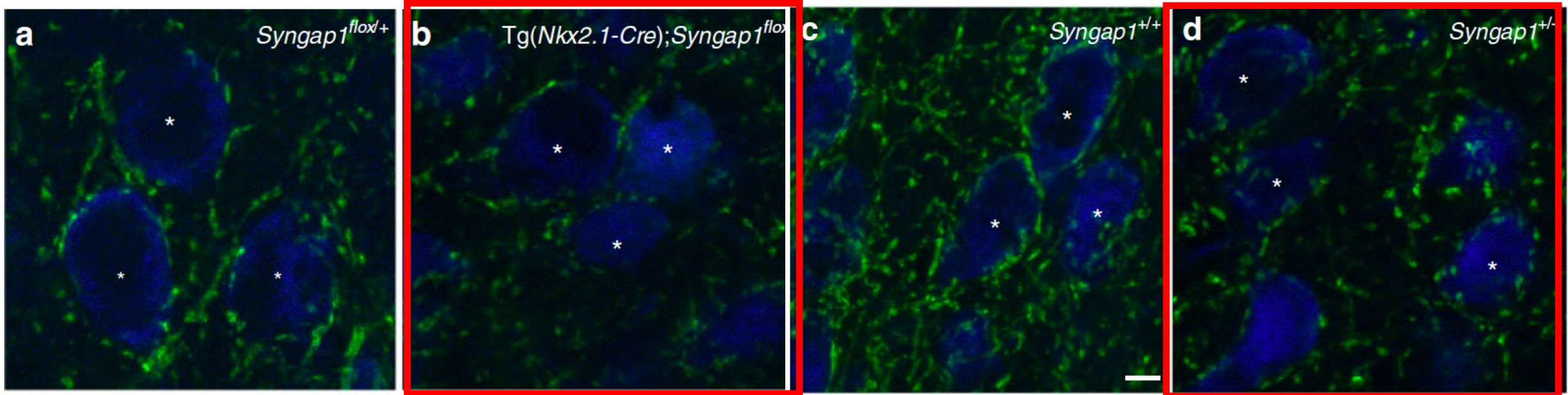
Feedforward inhibition regulates temporal resolution of neuronal integration in rat hippocampal pyramidal cells.

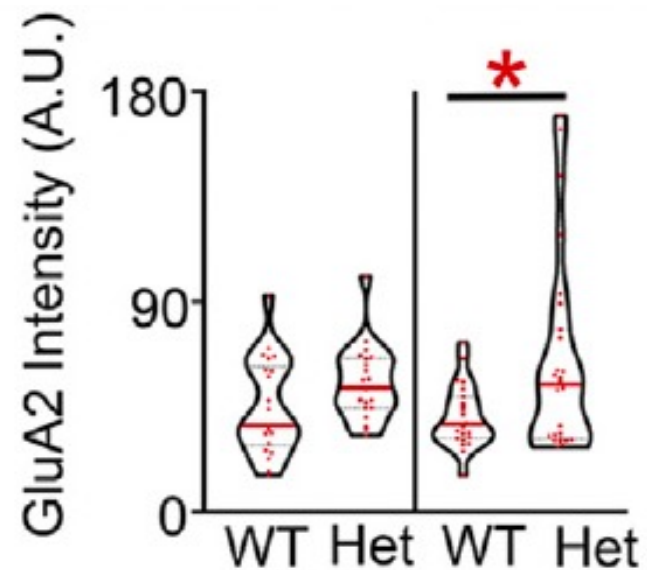
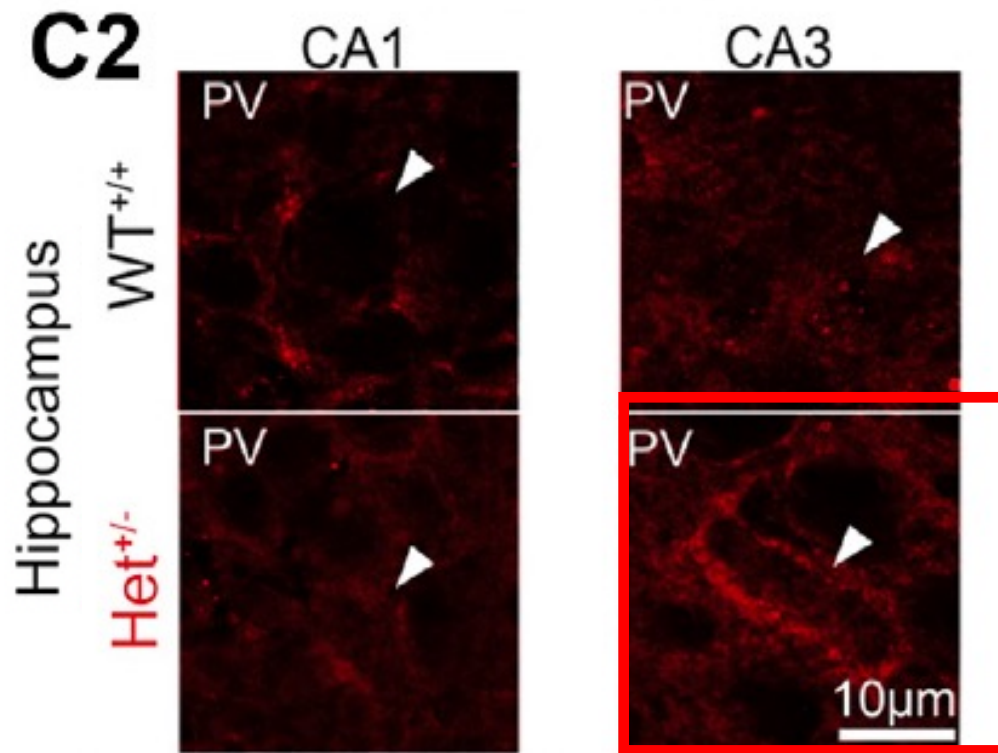
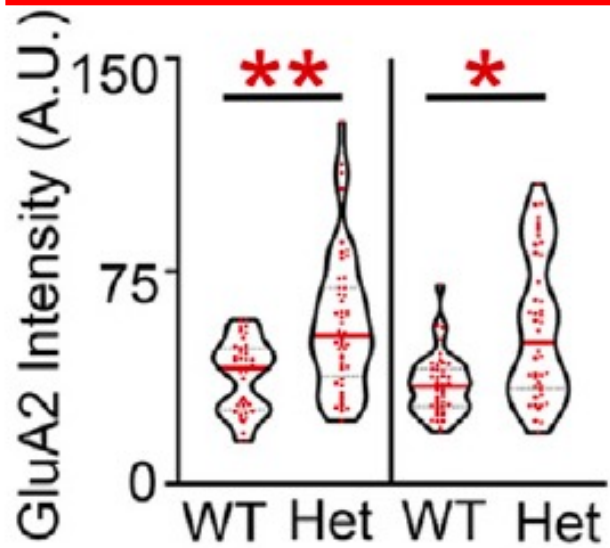
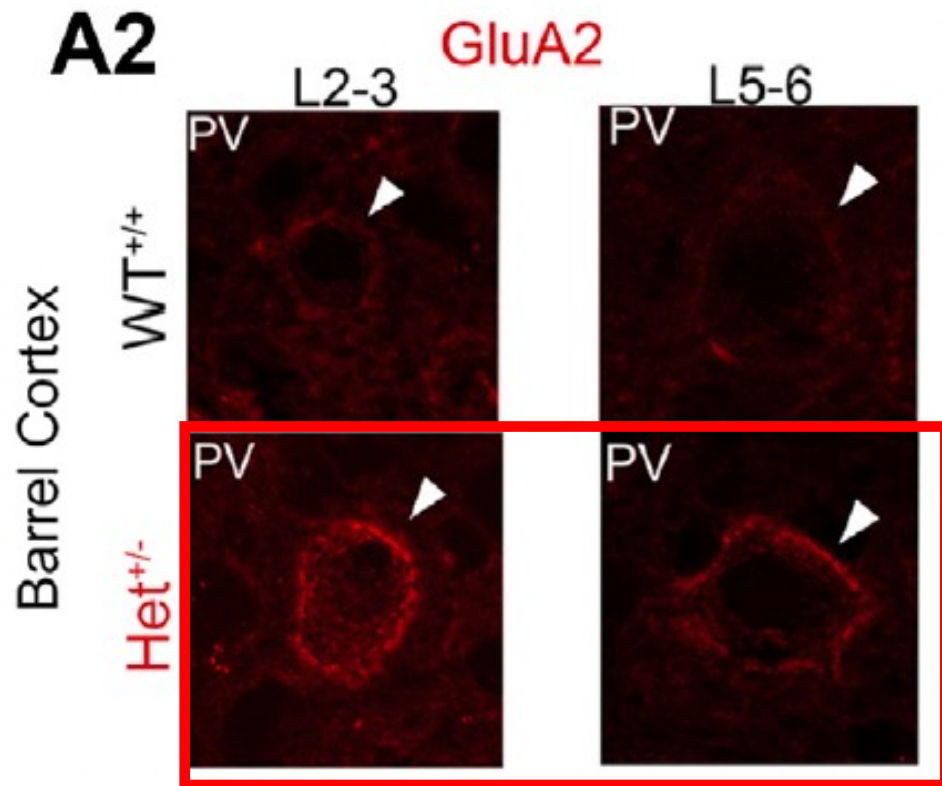
Pouille and Scanziani. 2001, *Science*

Region specific abnormalities in Parvalbumin interneurons from Syngap1^{+/-} mice

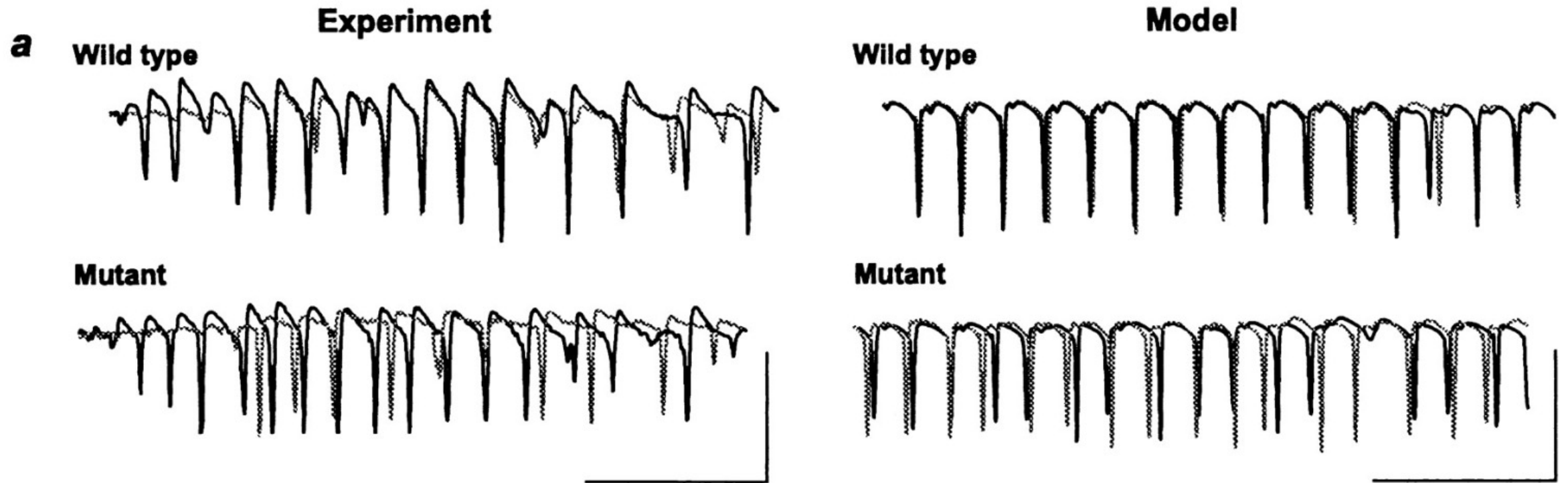


Reduced PV IN perisomatic innervation in the somatosensory cortex of $Syngap1^{+/-}$

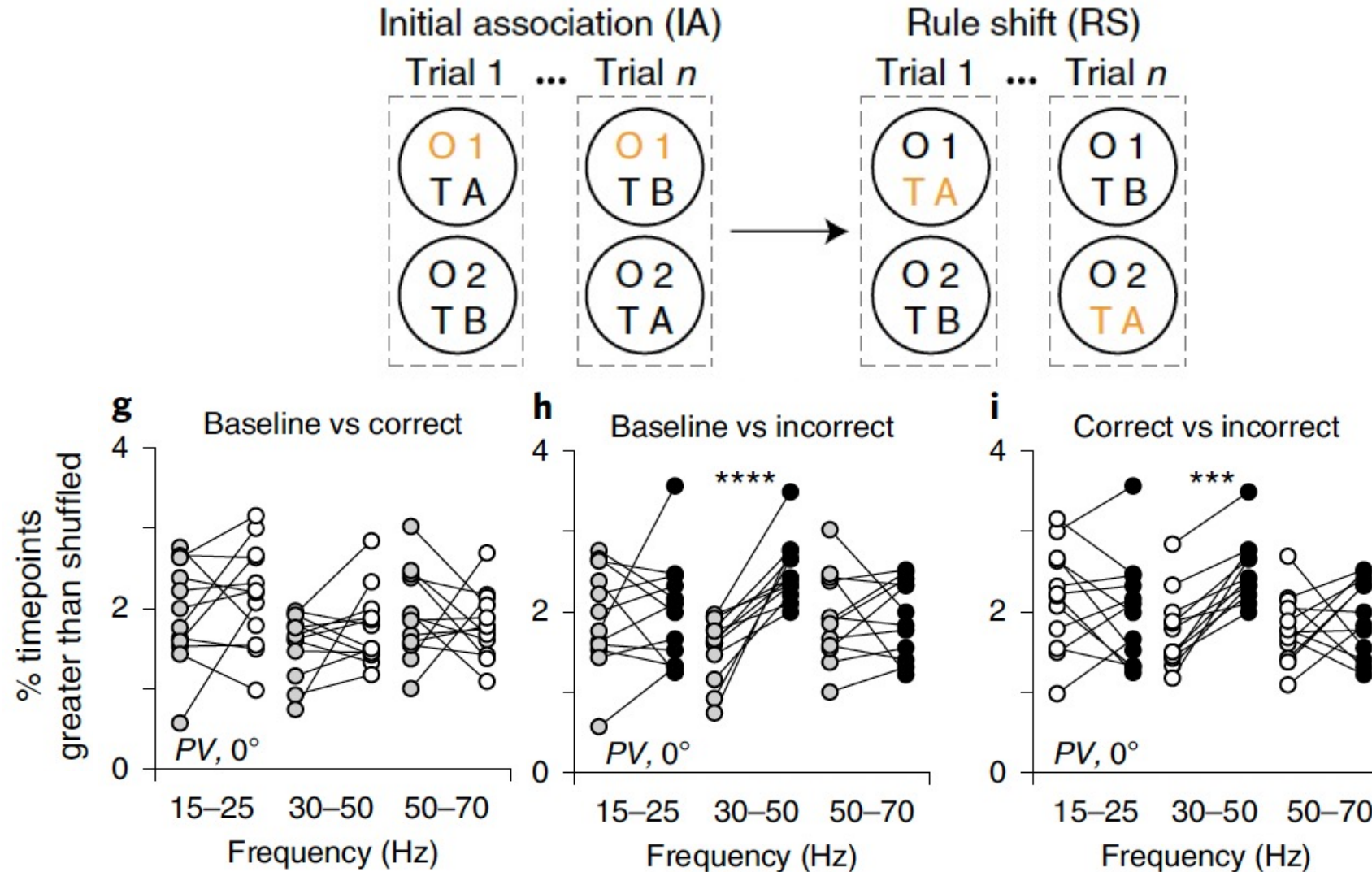




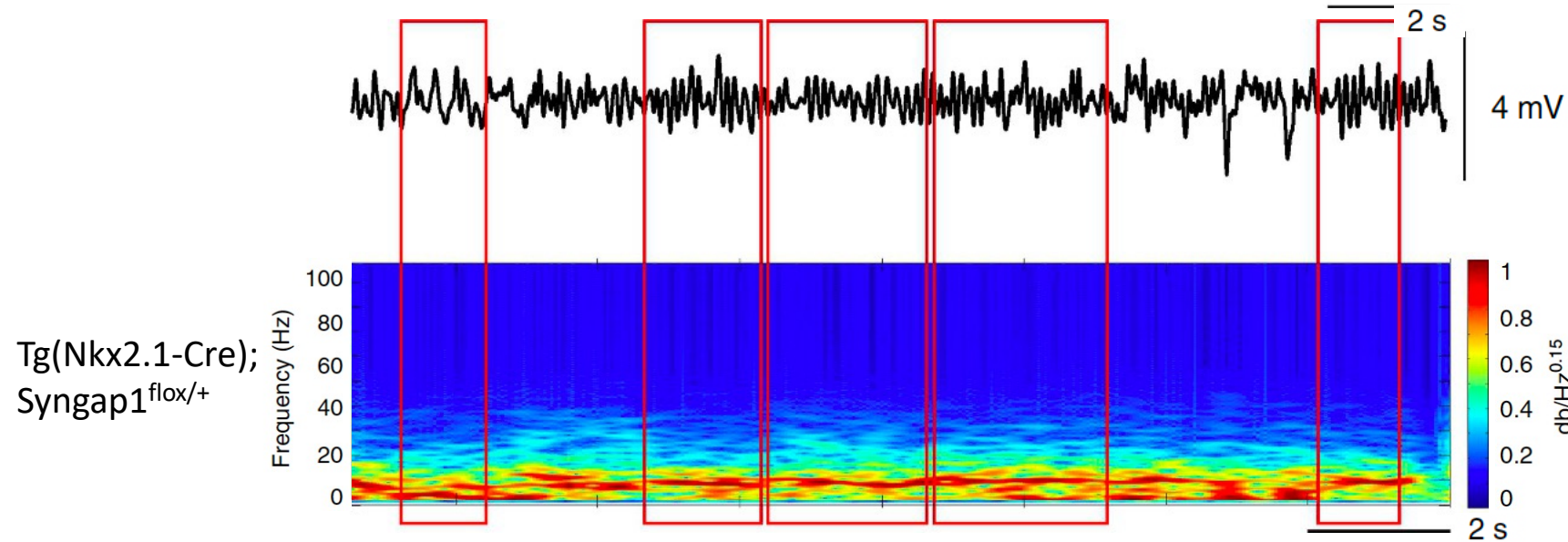
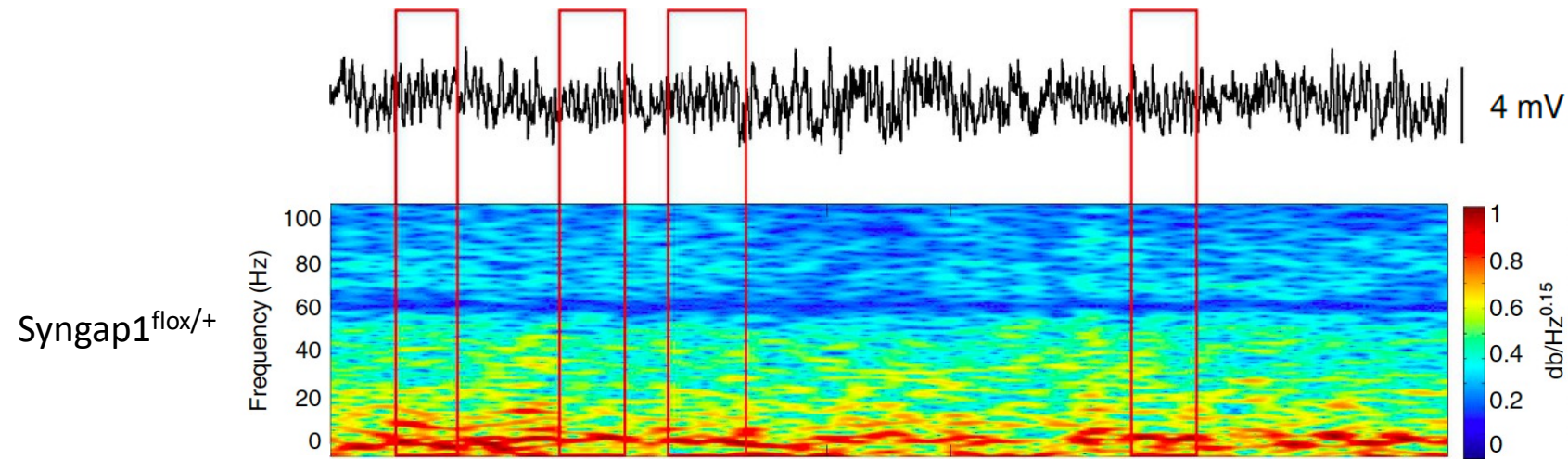
Increased GluA2 expression disrupts long-range synchrony of gamma oscillations



Long-range gamma synchrony in PV IN for behavioral adaptation

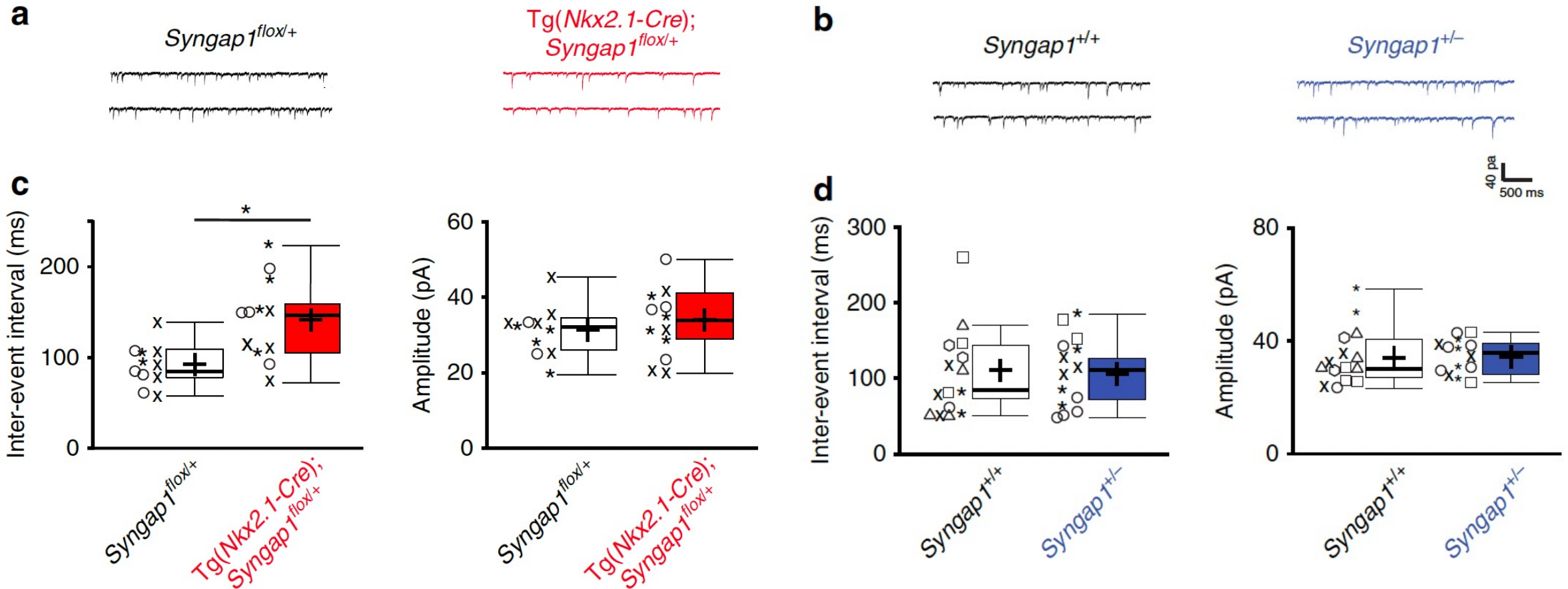


Disrupted gamma oscillations during active exploration



Decreased PV IN activity in Syngap1 haploinsufficiency specific to MGE derived interneurons

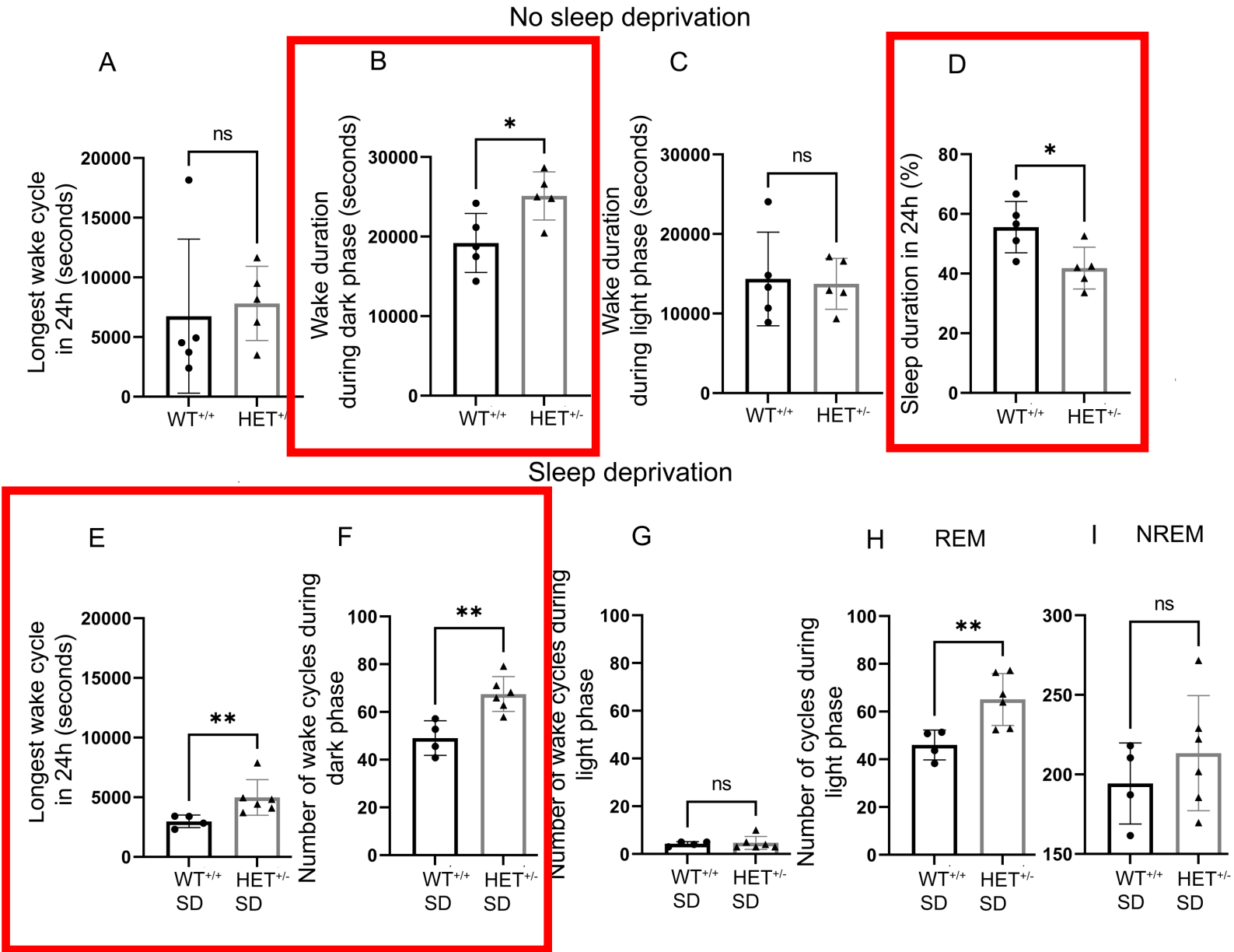
Somatosensory L2/3



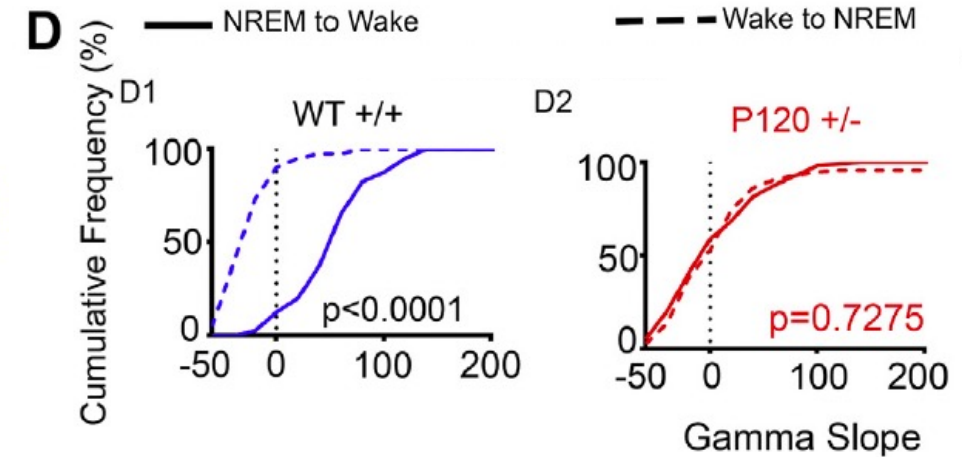
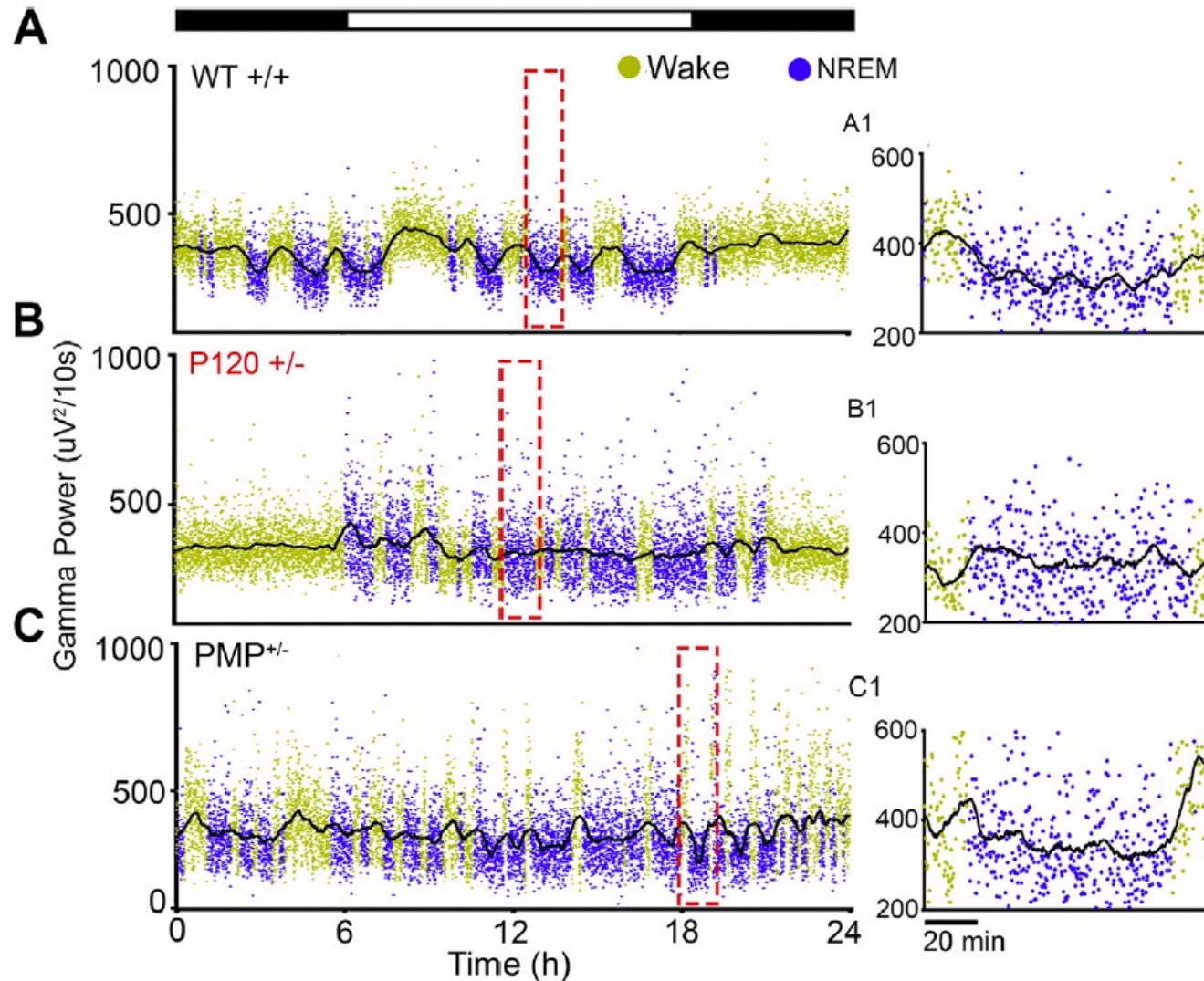
Summary

- SynGap regulates AMPAR insertion at the post synaptic density
- Region specific abnormalities in PV IN in Syngap1^{+/-} mice.
 - Decreased level of PV IN in the prefrontal cortex
 - Increased level of GluA2 in PV IN located in the somatosensory cortex and the hippocampus
- Increased GluA2 expression disrupts long range gamma synchrony
- Syngap1 haploinsufficiency specific to IN from MGE disrupts gamma oscillations.
- Syngap1^{+/-} specific to MGE derived INs showed decreased level of mIPSC activity.
- However, INs in Syngap1^{+/-} germline mutation display no difference in mIPSC activity. This suggests a compensatory mechanism **in response to inhibitory synaptic deficits.**

Altered sleep architecture in juvenile Syngap1^{+/-}

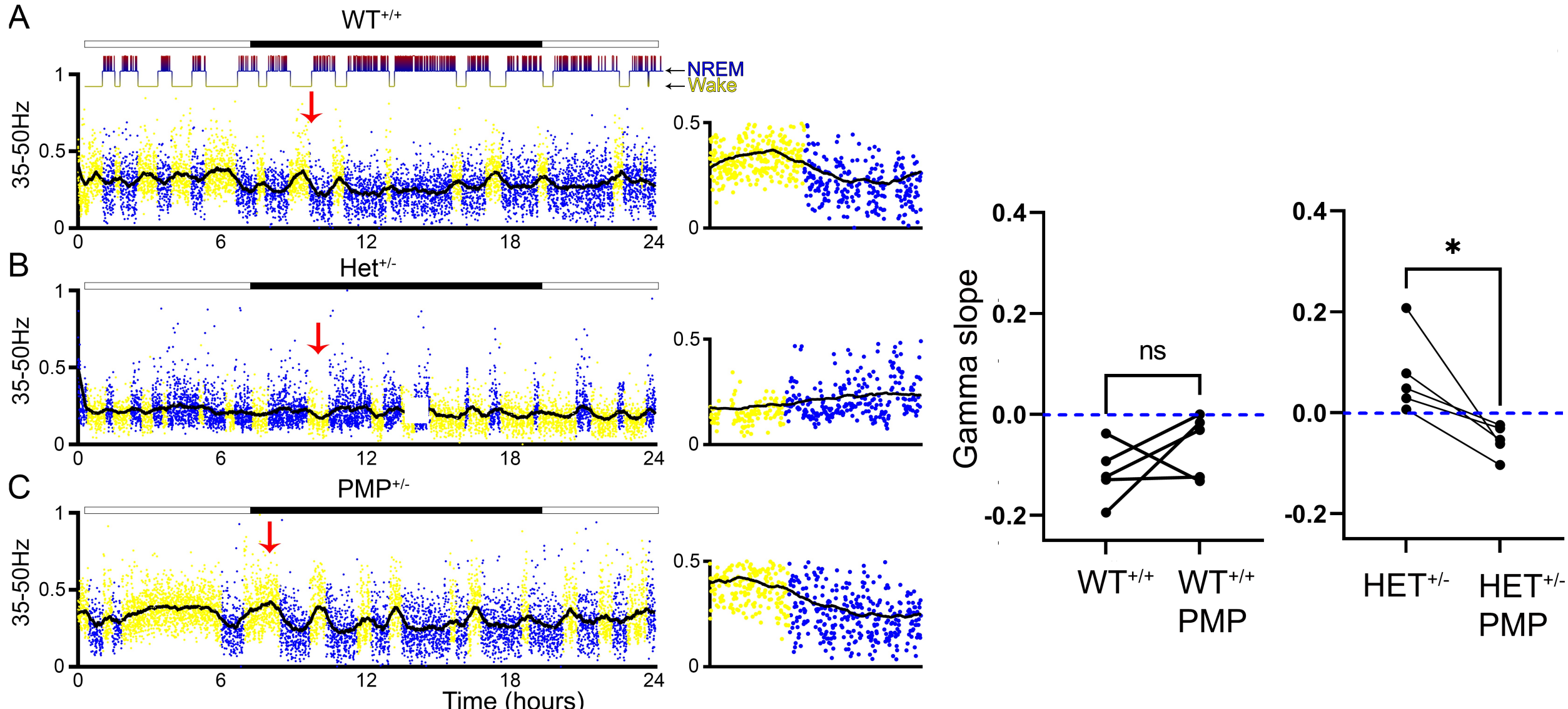


Gamma dysregulation during sleep transitions in adult *Syngap1*^{+/-} mice

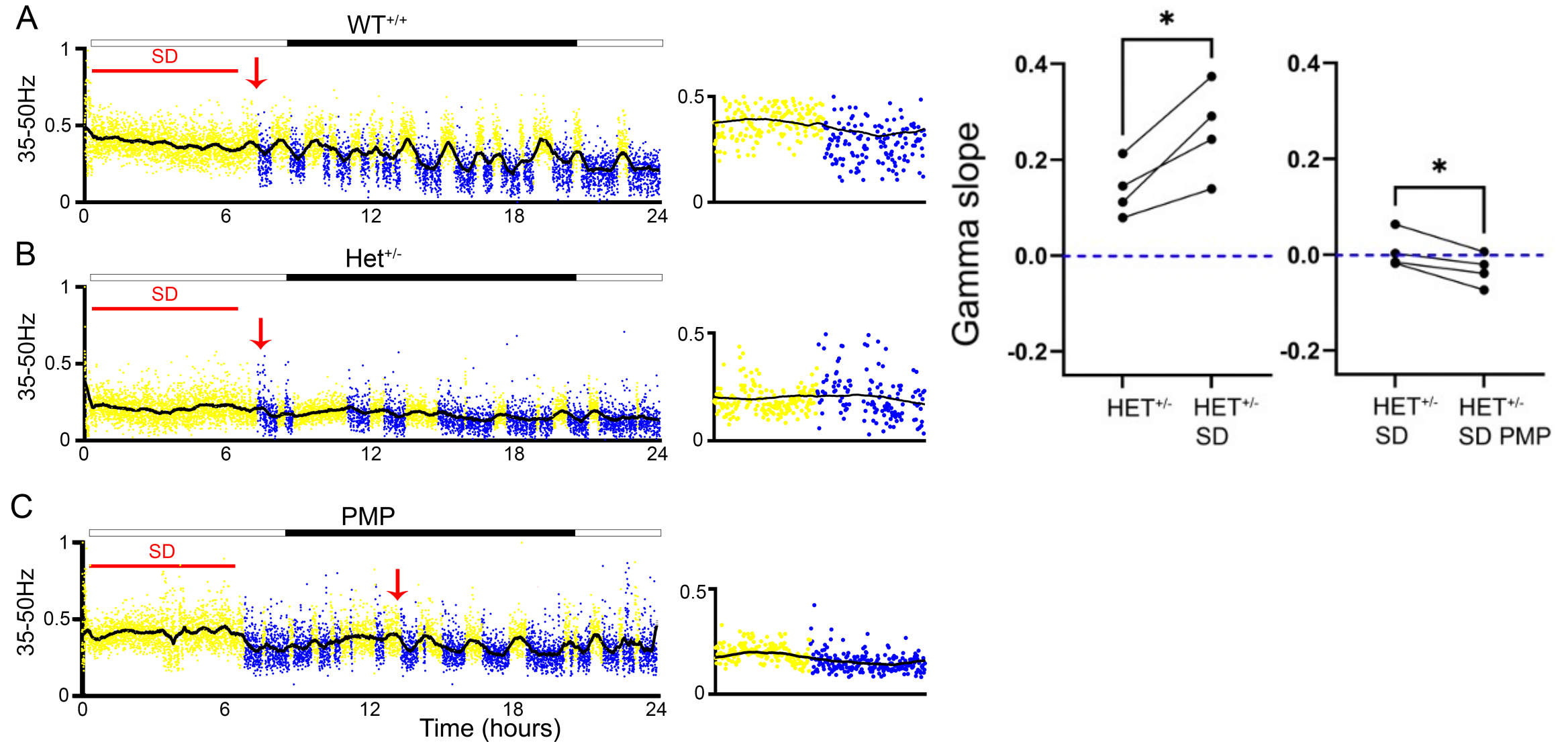


Sullivan et al. 2020,
Biological Psychiatry

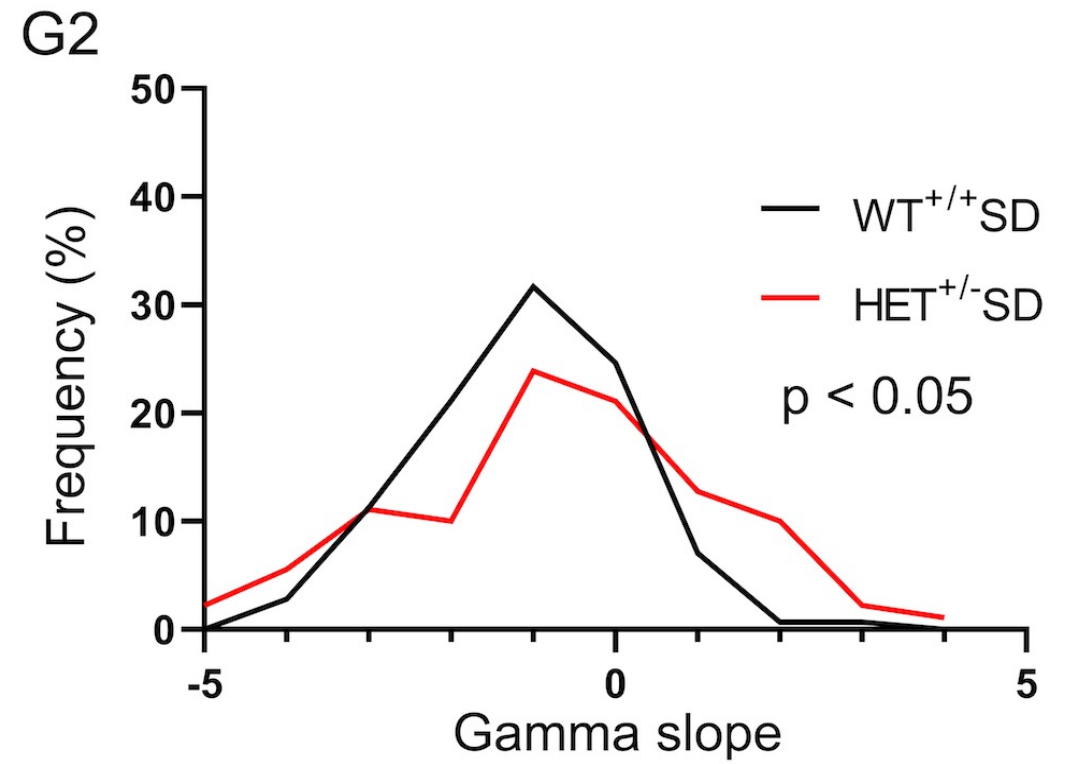
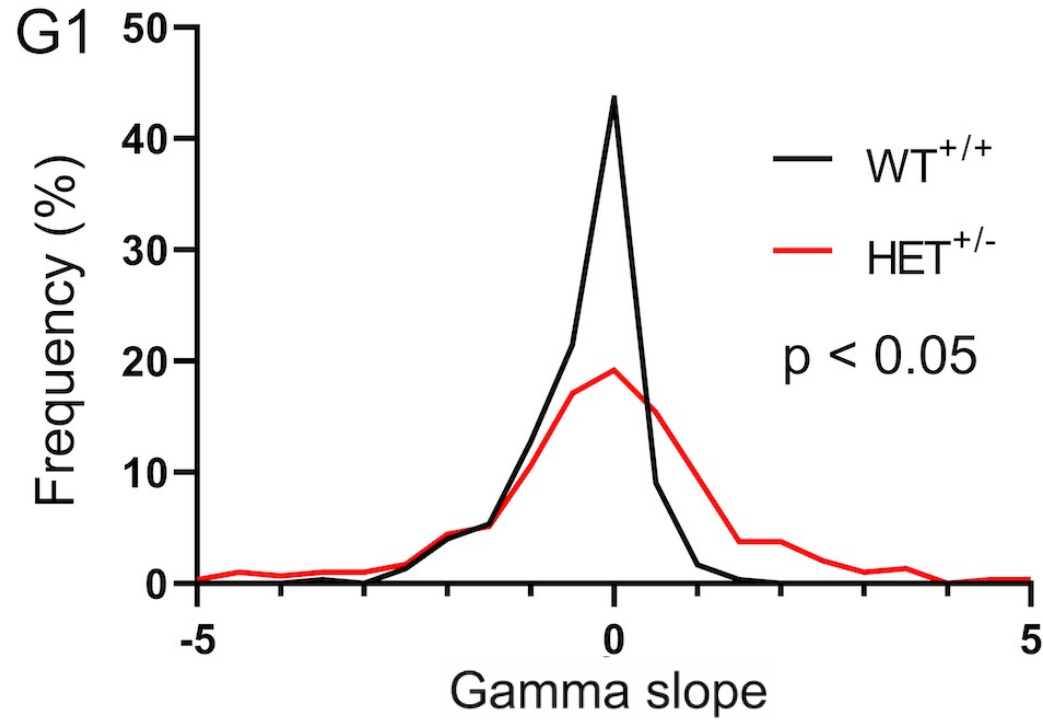
Low-dose PMP alleviated gamma dysregulation in juvenile *Syngap1*^{+/-} mice



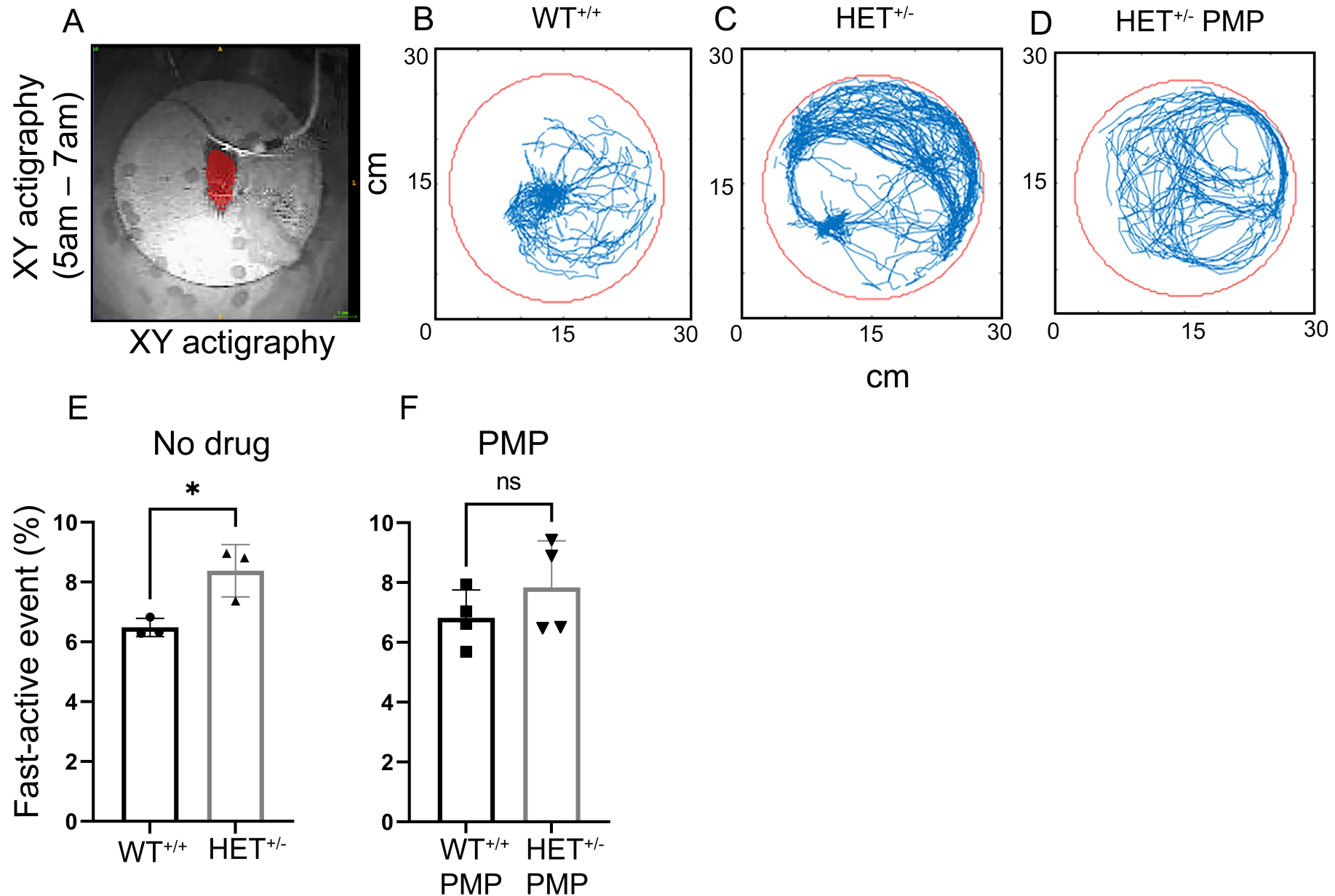
Aggravated cortical gamma dysregulation after sleep deprivation



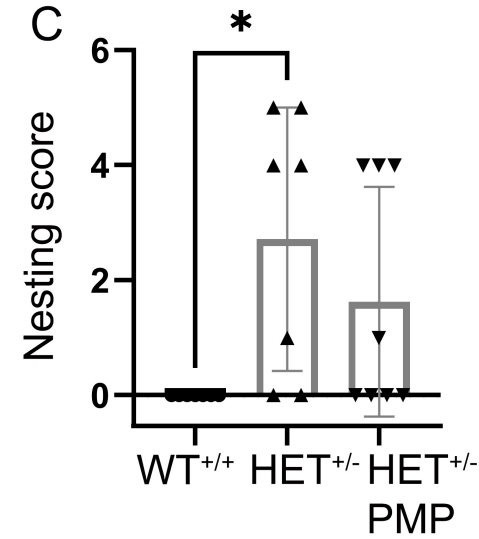
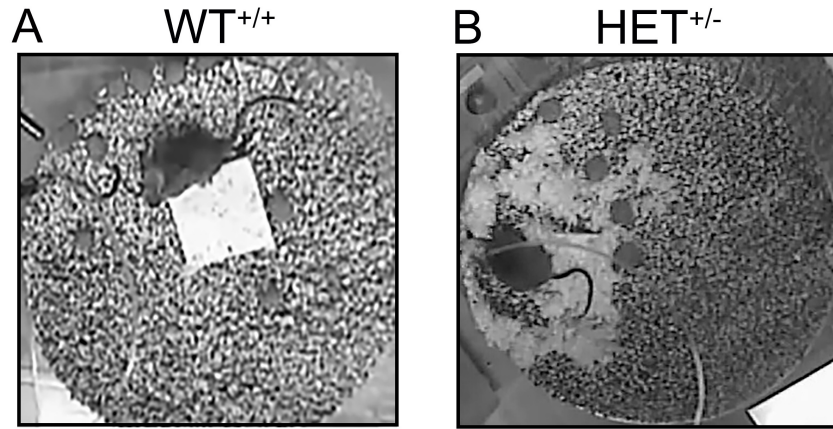
Gamma dysregulation in REM to NREM sleep transitioning points



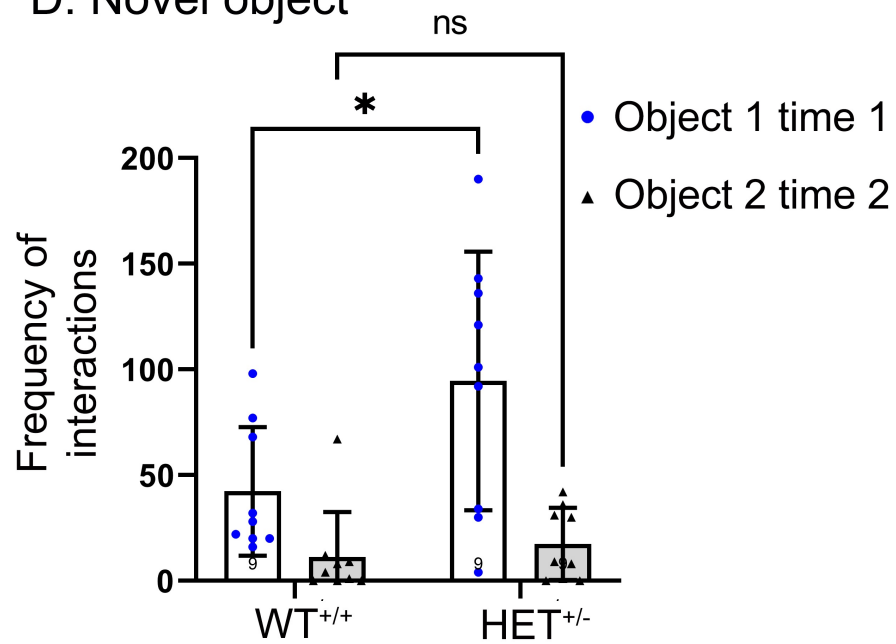
Hyperactivity in juvenile *Syngap1*^{+/-} mice



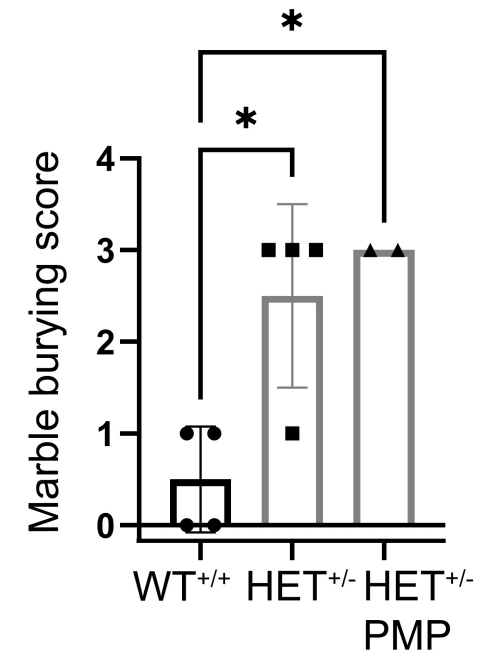
Nesting score



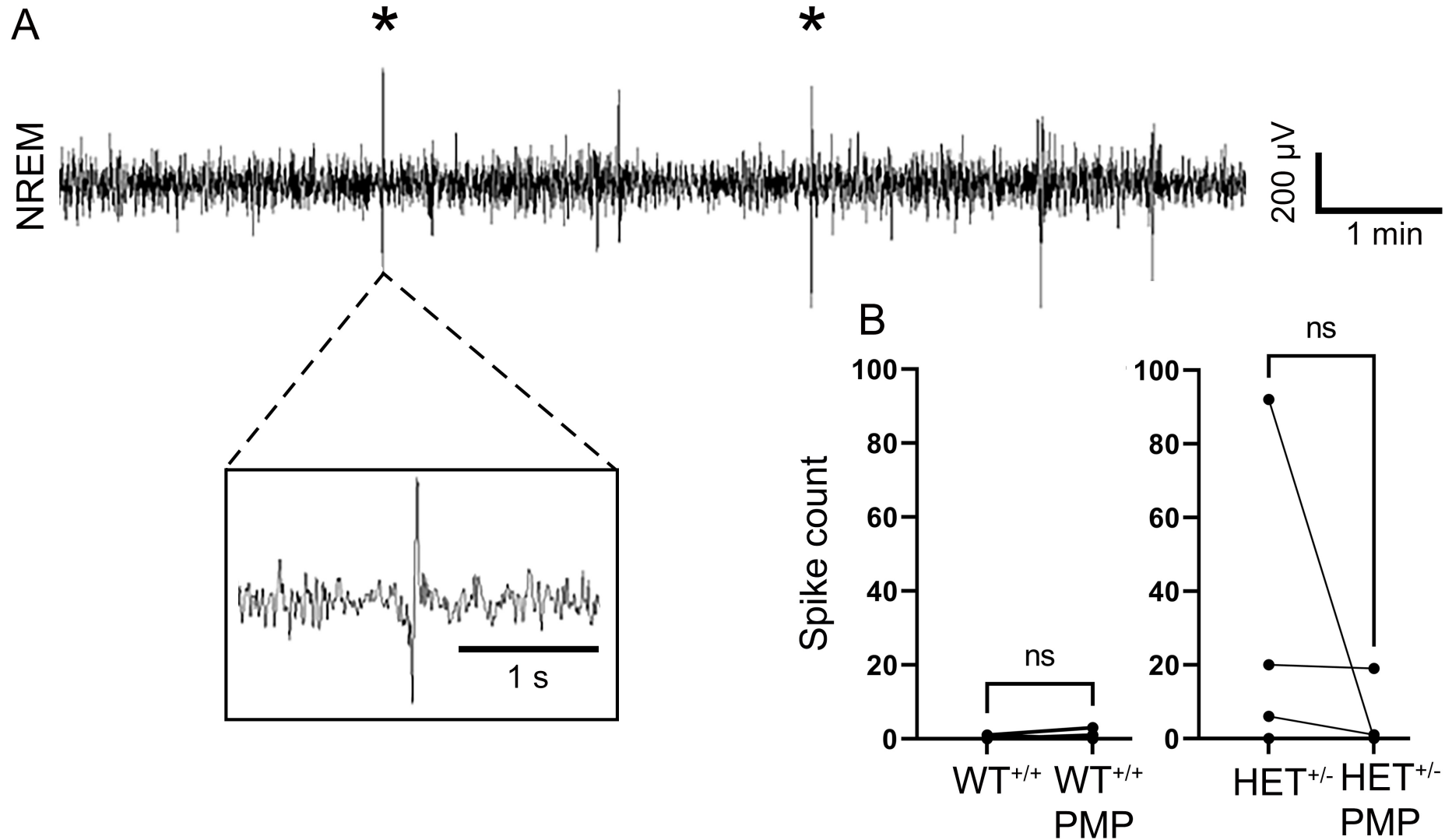
D. Novel object



E. Marble burying



Cortical spikes present predominantly during NREM



Remaining questions

Does inducing sleep deprivation in juvenile Syngap1^{+/-} change GluA2 expression level?

Change in activity pattern of PV IN in a single cell to a thalamocortical network model in response to varying τ . In collaboration with Sedona Ewbank @ Airan Lab, Stanford.

Identification of gamma dysregulation in the raw EEG signal

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