

# A VTA circuit model: Toolbox for the study of addictions

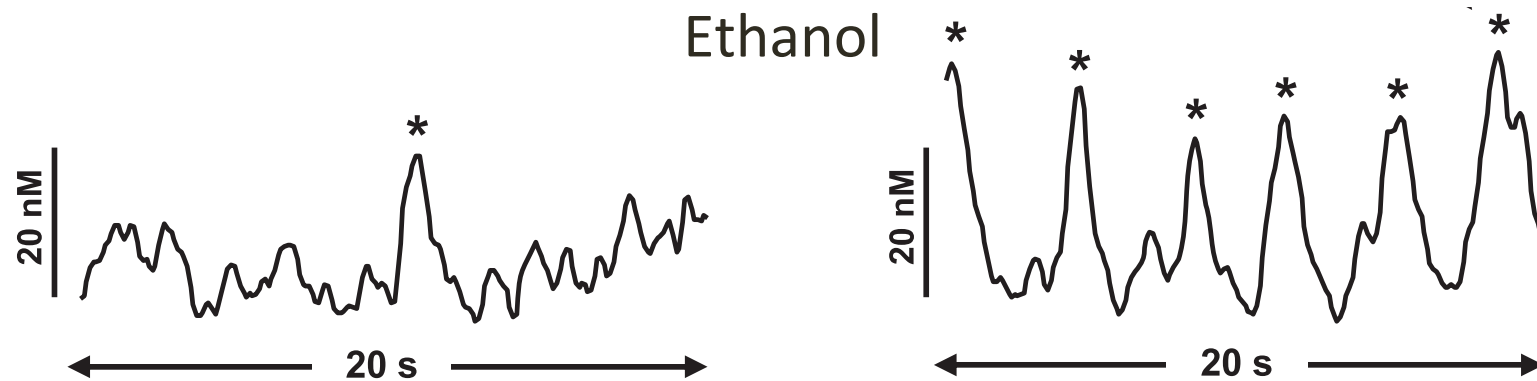
Alexey Kuznetsov

Indiana Univ.-Purdue Univ. at Indianapolis

CRCNS PI Meeting, October 25, 2016

CRCNS AWARD R01 AA022821

# Addictive drugs enhance dopamine transients



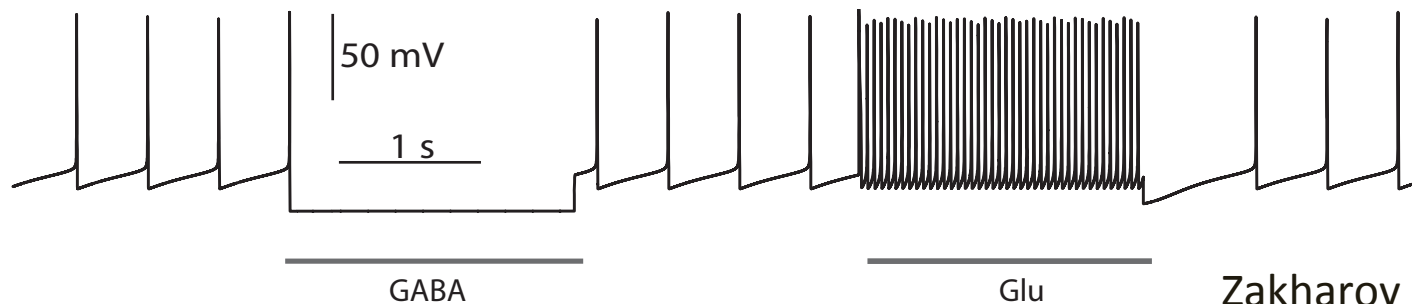
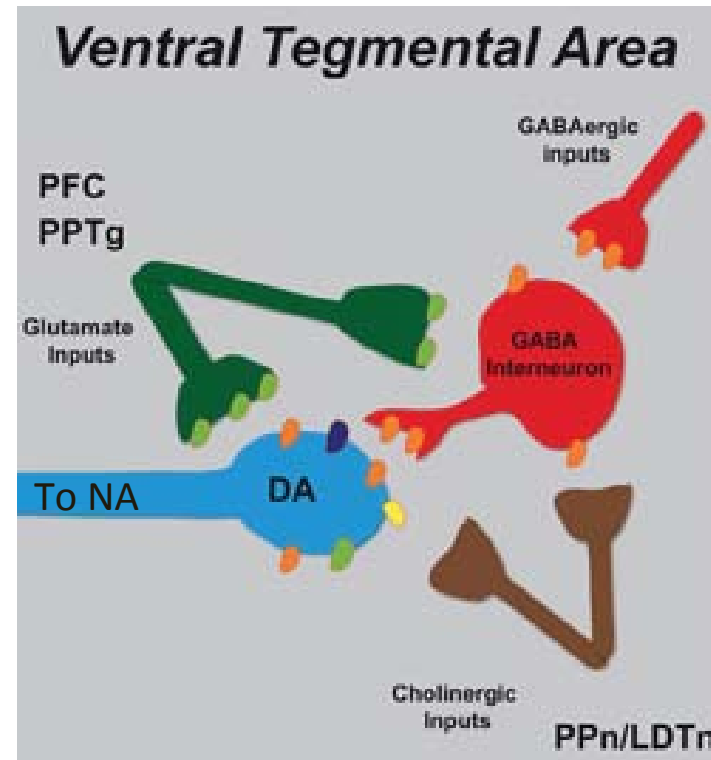
Robinson et al. 2009

- How the DA transients are enhanced?

# VTA circuitry

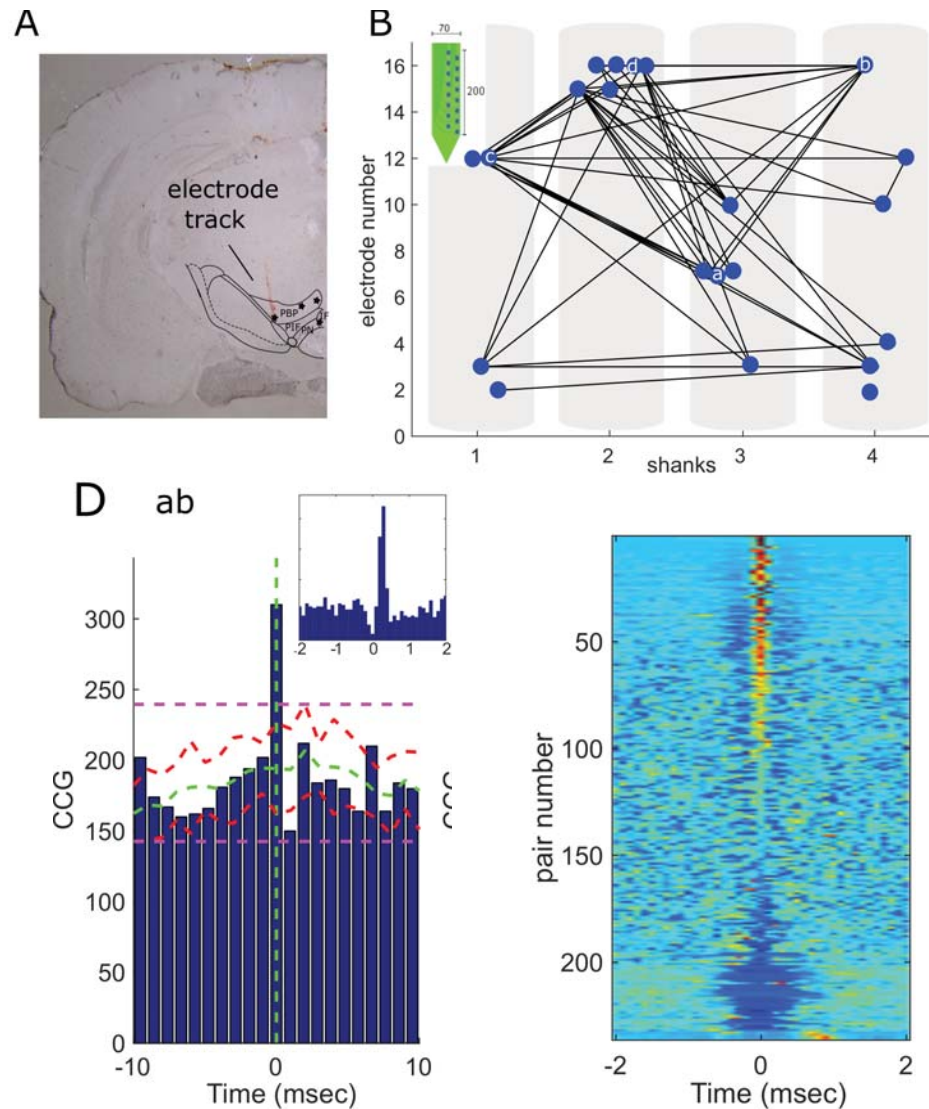
- Inhibitory input – GABA; suppresses electrical activity
- Excitatory input – Glutamate (Glu) enhances electrical activity
- Transient excitation evokes bursts, which cause the dopamine transients

Feduccia et al. 2012



Zakharov et al. 2016

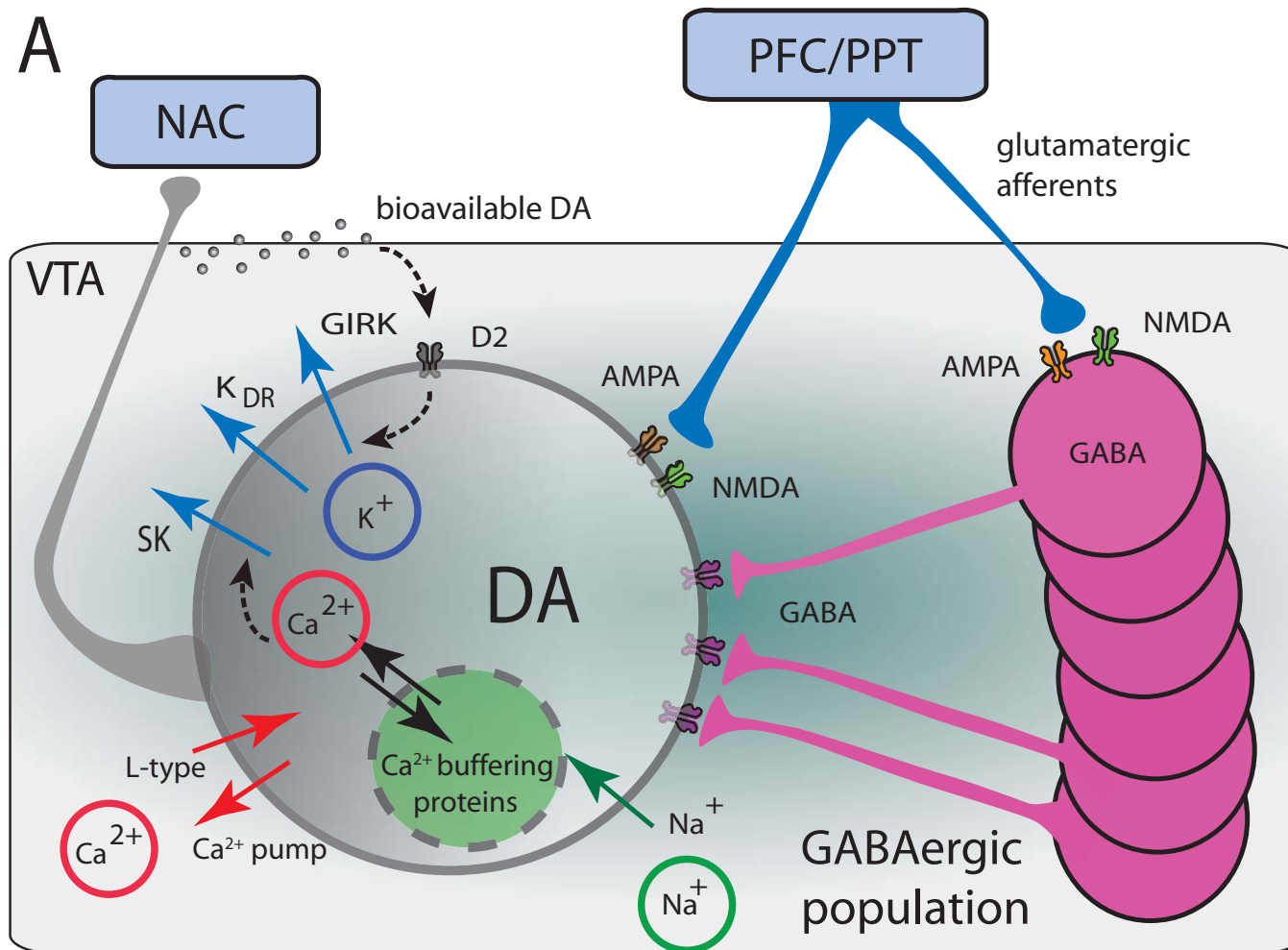
# VTA GABA synchronization



- GABA neurons are synchronized across shanks and electrodes
- Spikes are correlated within 1 msec, but slightly off zero
- About 30% of all GABA neurons are synchronized

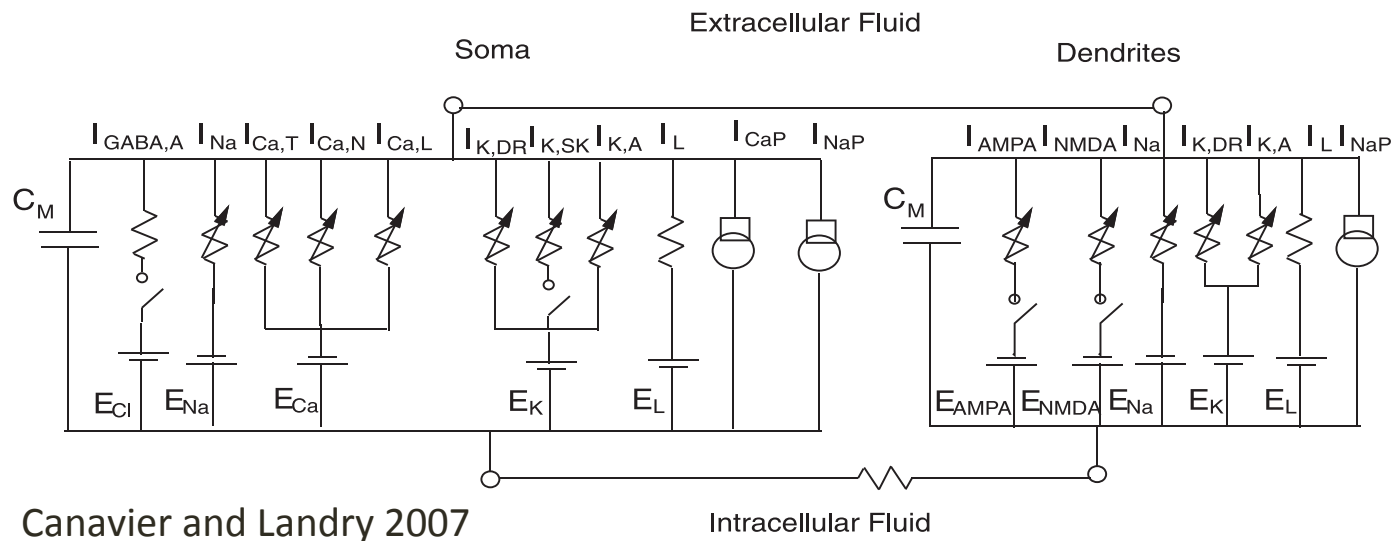
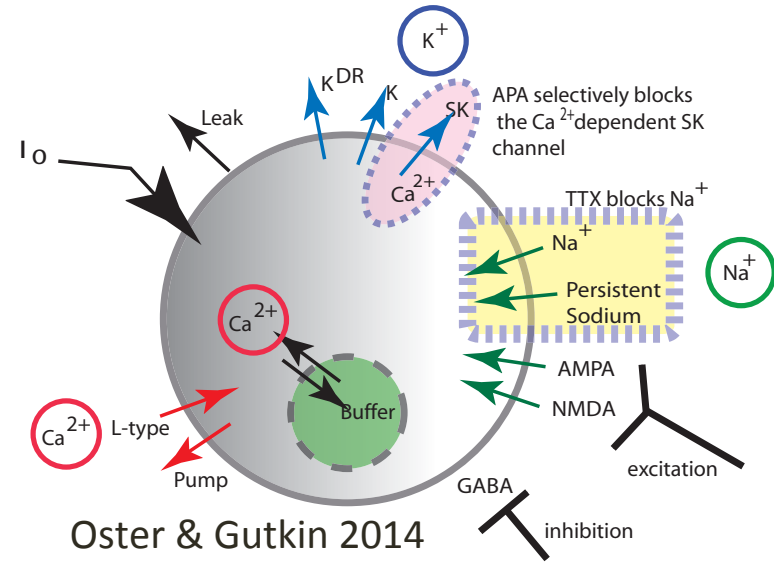
Myroshnychenko et al. in prep.  
Morozova et al. 2016

# The role of the GABA population

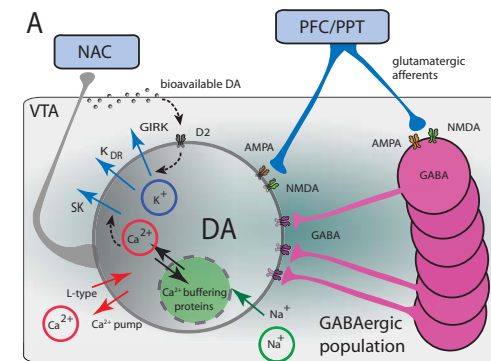
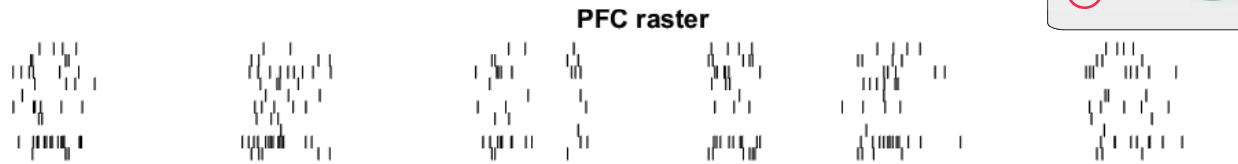


# Conductance-based modeling

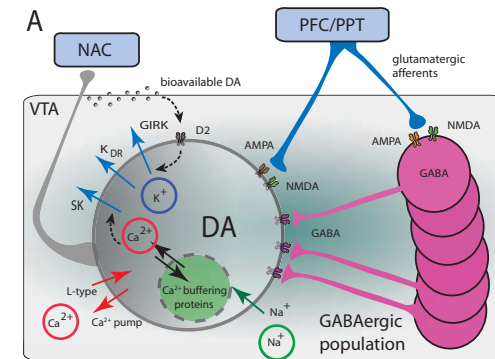
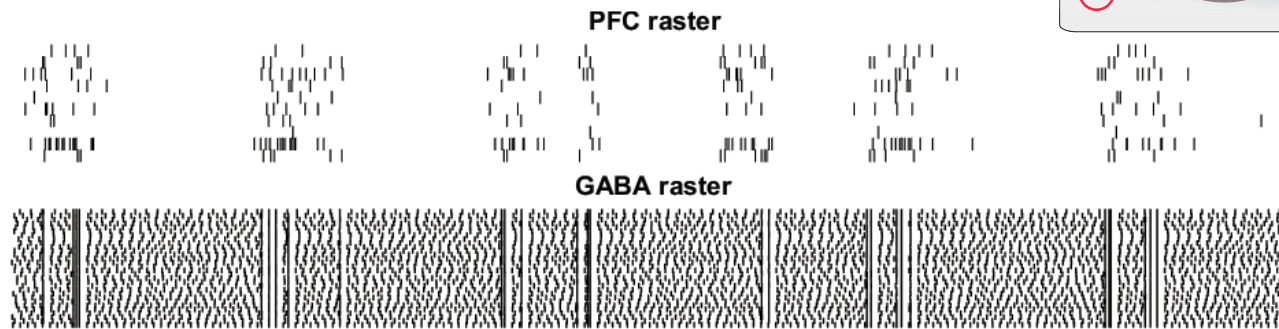
- Hodgkin and Huxley 1952
  - Electrical circuit formalism
- $$C_m \frac{dv}{dt} = \sum_j I_j$$
- Specific for DA/GABA neuron



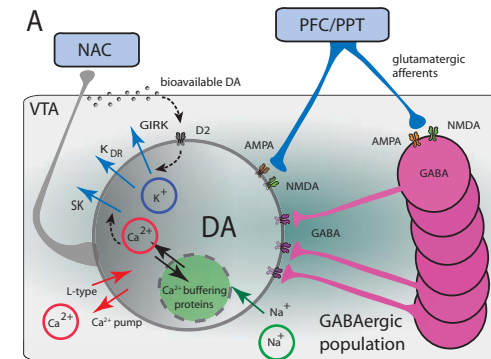
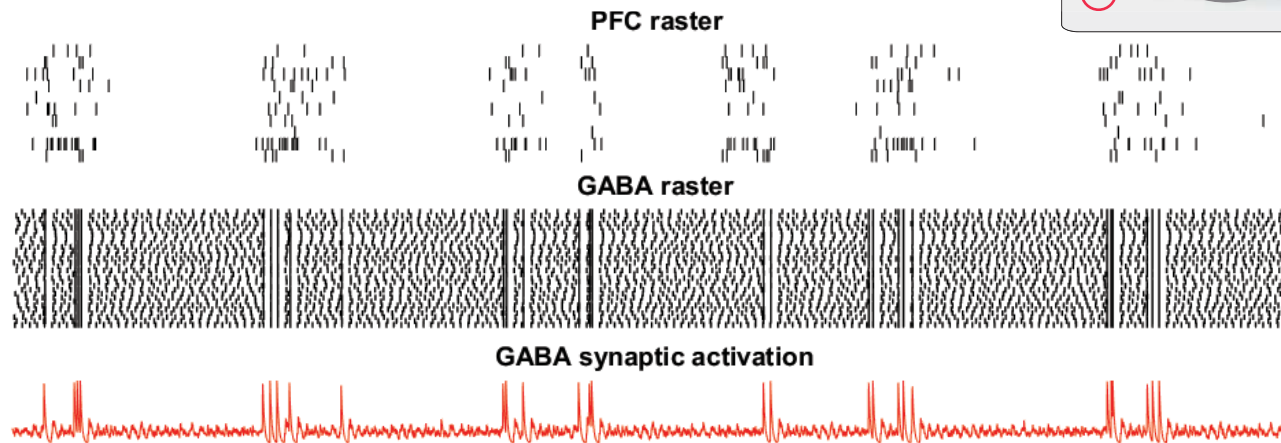
# Synchronized GABA increases bursting



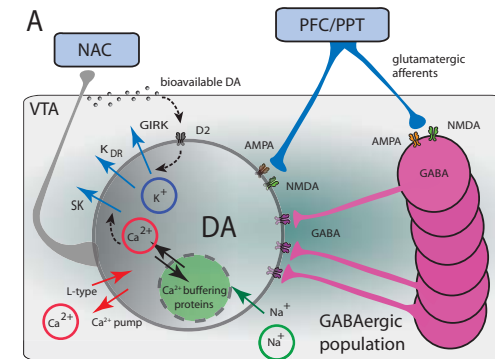
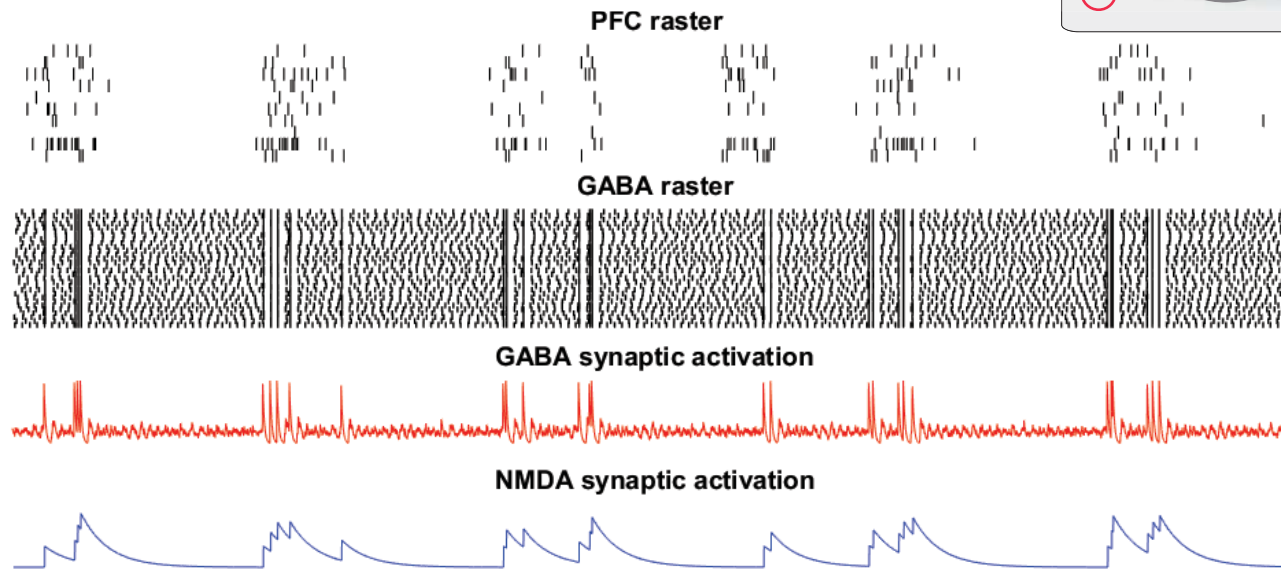
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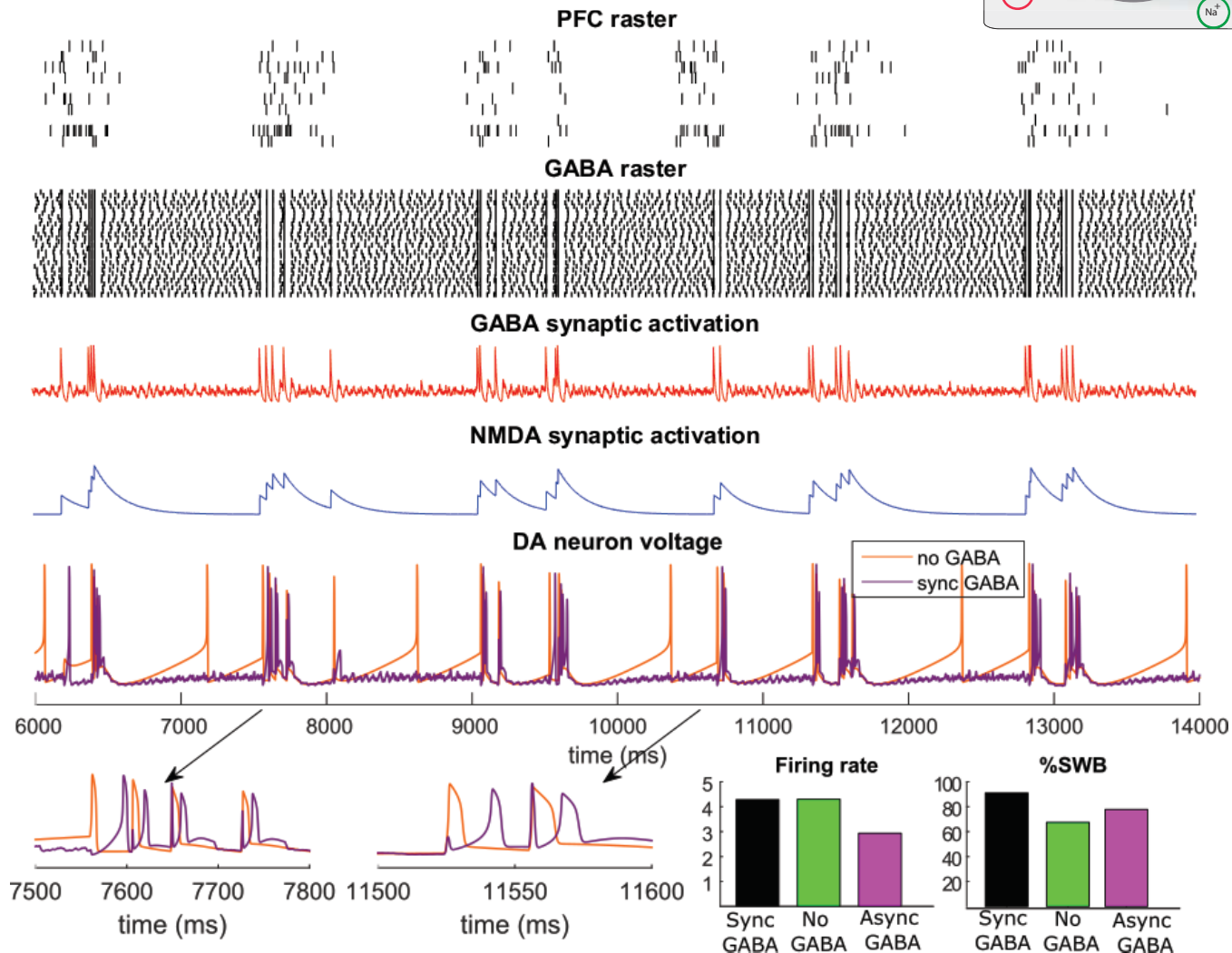
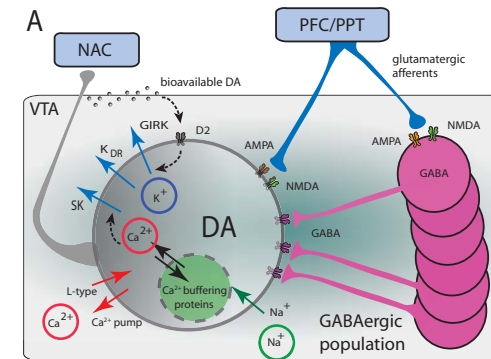
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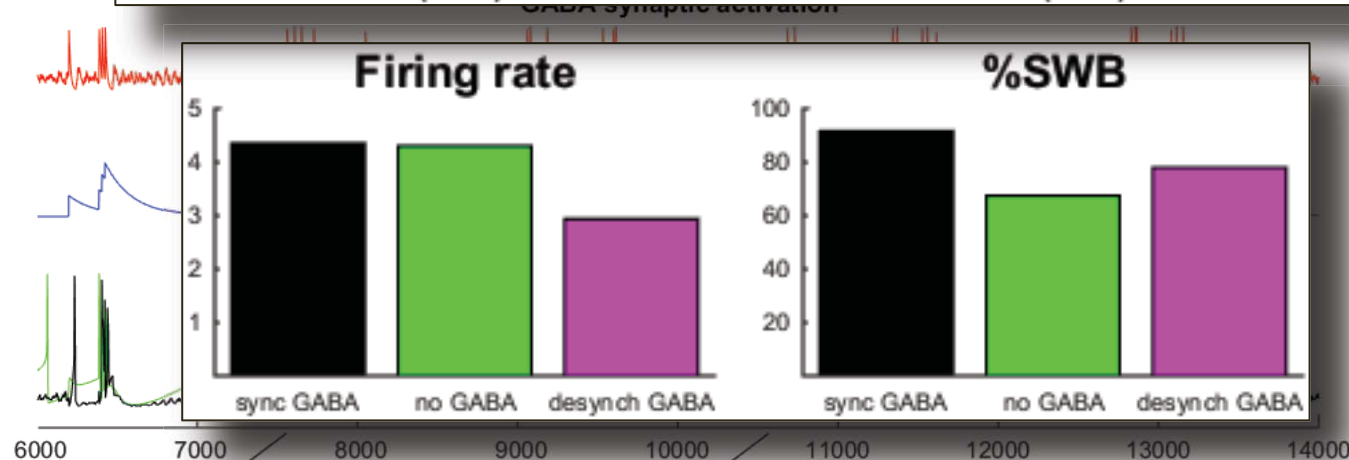
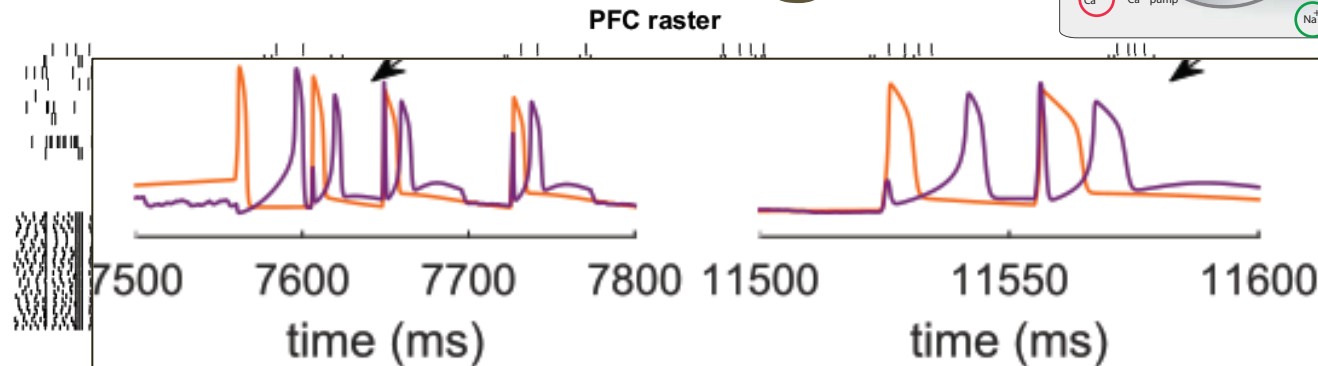
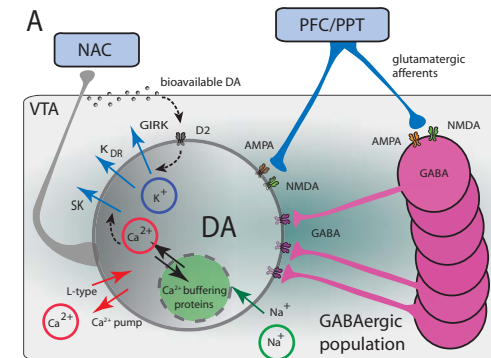


# Synchronized GABA increases bursting



Morozova et al. 2016

# Synchronized GABA increases bursting



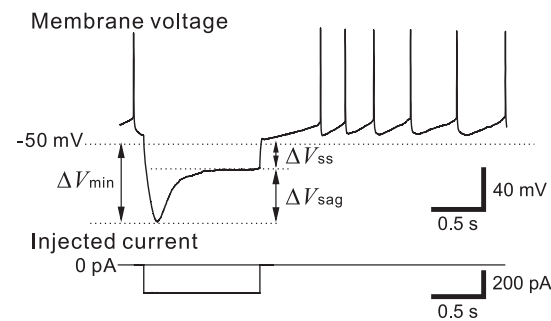
- Variable synchrony of the GABA population switches the system from GABA inhibiting to GABA enhancing bursting

# How EtOH enhances DA transients?

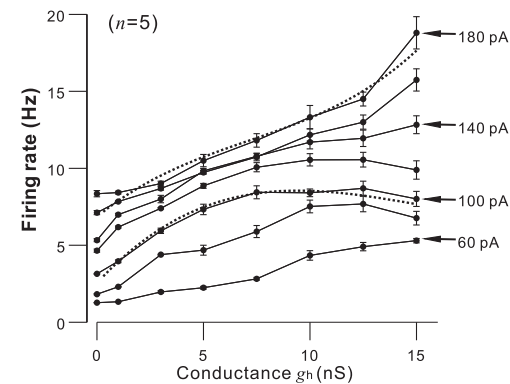


# How EtOH enhances DA transients?

- EtOH increases excitability of the DA neuron:
  - Hyperpolarization-activated cationic current  $I_h$  (Okamoto et al. 2006, Brodie and Appel 1998, Tateno et al. 2011)

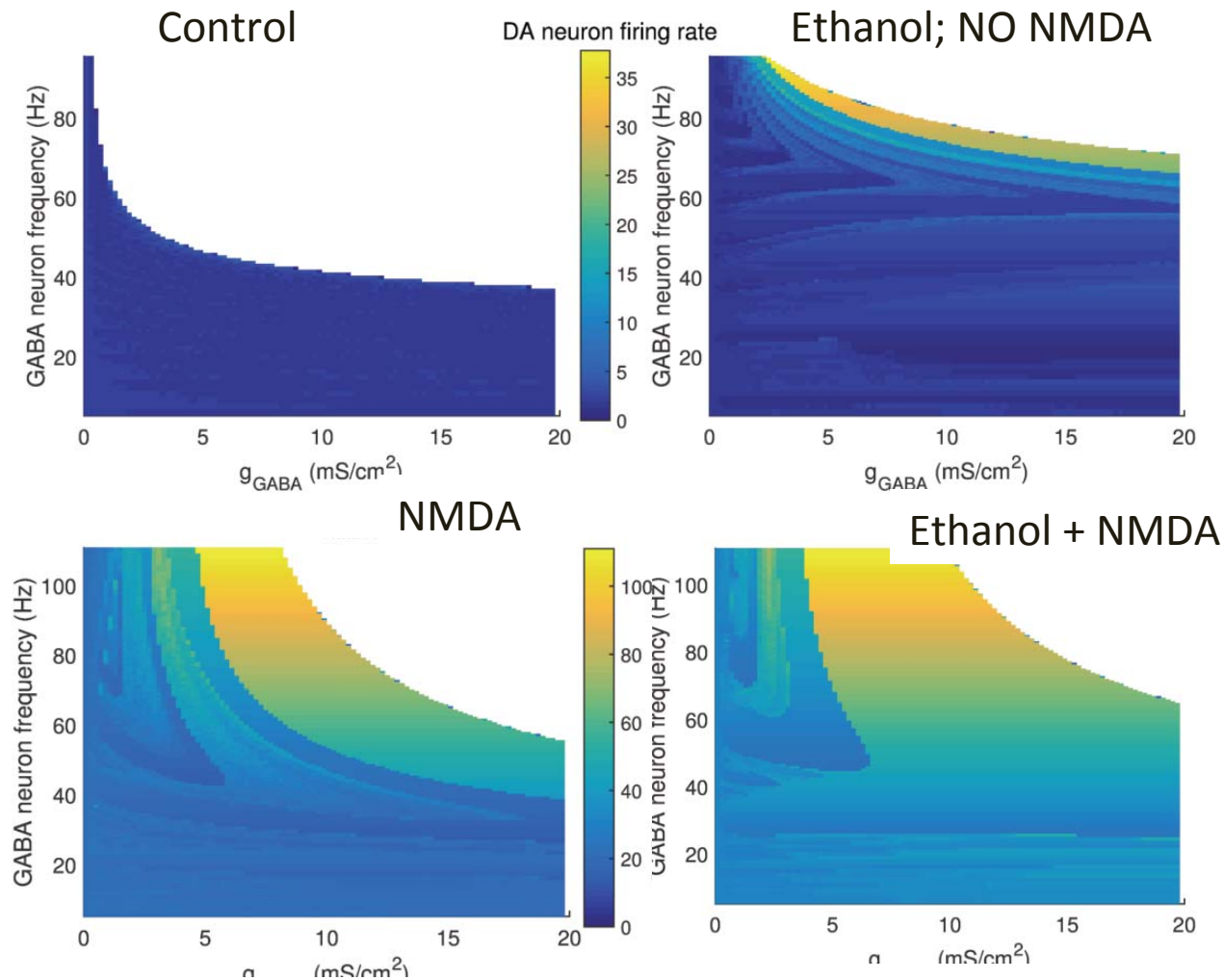


Tateno et al. 2011

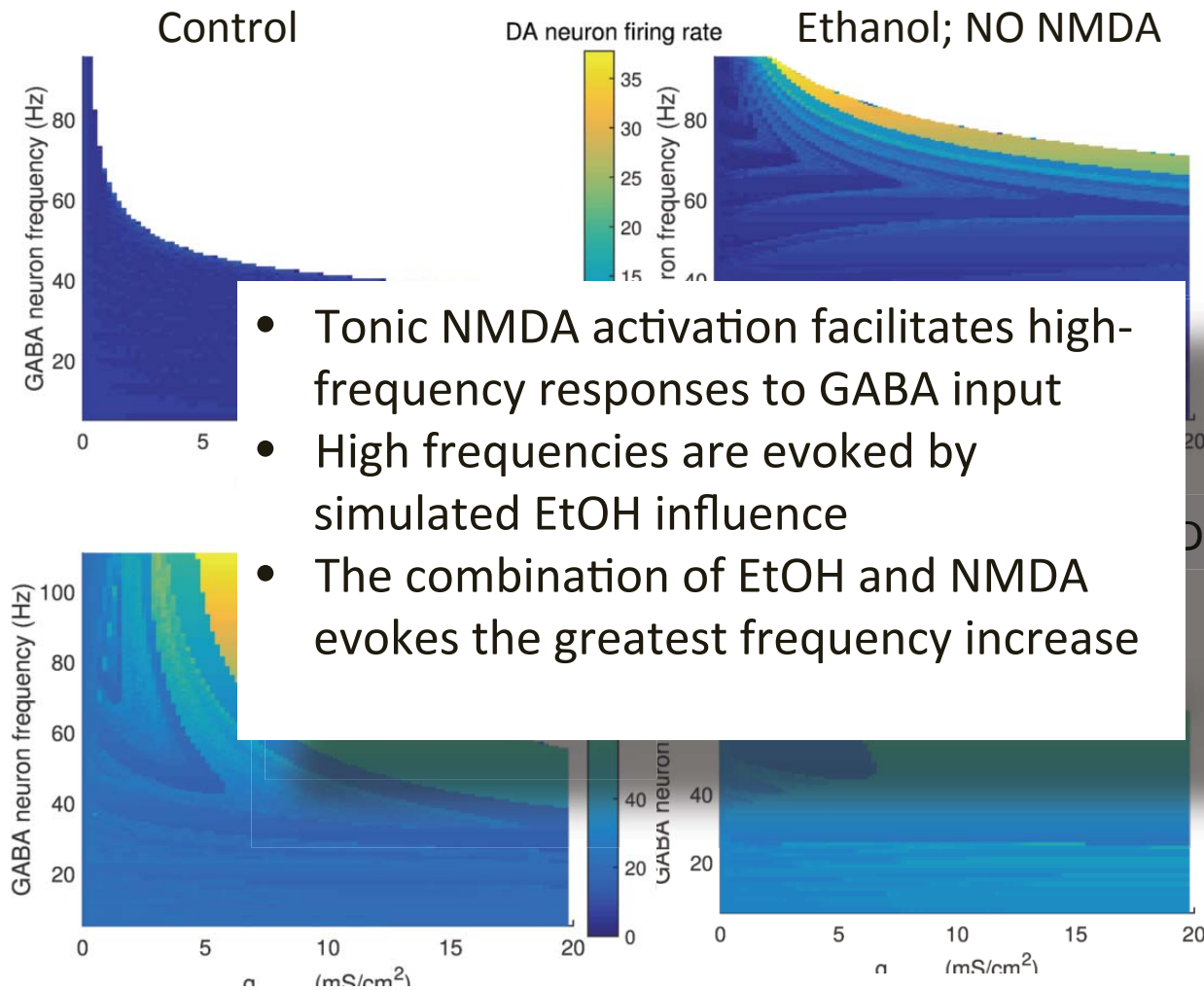


- A-type  $K^+$  current (Melis et al 2007)
- Slow AHP currents (Appel et al. 2003)

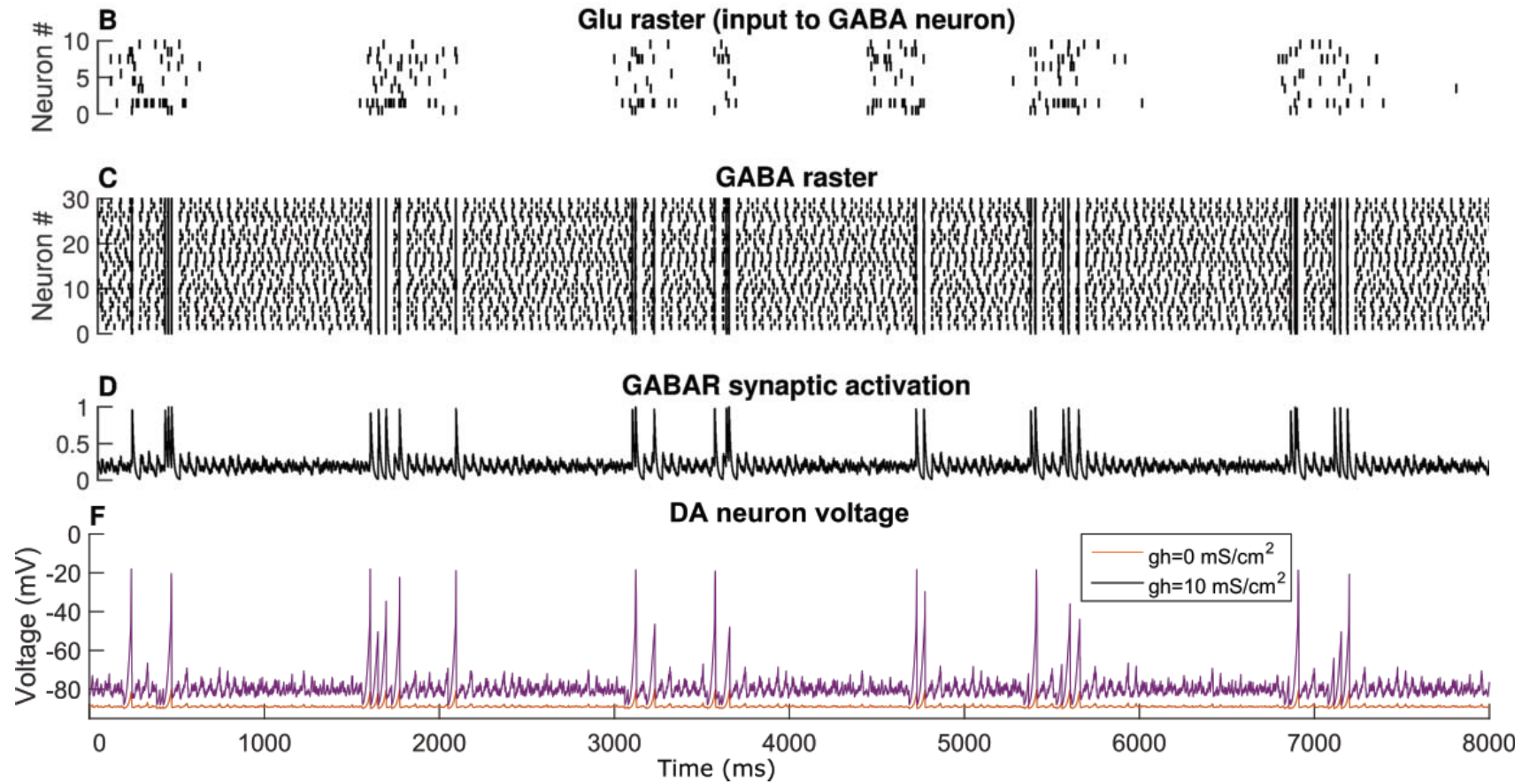
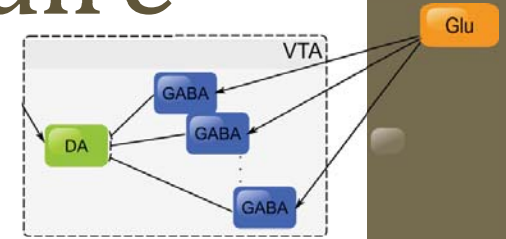
# GABA-induced bursts require no NMDA in EtOH



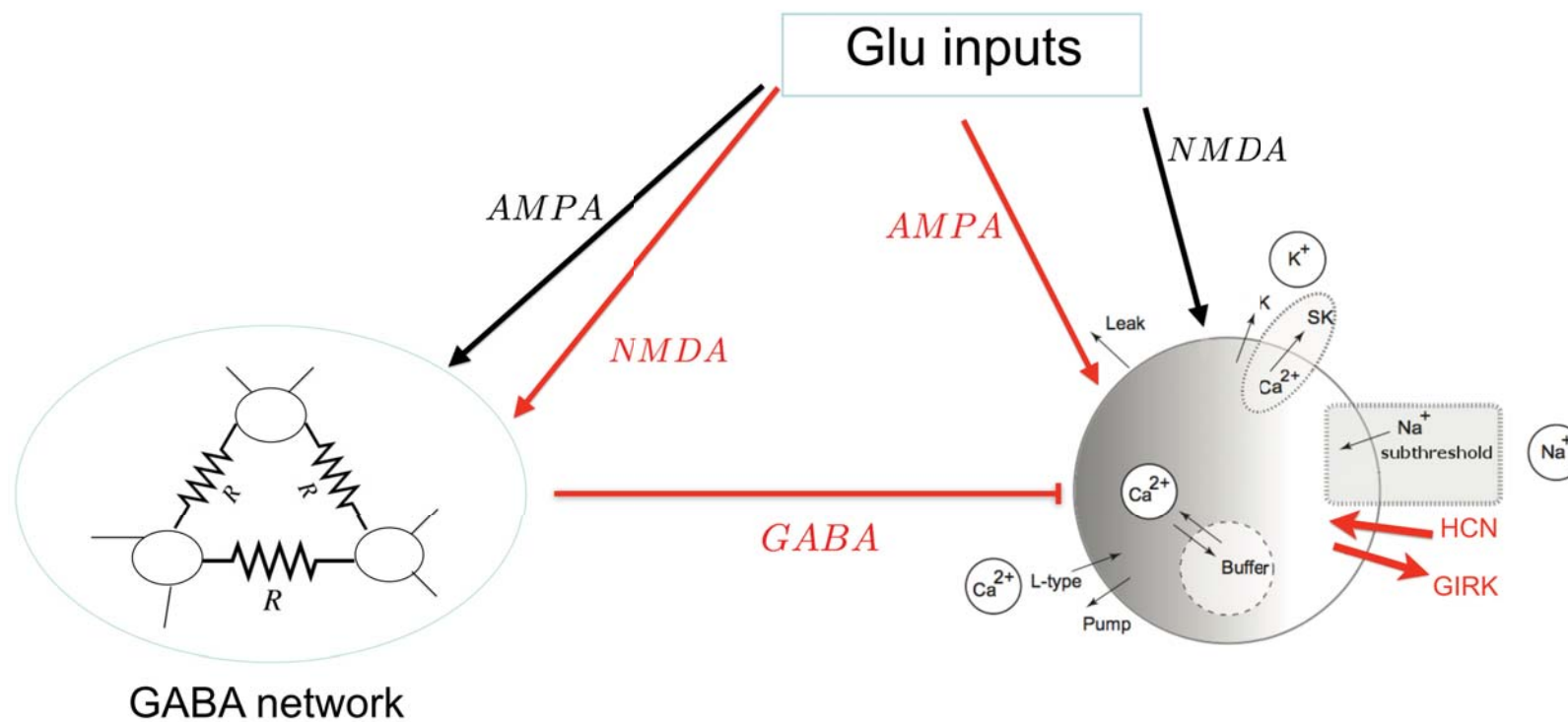
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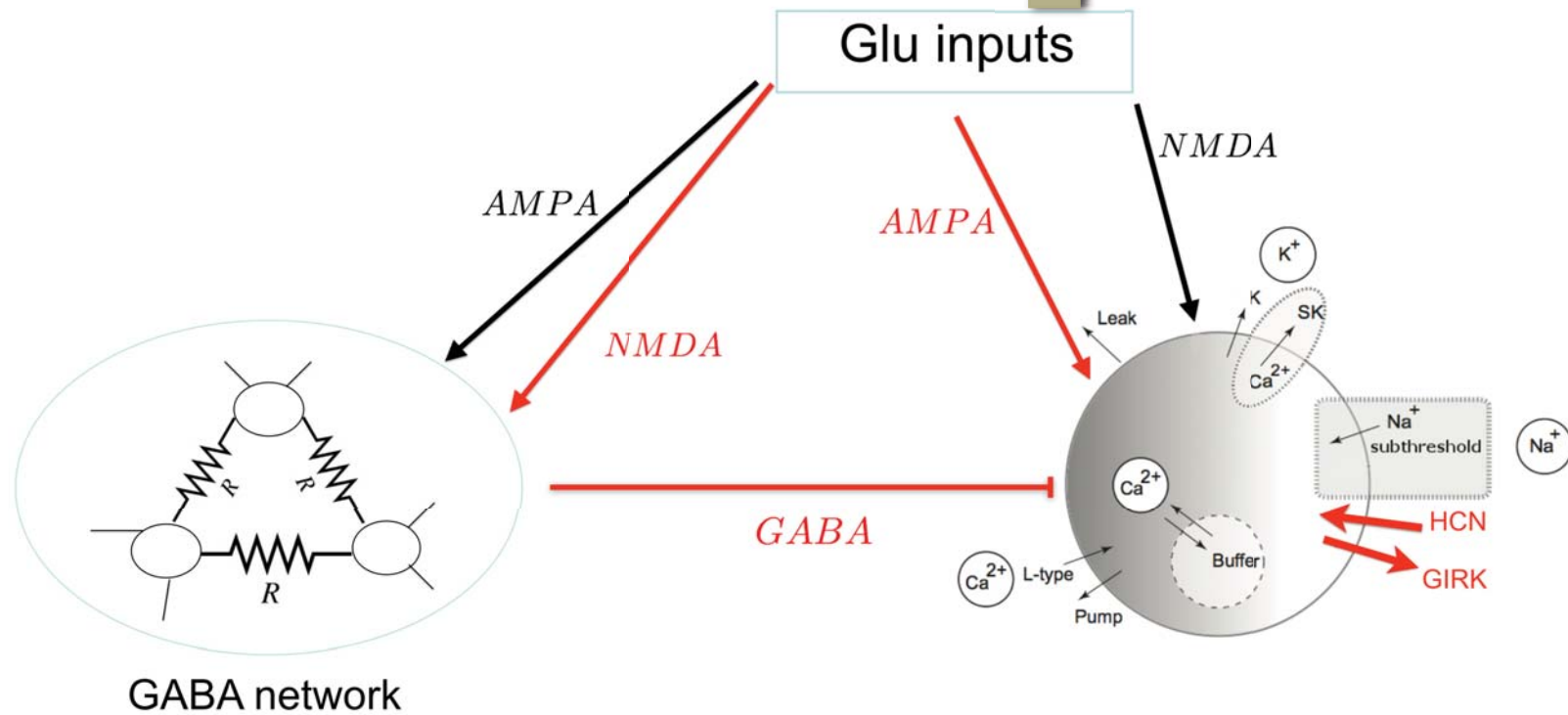
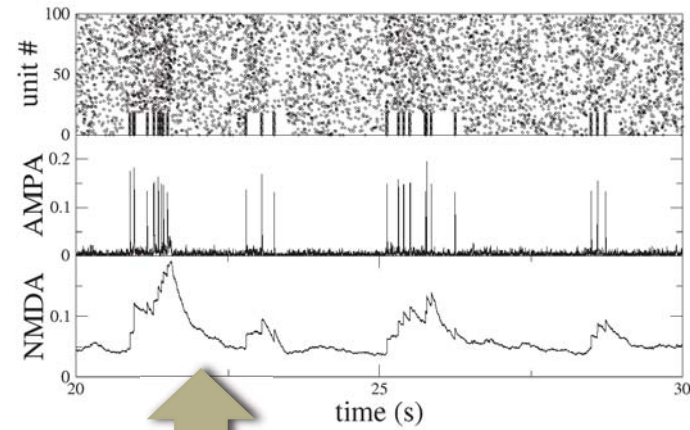


# Ethanol targets



di Volo et al. in prep.

# Ethanol targets

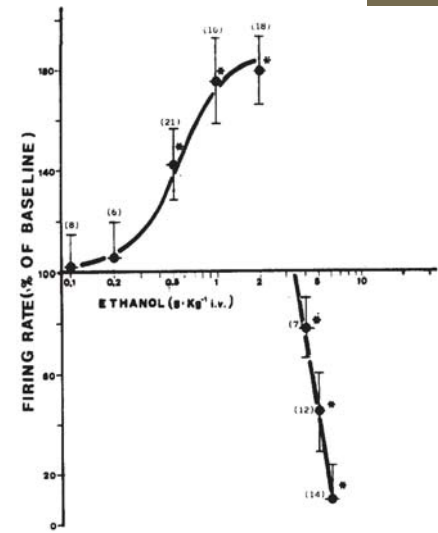


di Volo et al. in prep.

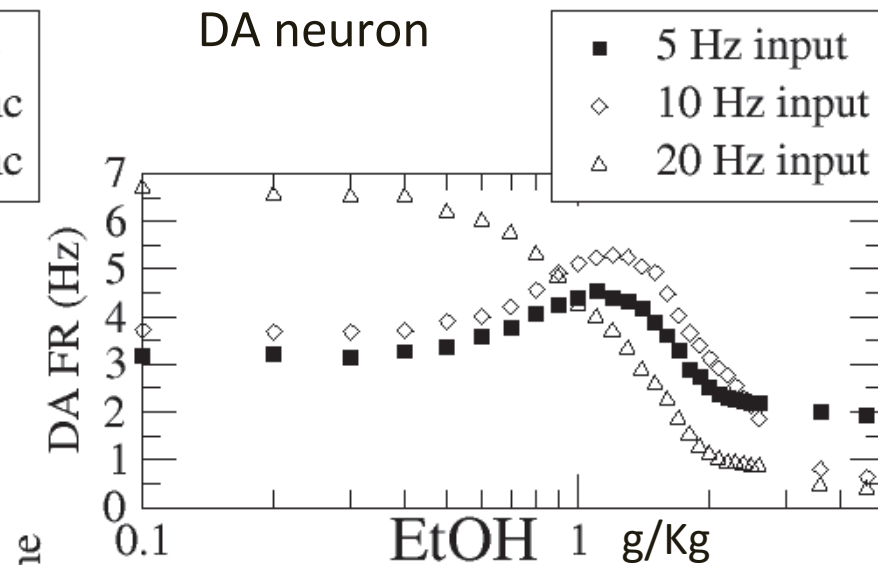
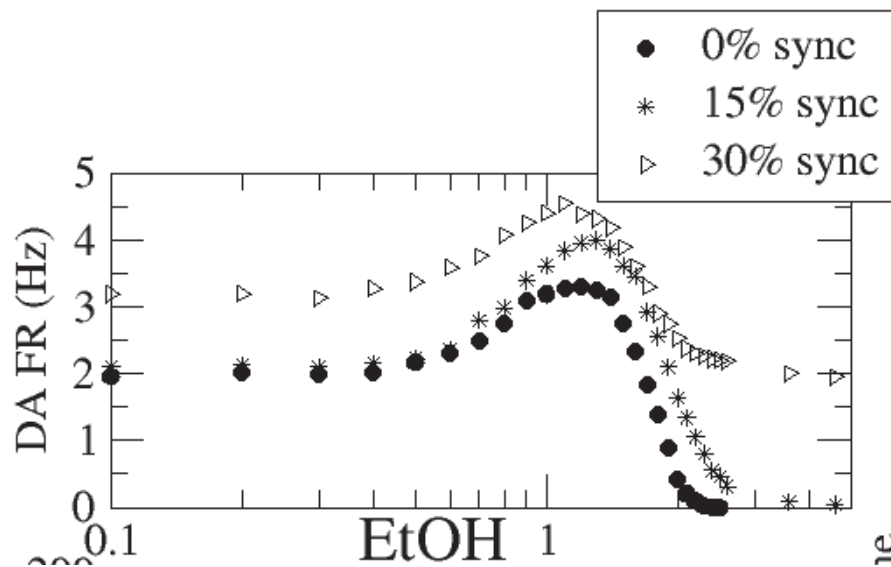
# Ethanol modulation of DA neuron firing

- Both low and high % of synchronized Glu input reduces the relative increase in the DA neuron firing rate below experimentally observed.

- At higher Glu input average frequency EtOH only inhibits the DA neuron



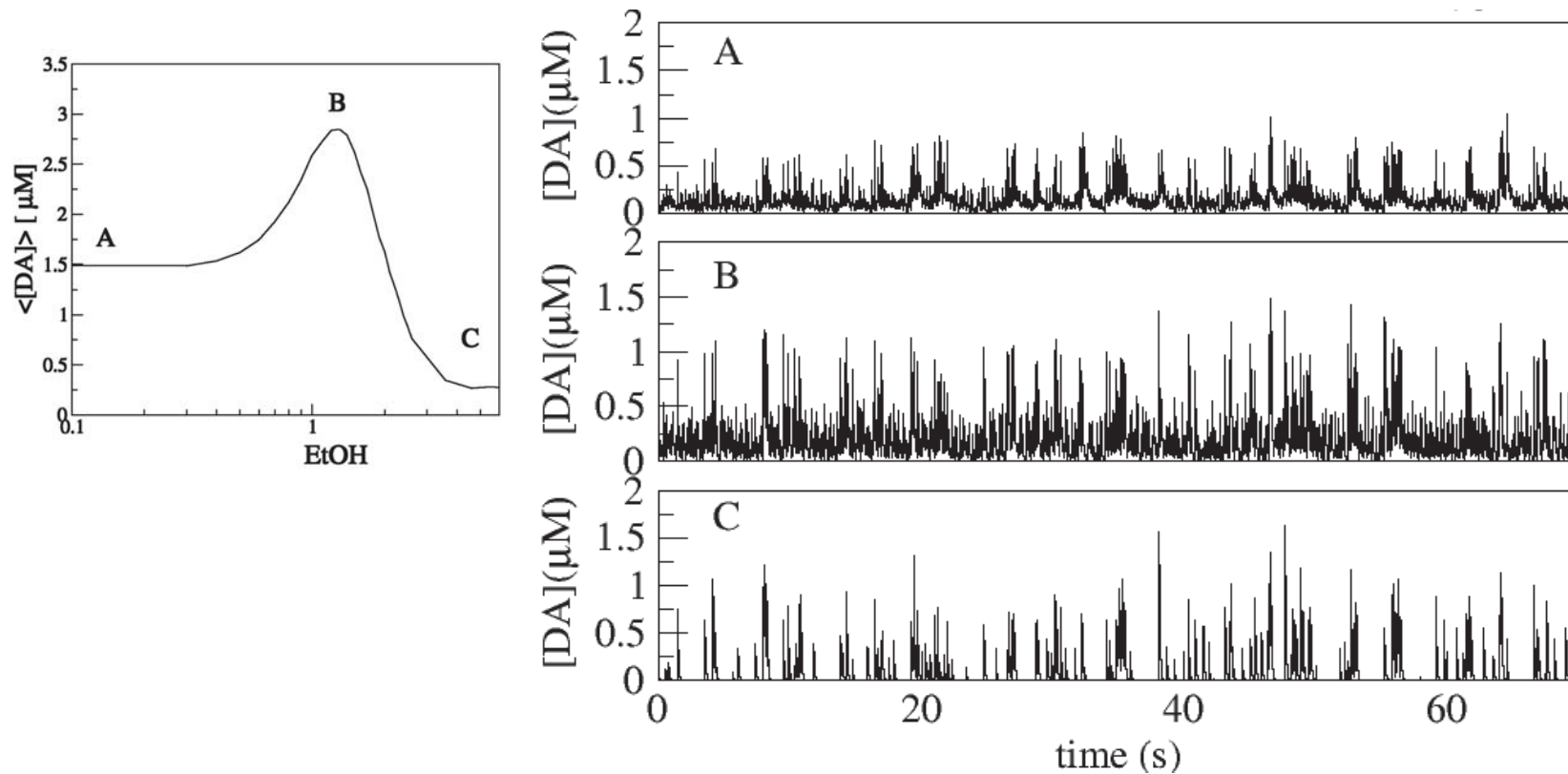
Mereu et al 1984



di Volo et al. in prep.

# Ethanol modulation of DA transients

- DA transients follow the firing pattern of the neuron



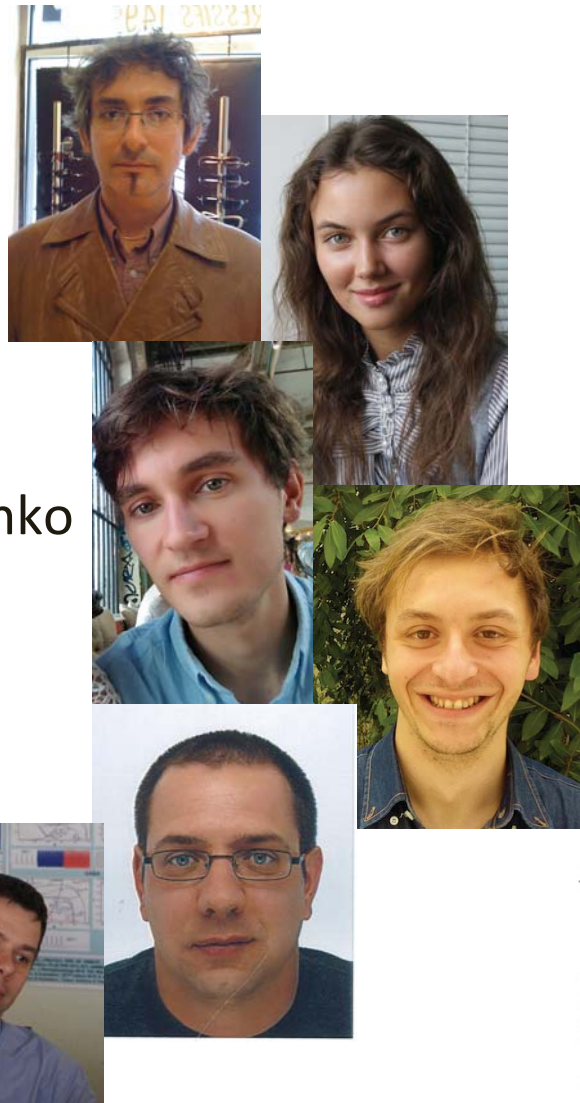
# Summary

- Synchronous input from GABA neurons increases bursting and firing rate of the VTA DA neurons
- Ethanol facilitates DA neuron firing via synchronized GABA inputs
  - Inhibitory inputs (e.g. NAc) gain control of the VTA
- Ethanol influences how the VTA processes Glu inputs:
  - low-frequency Glu input evokes greater DA neuron excitation
- The code will be available after publishing



# Collaborations

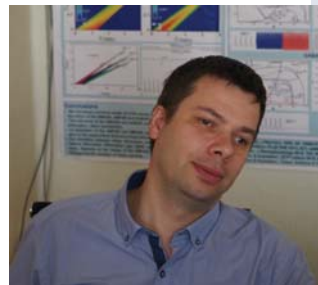
- Christopher Lapish
- Boris Gutkin
- Manuel Mamelli
- Ekaterina Morozova
- Maxim Myroshnichenko
- Matteo di Volo
- Gregory Dumont
- Denis Zakharov

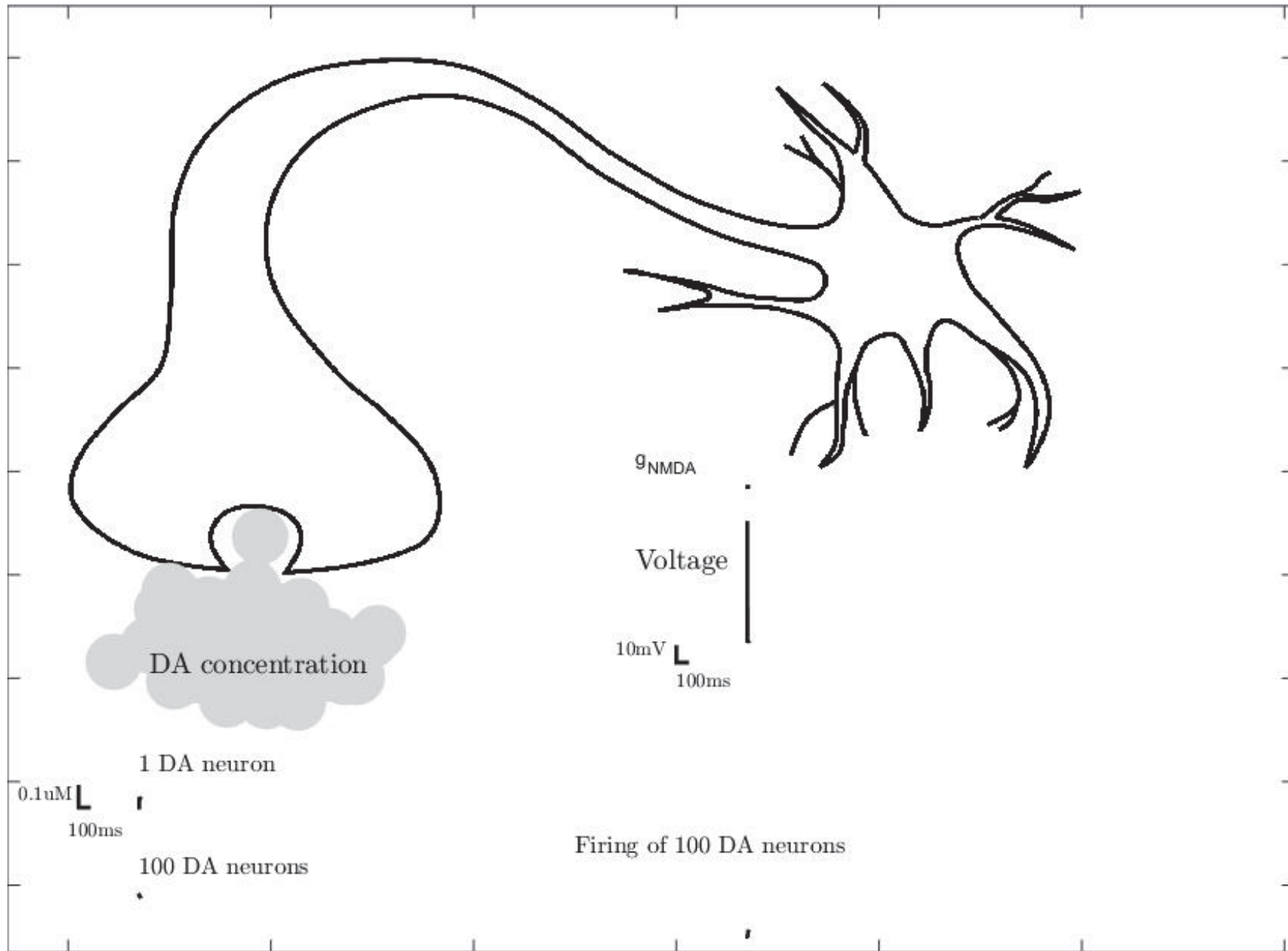


# Collaborations

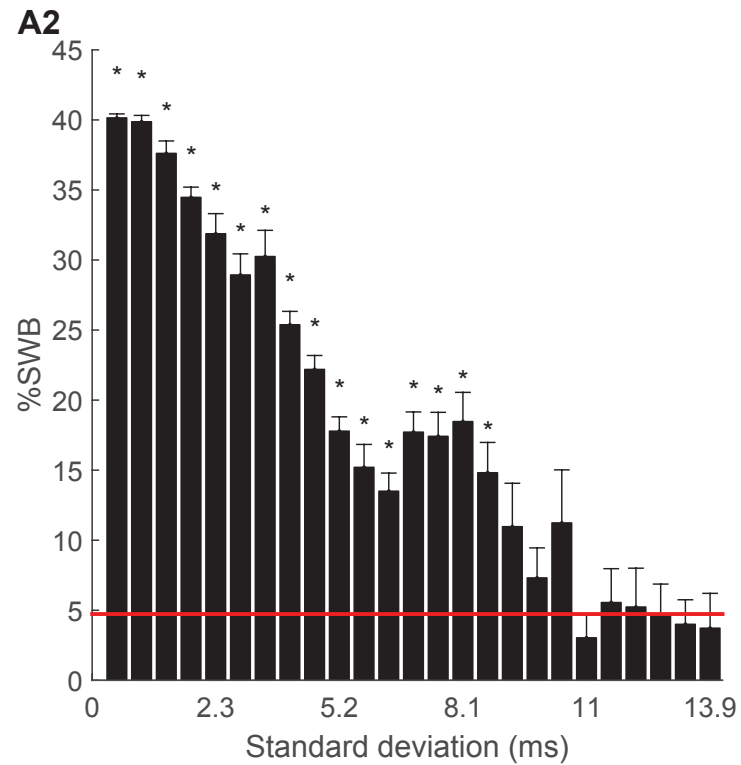
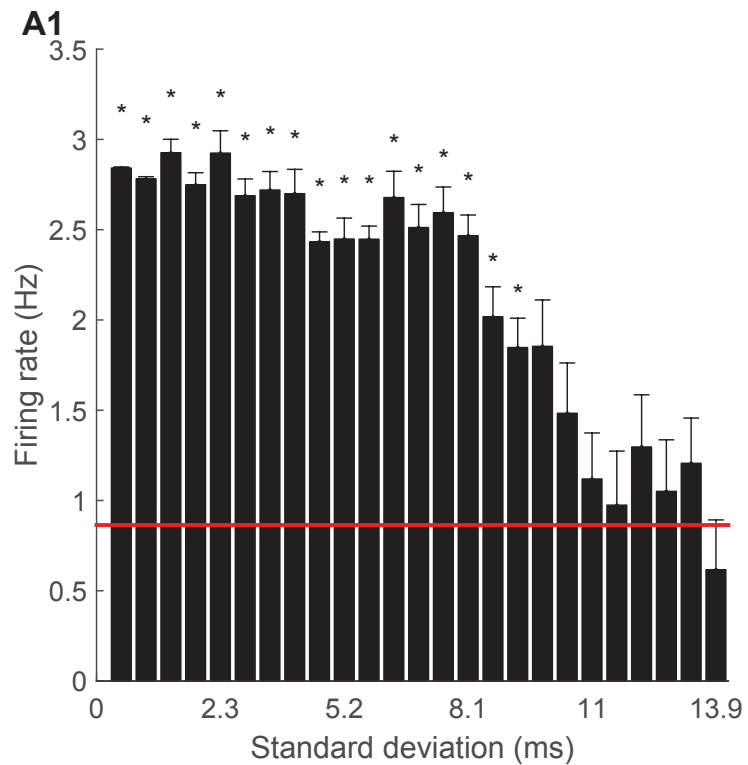
Thank you

- Christopher Lapish
- Boris Gutkin
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- Ekaterina Morozova
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- Matteo di Volo
- Gregory Dumont
- Denis Zakharov



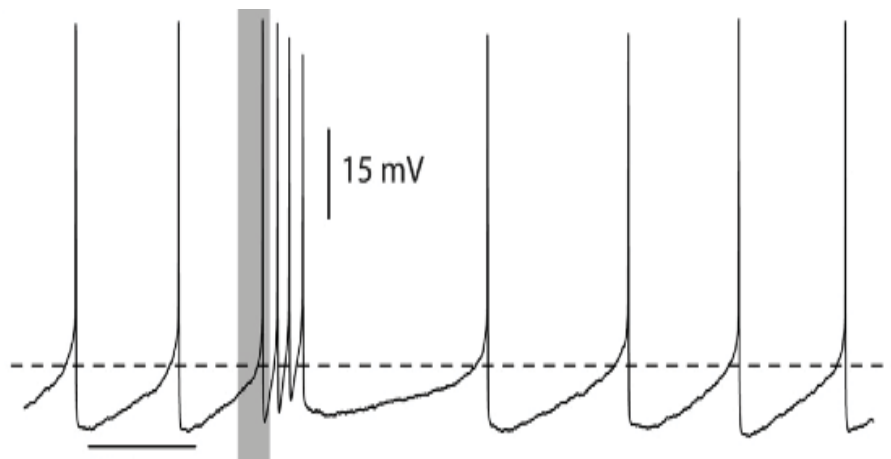


# Precision of the synchronization required

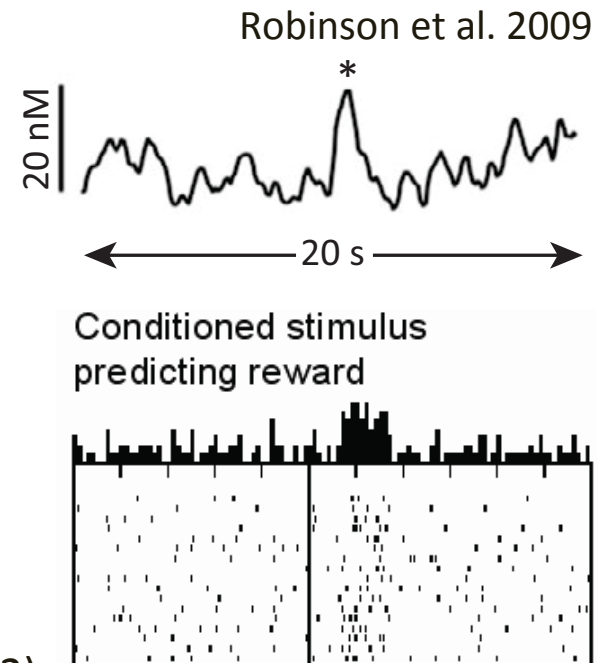


# Dopamine neuron

- Activity patterns: low-frequency firing and high-frequency bursts
- The bursts cause a higher release of DA
- In vivo, bursts are linked to unpredicted reward
- In vitro, bursts are linked to transient synaptic activation

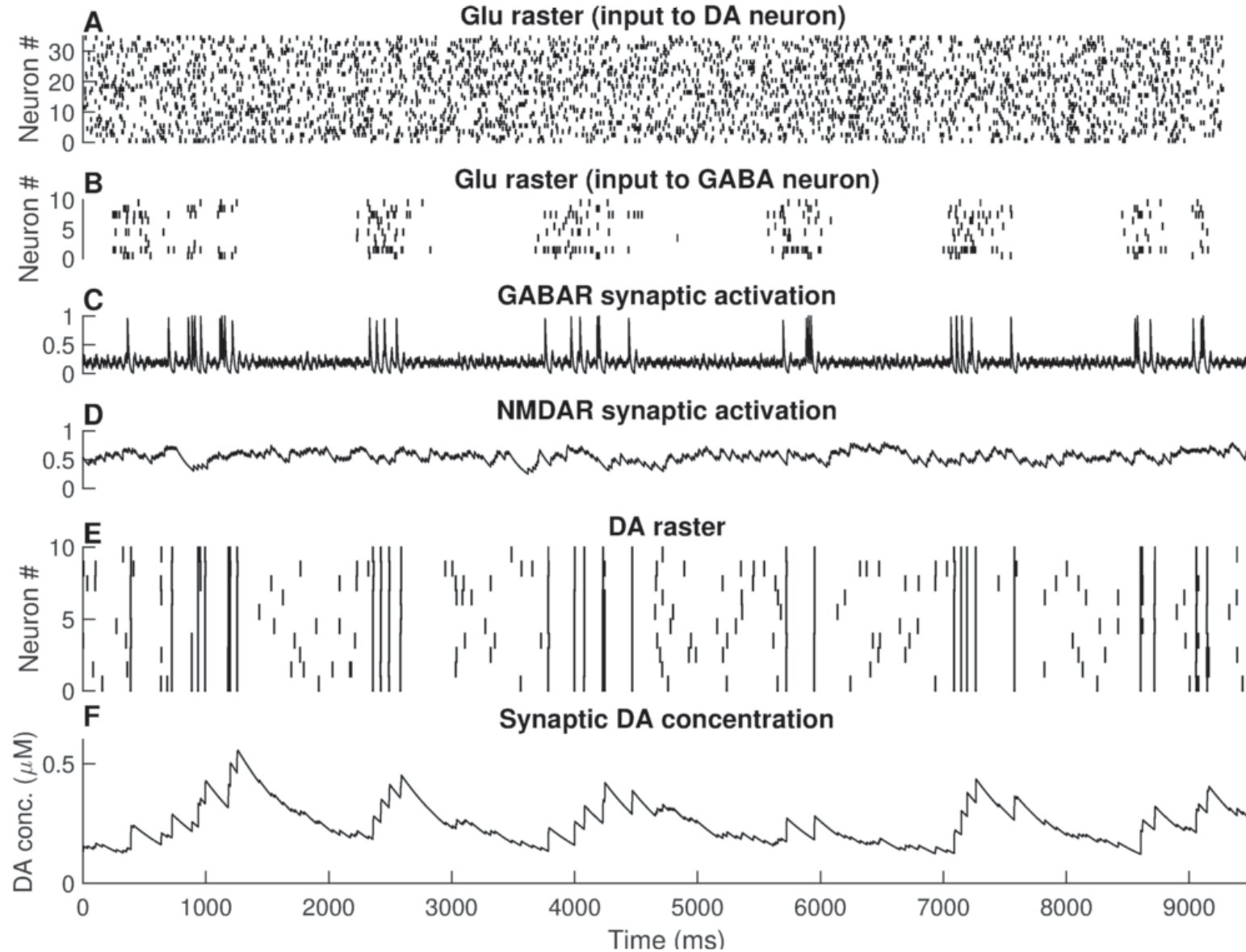
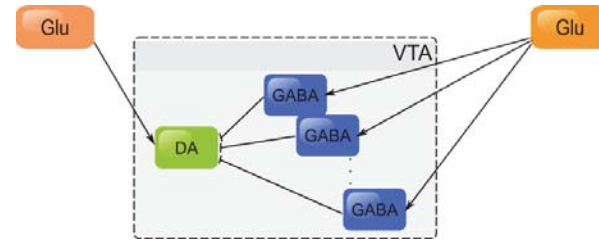


Deister et al. (2009)



Shultz et al. (1992)

# Synchronized GABA input produces DA transients



# Synchrony of GABA population

- Variable synchrony of the GABA population switches the system from GABA inhibiting to GABA enhancing bursting

