Schizophrenia and Amphetamine Abuse: Common Pathophysiological Mechanisms

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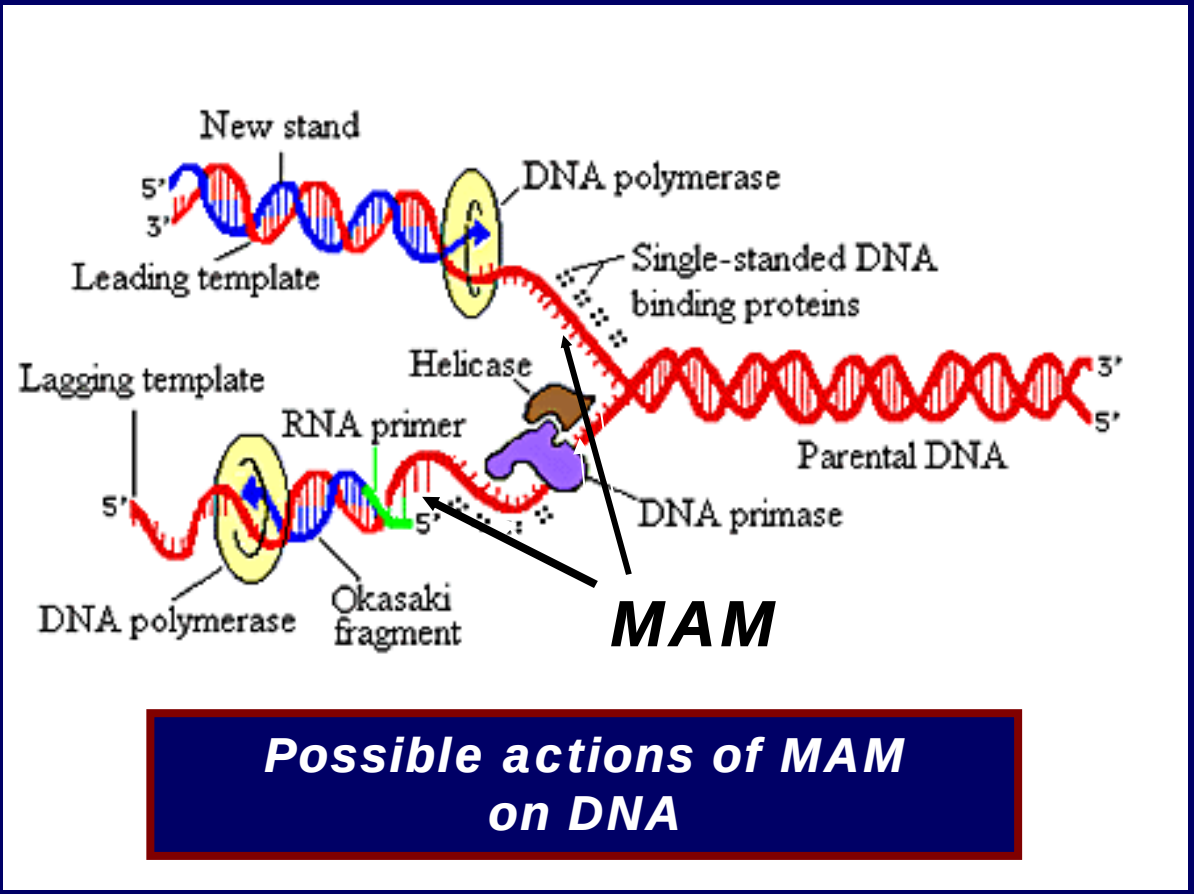
MAM developmental model of schizophrenia: mitotoxin administered to rats at GD 17 and test as adults



Adapted from accessexcellence.org (National Health Museum)

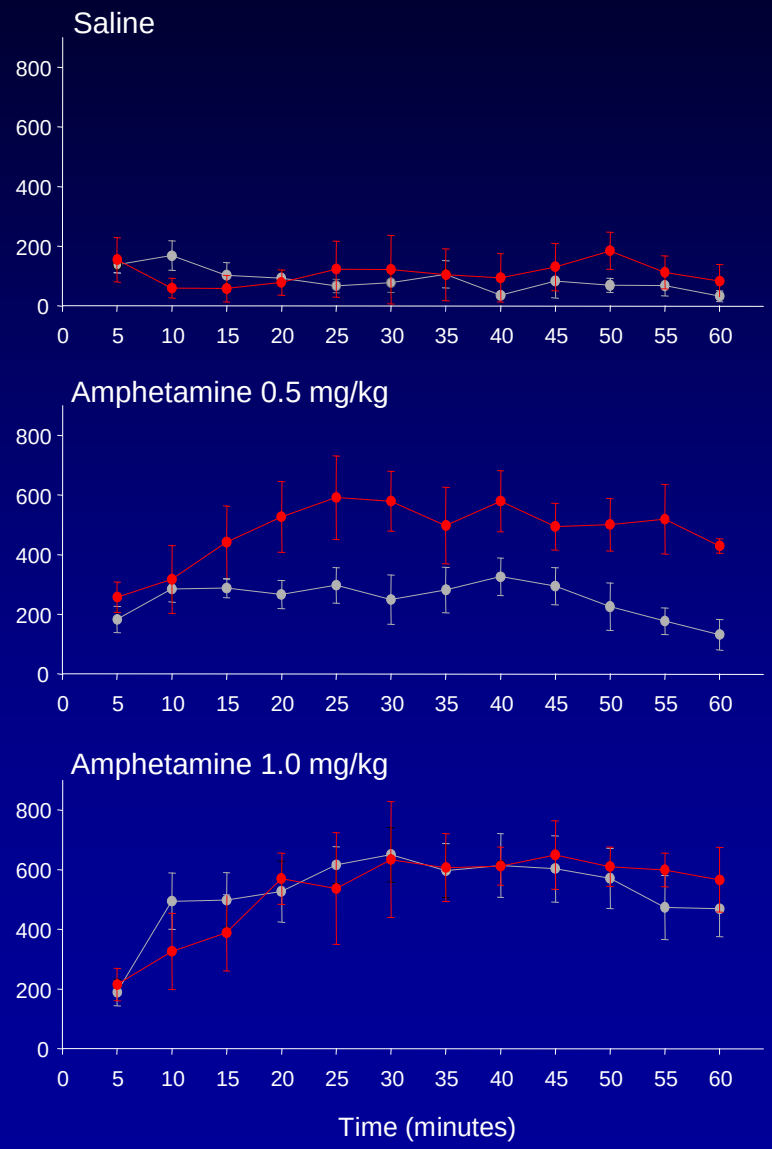
MAM developmental model of schizophrenia

1. Anatomical Evidence:
   - thinning of limbic cortical structures
   - increased cell packing density

2. Behavioral Evidence:
   - impairment in prepulse inhibition of startle
   - impairment in reversal learning

3. Pharmacological Evidence:
   - increased response to PCP
   - increased locomotion to amphetamine in adult
   - no difference in response to amphetamine in prepubertal stage

Augmented Response to Amphetamine In Post-Pubertal MAM-Treated Rats



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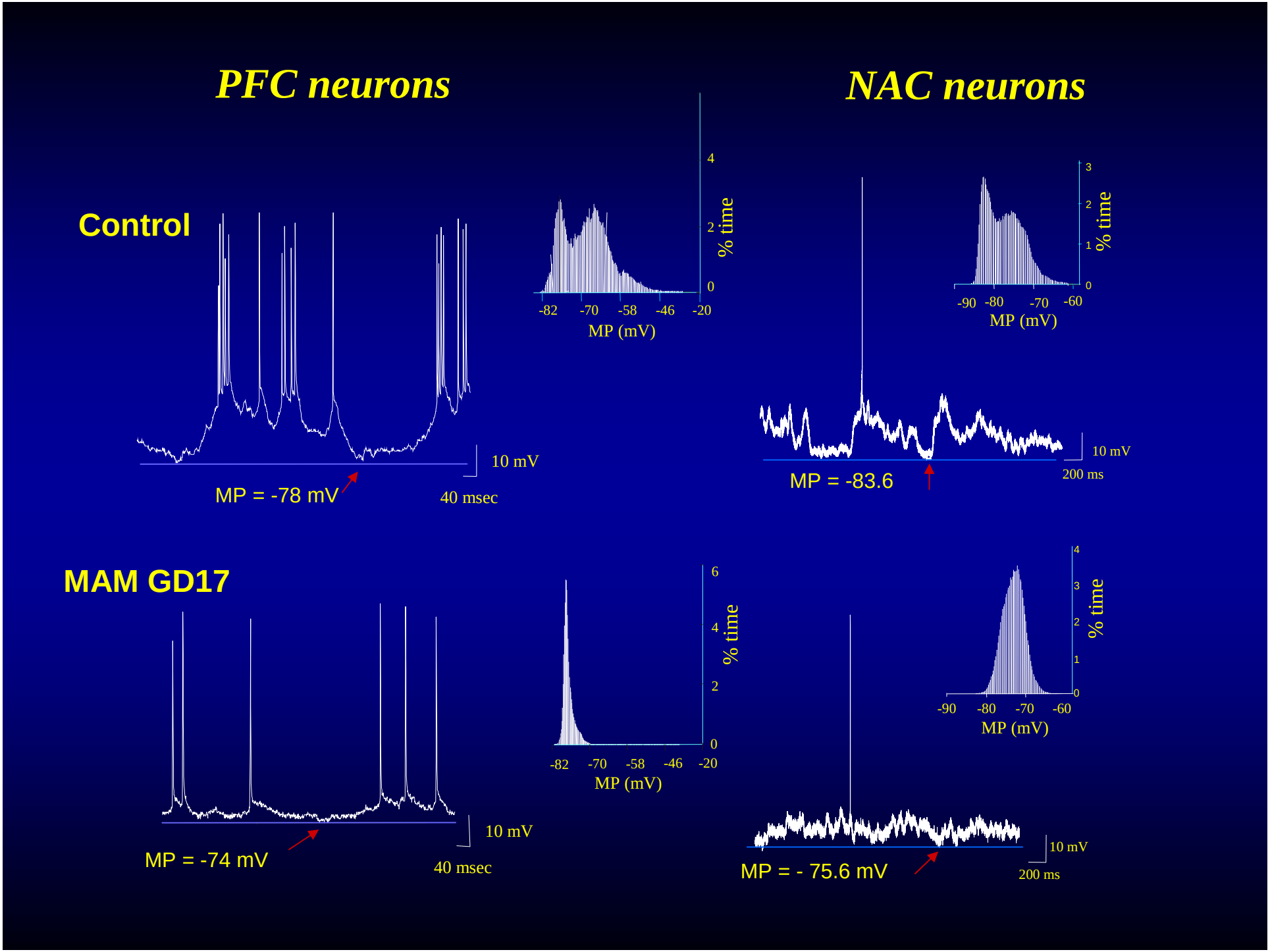
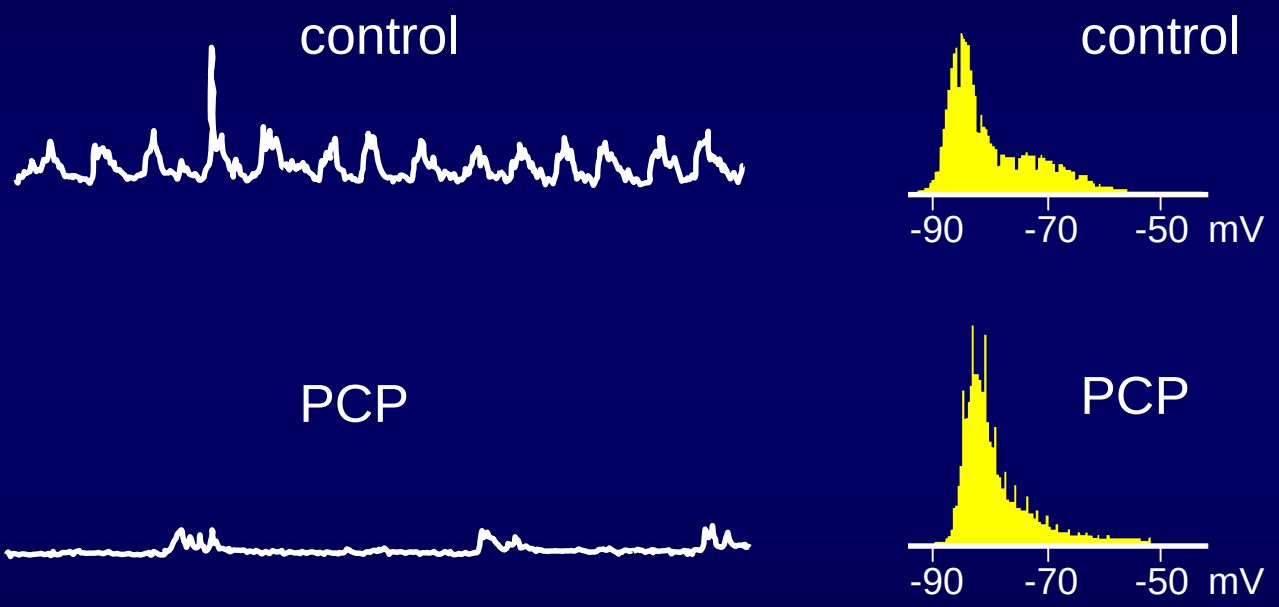
Compare electrophysiological properties of neurons in controls versus the MAM model


PFC neurons
NAC neurons
Control
MAM GD17
% time
MP (mV)
-82 -70 -58 -46 -20
-90 -80 -70 -60
10 mV
40 msec
200 ms
MP = -78 mV
MP = -83.6
MP = -74 mV
MP = - 75.6 mV

Disruption of hippocampal gating of accumbens bistable states is also observed in the PCP model of schizophrenia



Bistable states are controlled by hippocampal afferents to the accumbens, and are disrupted in models of schizophrenia

Conclusion:

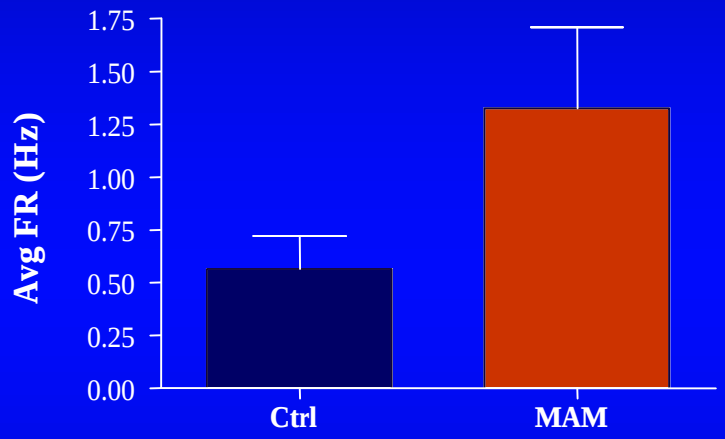
In the MAM model of schizophrenia, there is a disruption of hippocampal gating and a hyper-responsivity of the dopamine system similar to that observed in schizophrenia patients.

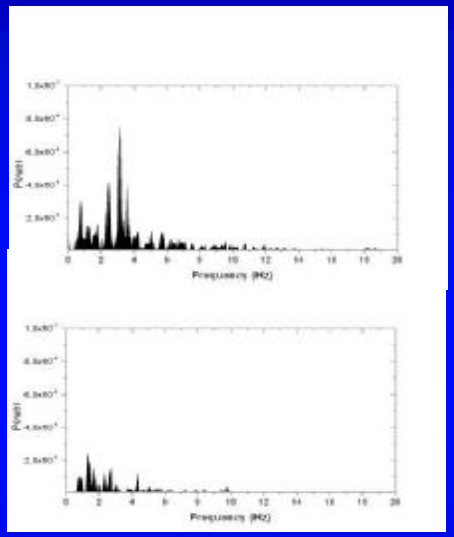
Dopamine hyper-responsivity is suggested to underlie the psychotic state in schizophrenia

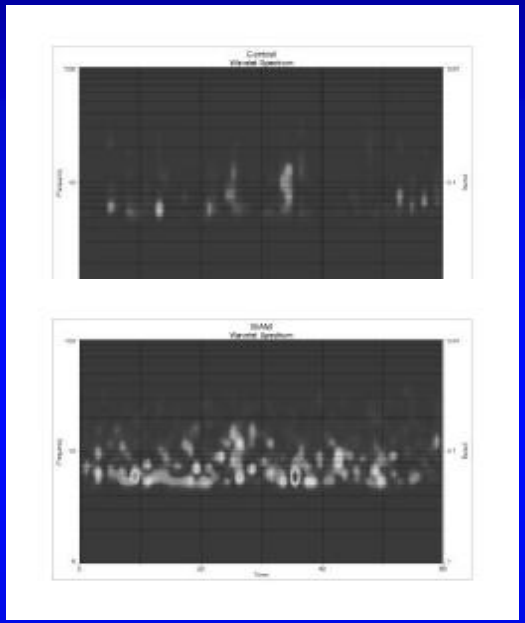
Emerging evidence suggests that hyperactivity in the hippocampus may be related to the psychotic state.

What is the state of the ventral hippocampus in the MAM-treated rat?

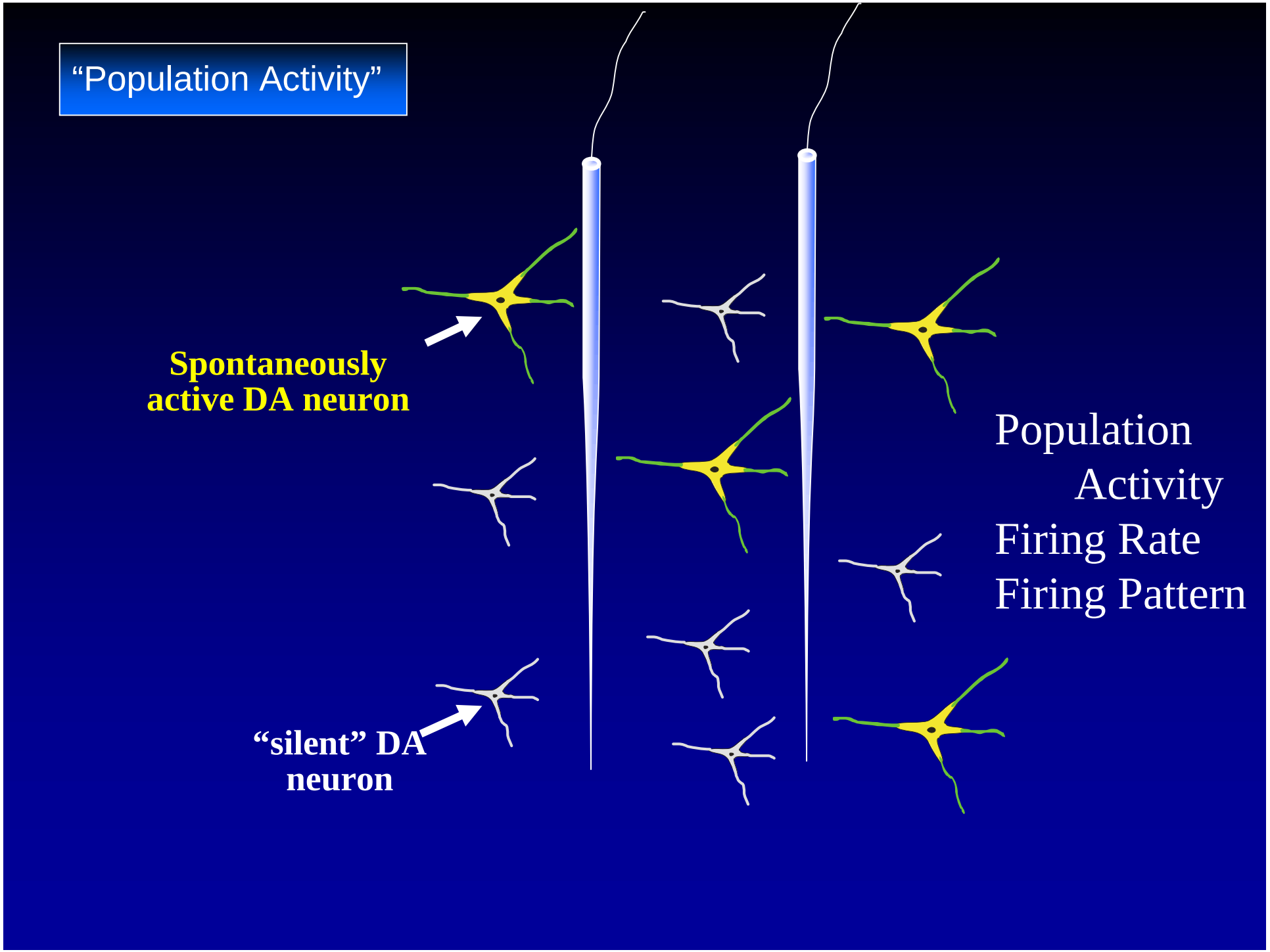
Hippocampal Activity in MAM-treated Rats



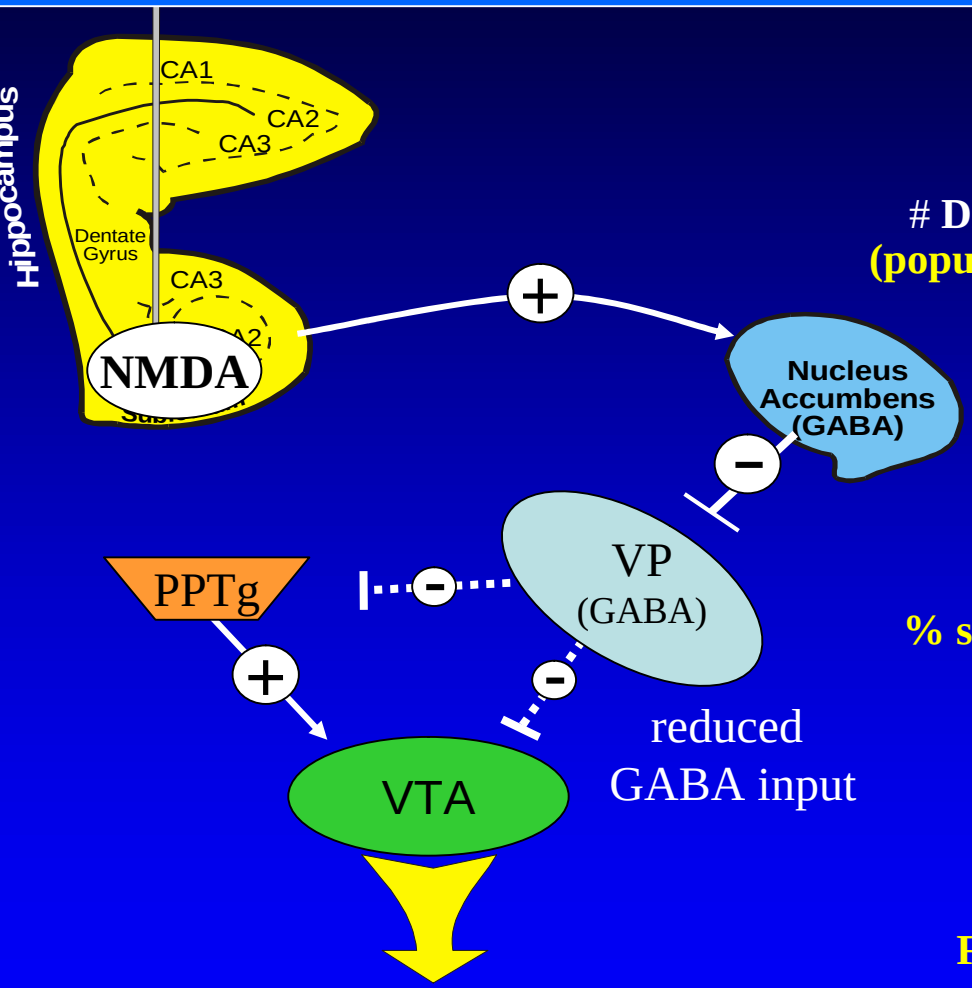




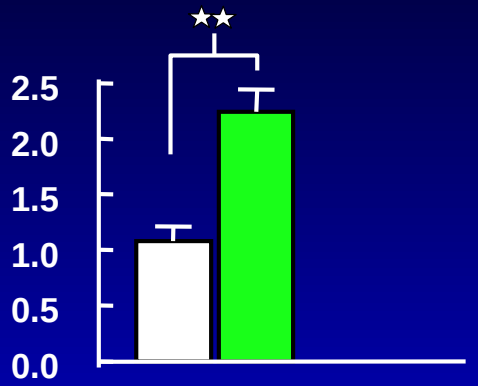
What is the relationship between hippocampal activity and DA system function?


"Population Activity"
Spontaneously active DA neuron
"silent" DA neuron
Population Activity
Firing Rate
Firing Pattern

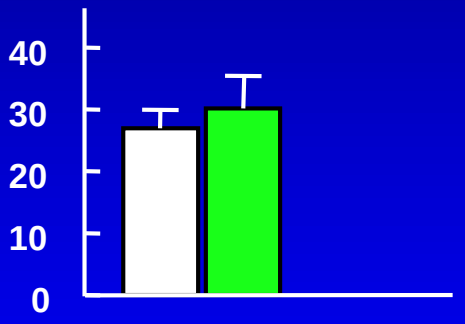
Activation of the *hippocampal-NAc pathway* increases DA neuron population activity, but does not affect burst firing



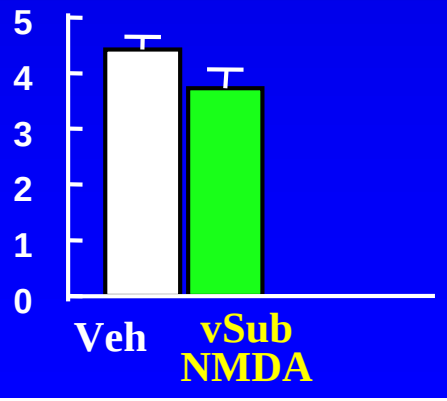
 # DA cells/track (population activity)



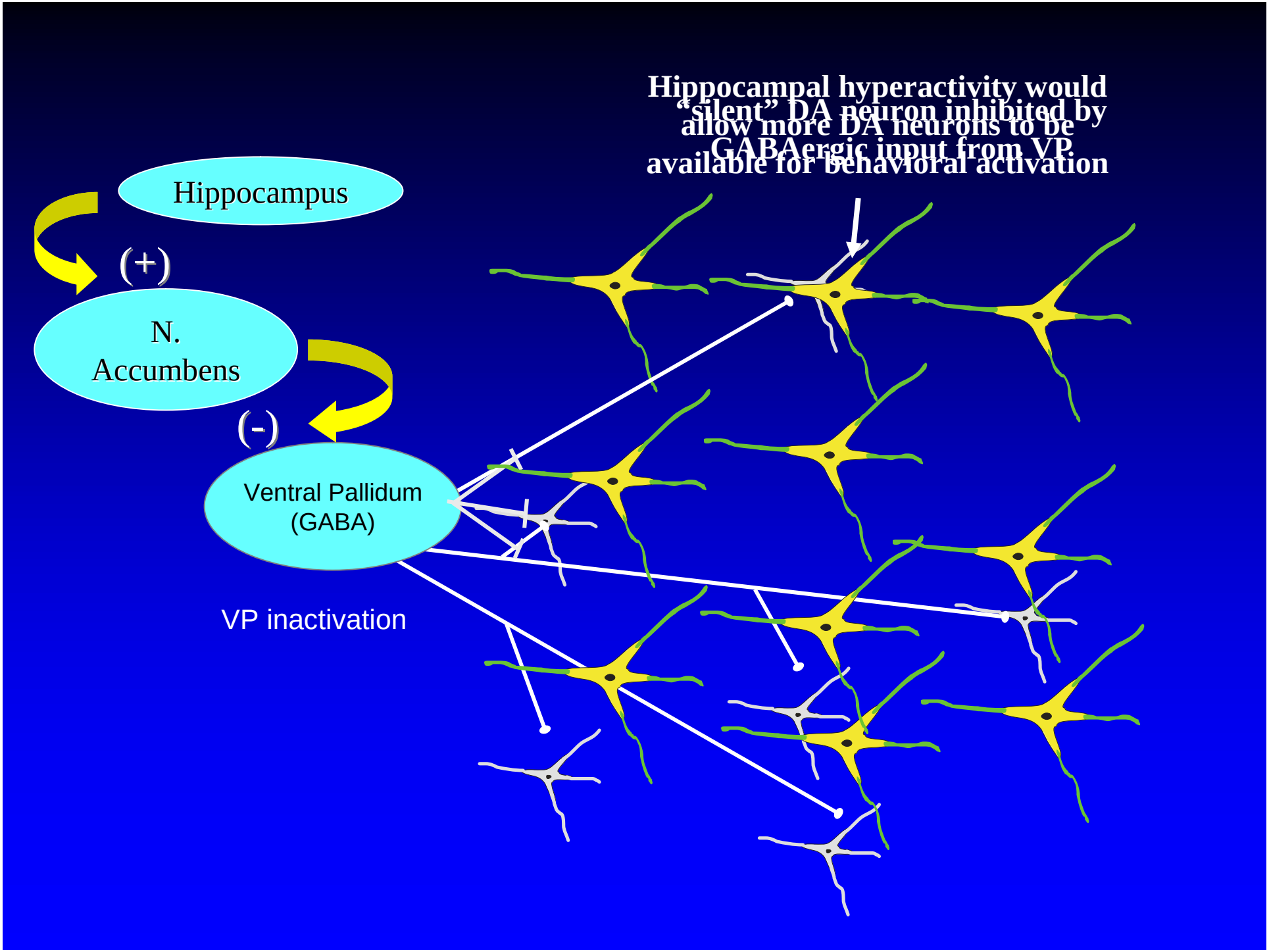
% spikes in bursts



Firing rate (Hz)



- DA neuron population activity
no effect bursting activity


Hippocampal hyperactivity would allow more DA neurons to be available for behavioral activation
"silent" DA neuron inhibited by GABAergic input from VP
Hippocampus
(+)
N. Accumbens
(-)
Ventral Pallidum (GABA)
VP inactivation

Regulation of DA neuron activity:

Modulation of Activity States

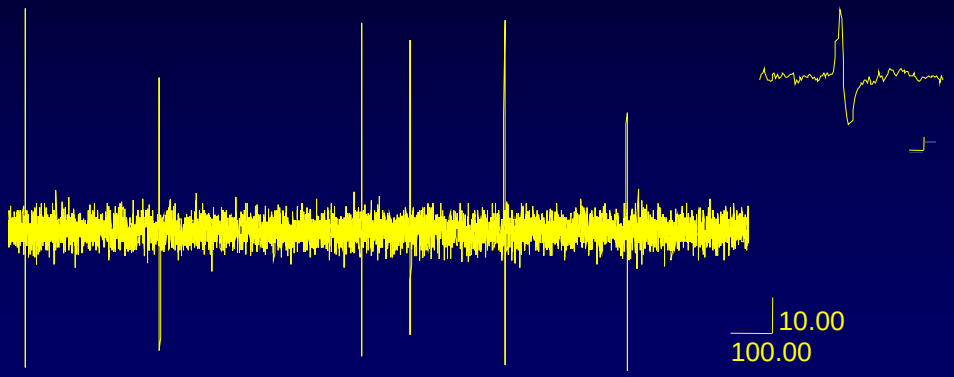
- proportion of DA neurons firing

Modulation of firing pattern

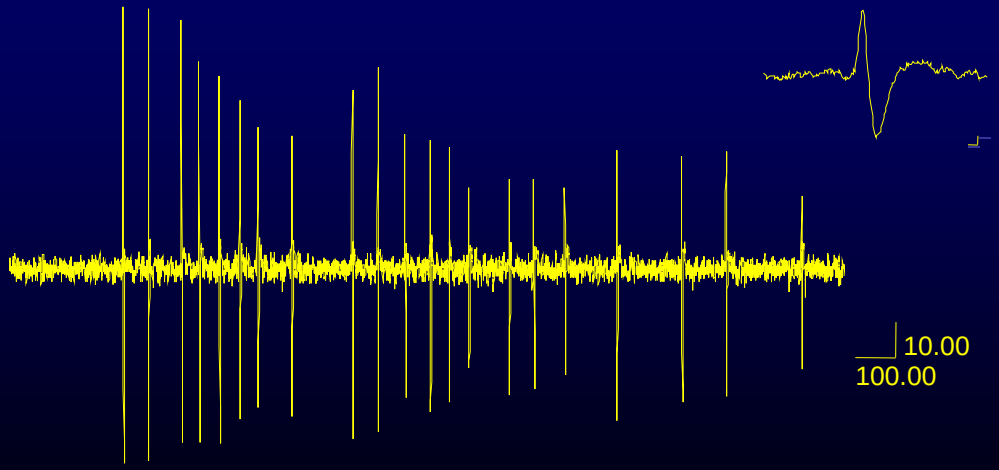
– Single spike firing – idling state

– Burst firing – when activated by demand

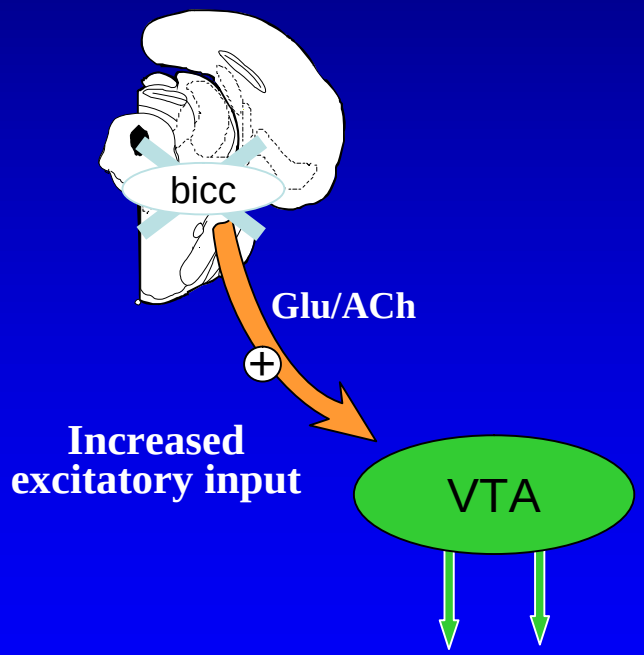
Irregular Firing



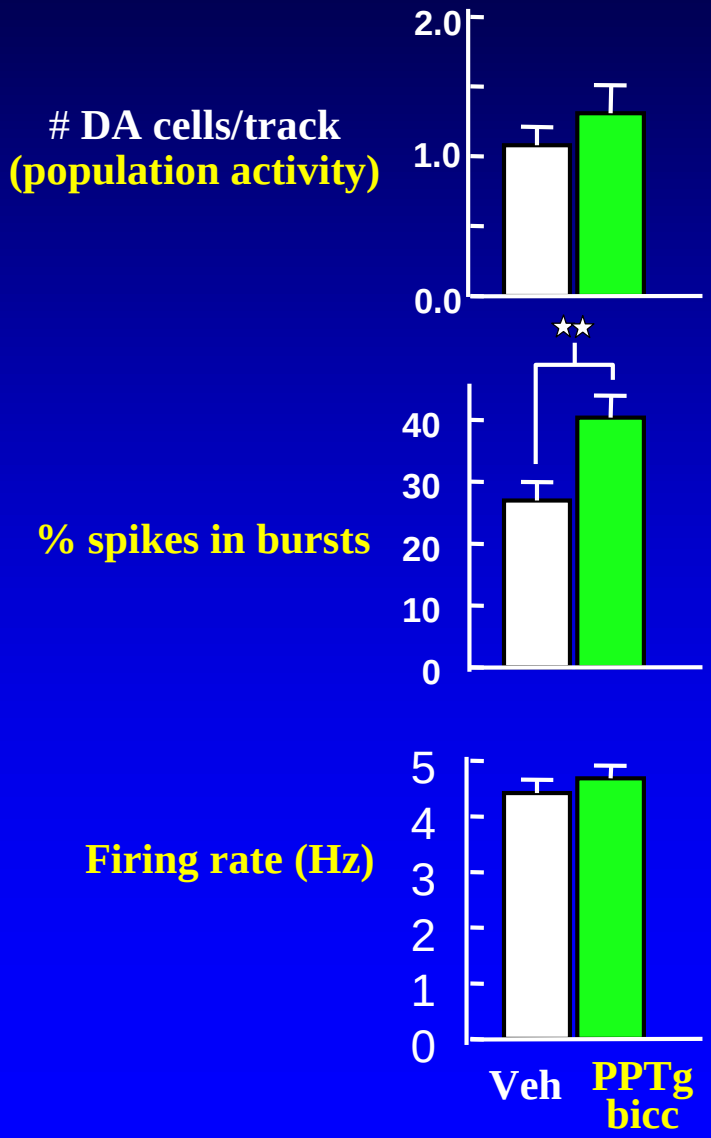
Burst Firing



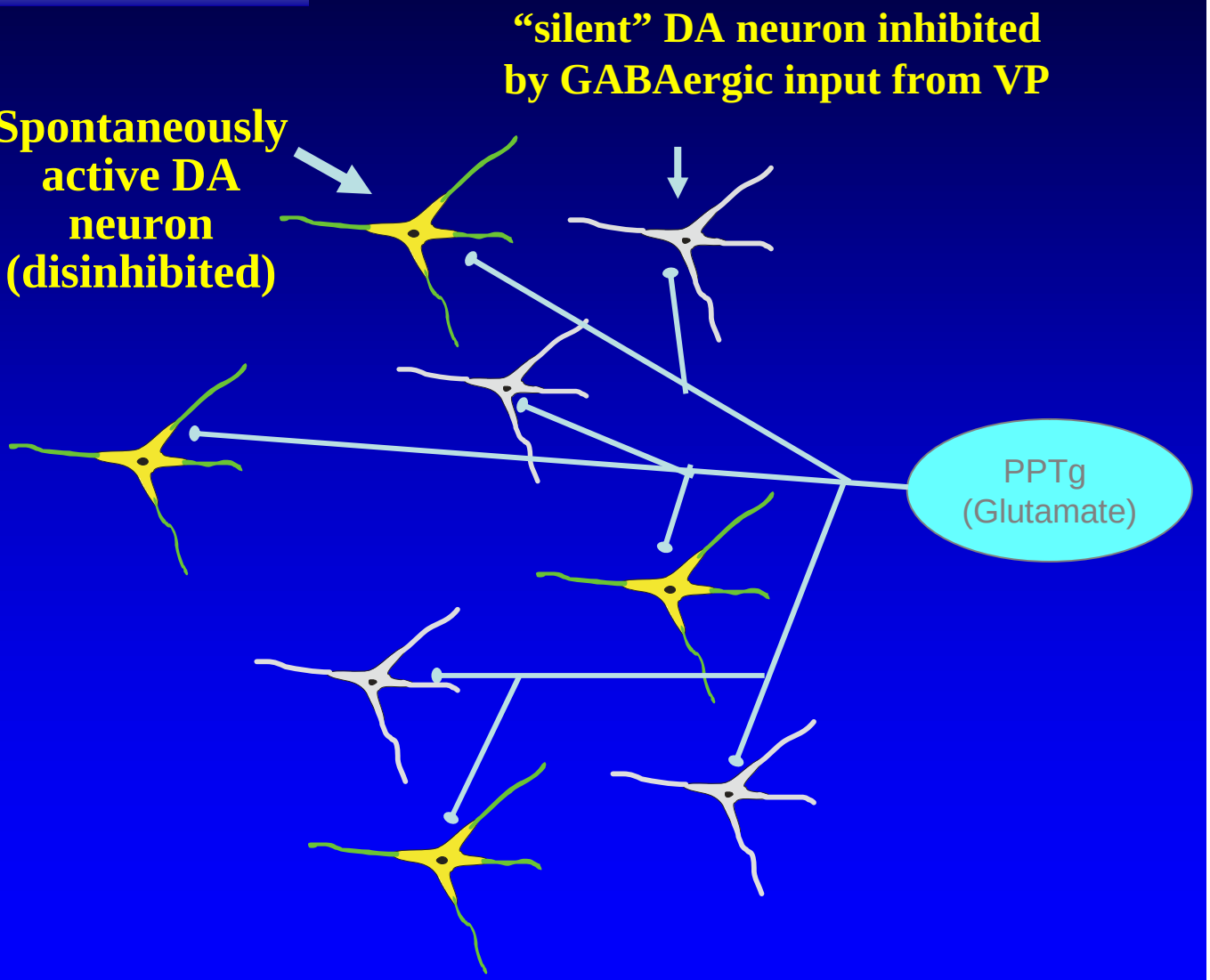
Activation of the *pedunculopontine nucleus* increases DA neuron burst firing, but does not affect population activity



Selective increase in DA neuron BURST FIRING



Regulation of Phasic DA Neuron Activity



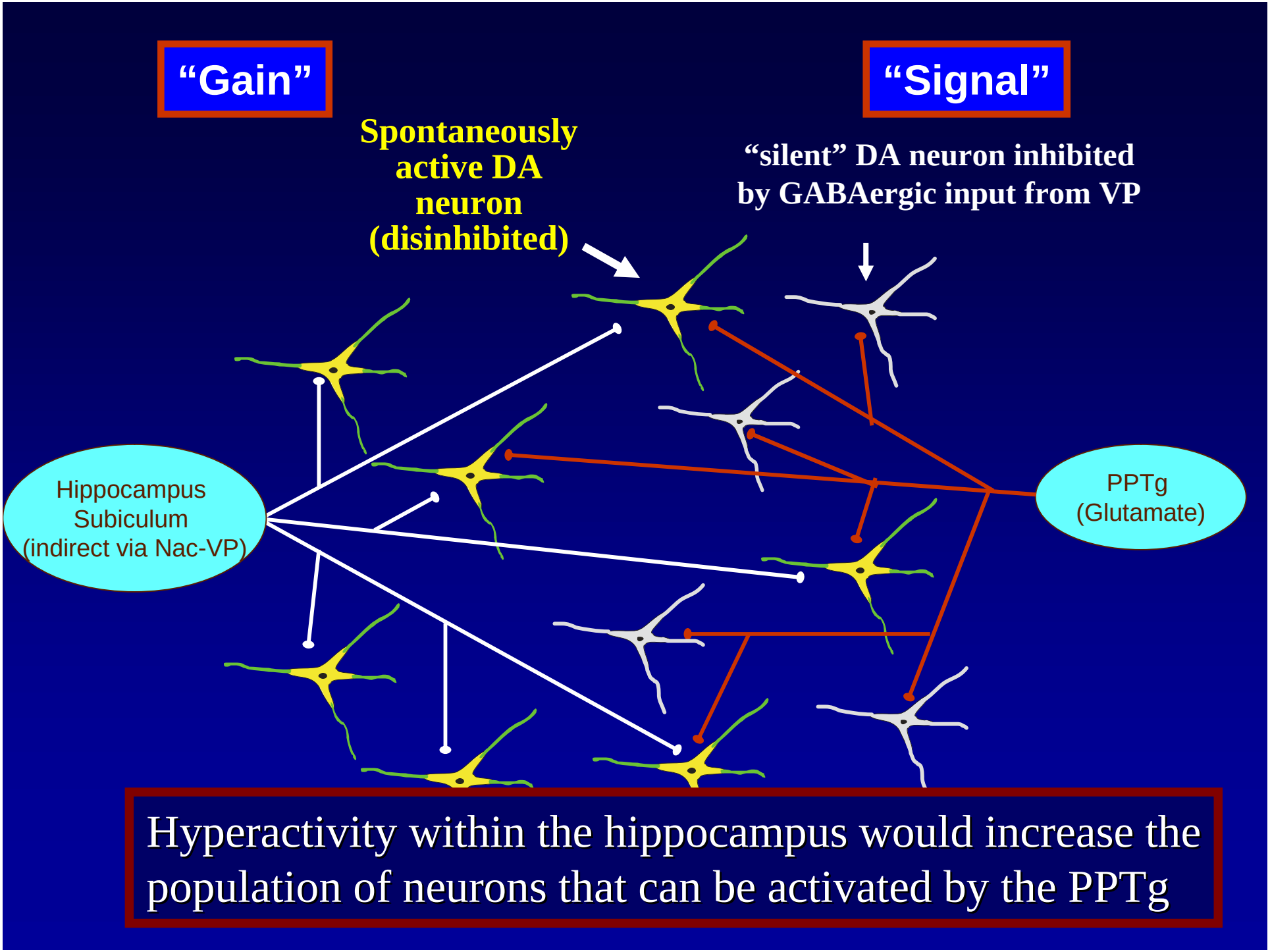
NMDA only affects depolarized, spontaneously firing DA neurons

Model:

By setting the baseline tonic discharge of dopamine neurons, the hippocampal subiculum (via the accumbens-ventral pallidum) controls the number of dopamine neurons that can be phasically activated by the PPTg

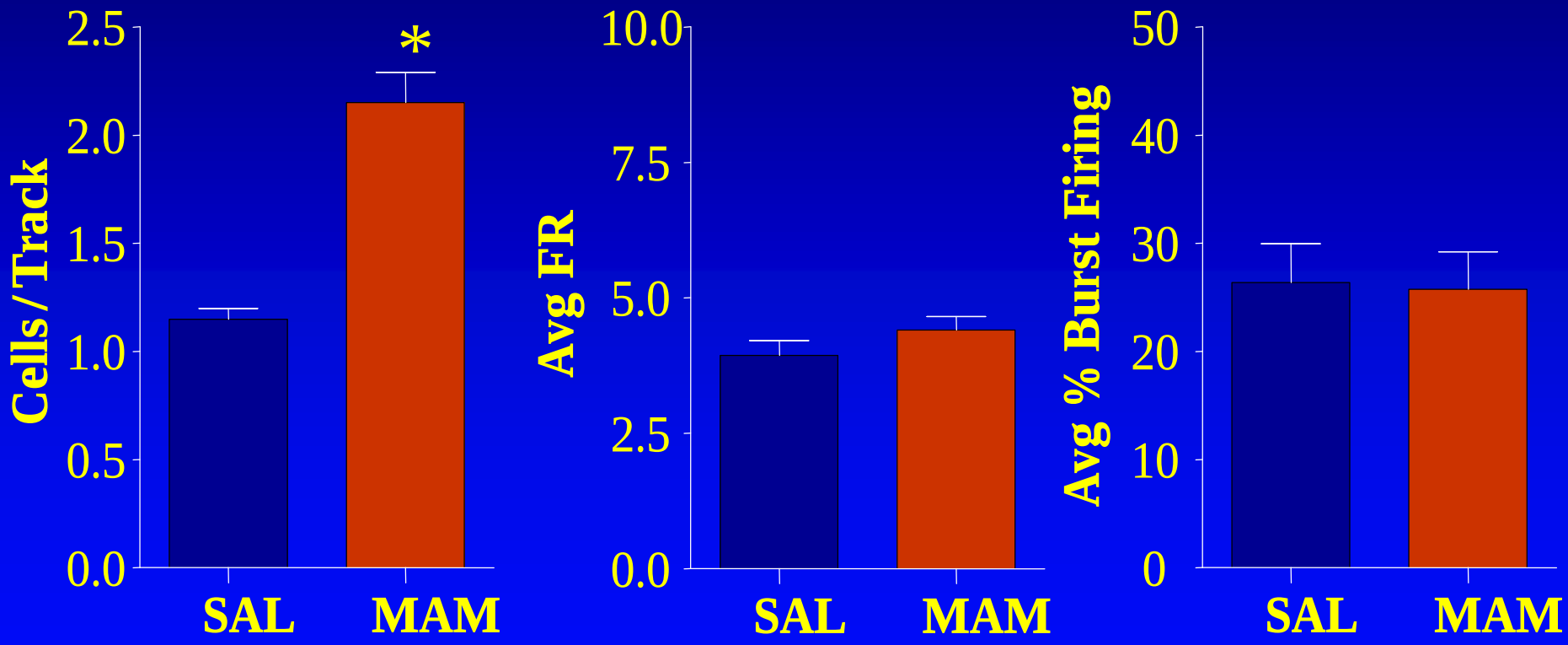
Therefore, the PPTg provides the “signal,” and the ventral subiculum is the “gain” or the level of amplification of this signal

The “gain” is a property of the context, and can be varied depending on the characteristics of the environment

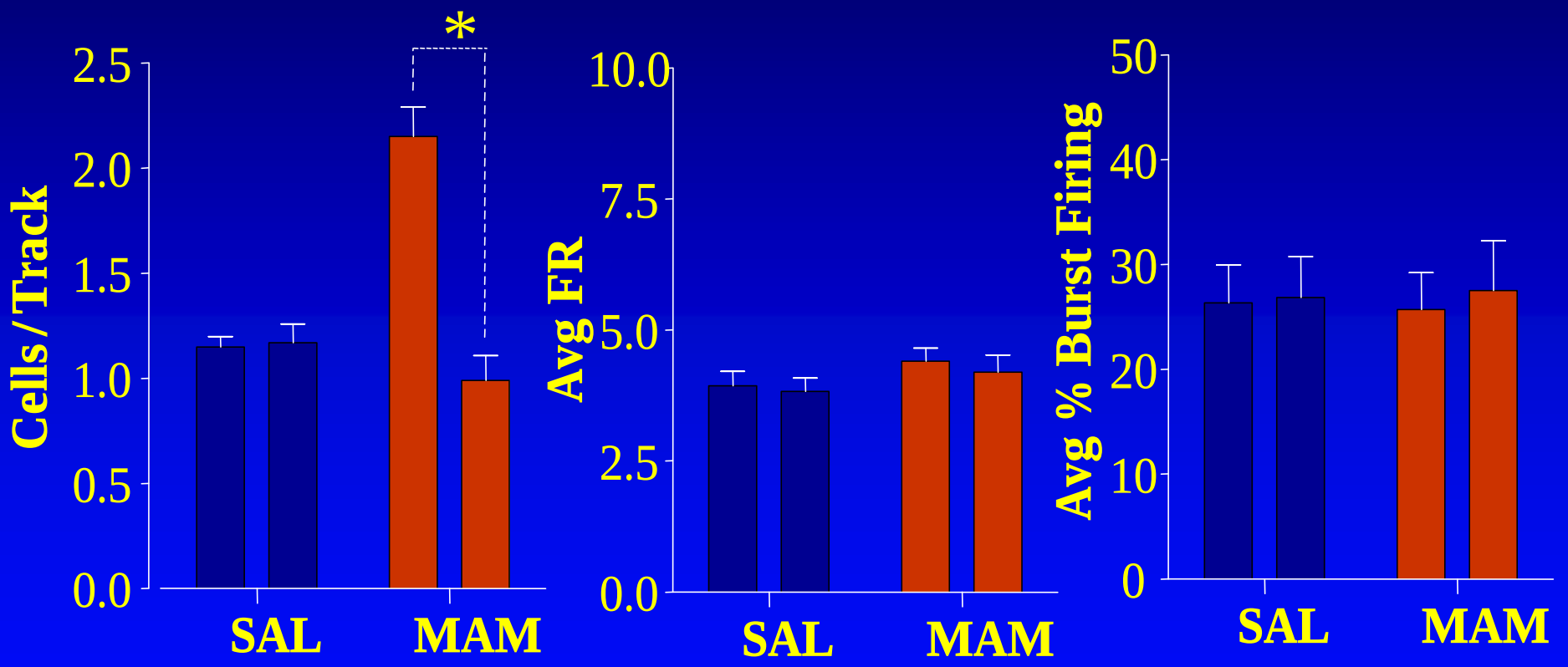

"Gain"
"Signal"
Spontaneously active DA neuron (disinhibited)
"silent" DA neuron inhibited by GABAergic input from VP
Hippocampus Subiculum (indirect via Nac-VP)
PPTg (Glutamate)
Hyperactivity within the hippocampus would increase the population of neurons that can be activated by the PPTg

Is the hippocampal hyperactivity in
the MAM model reflected in
the activity states of the DA neurons?

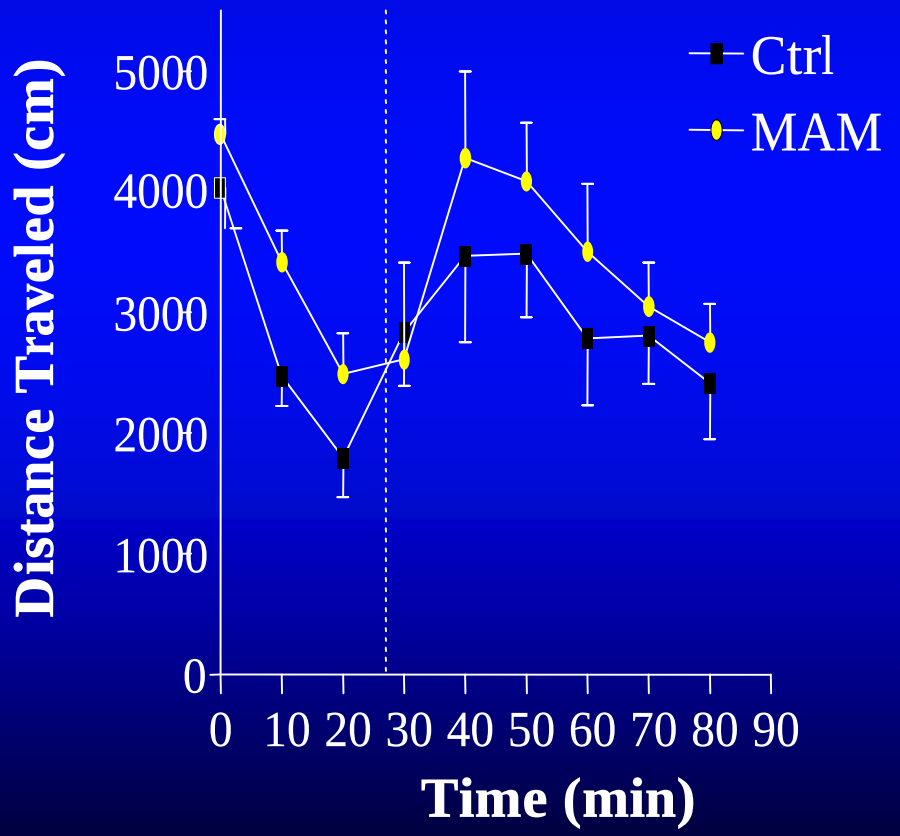
DA Neuron Activity in MAM-treated Rats

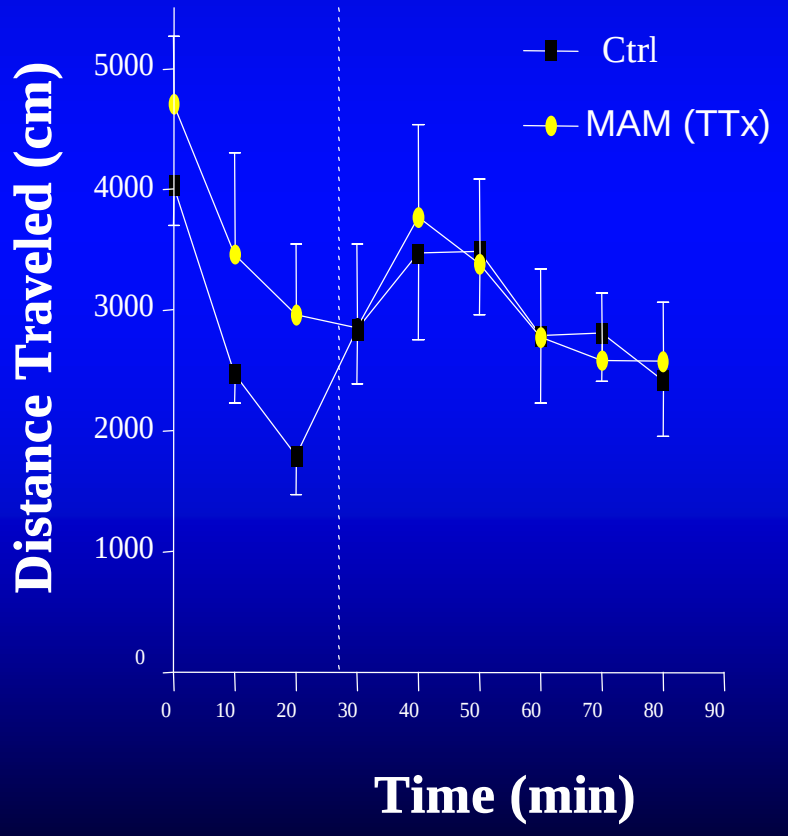


Effects of Hippocampus Inactivation on DA Neuron Activity



Effects of Hippocampal Inactivation on Amphetamine-Induced Hyperactivity





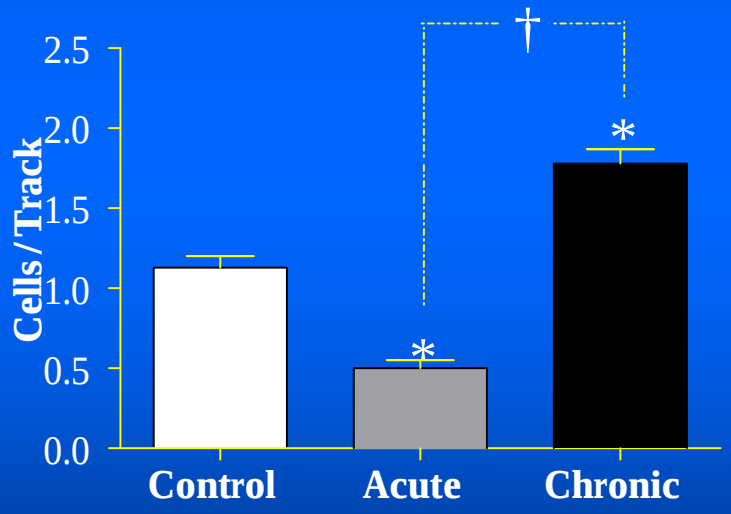
DA neuron activity and drug sensitization

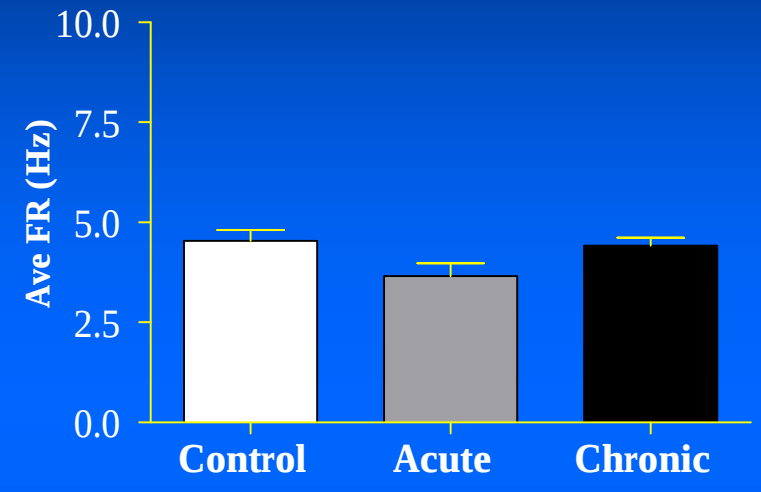
This type of dysregulation of tonic DA neuron firing appears to play a role in other hyperdopaminergic disorders, such as the sensitization that occurs following repeated amphetamine

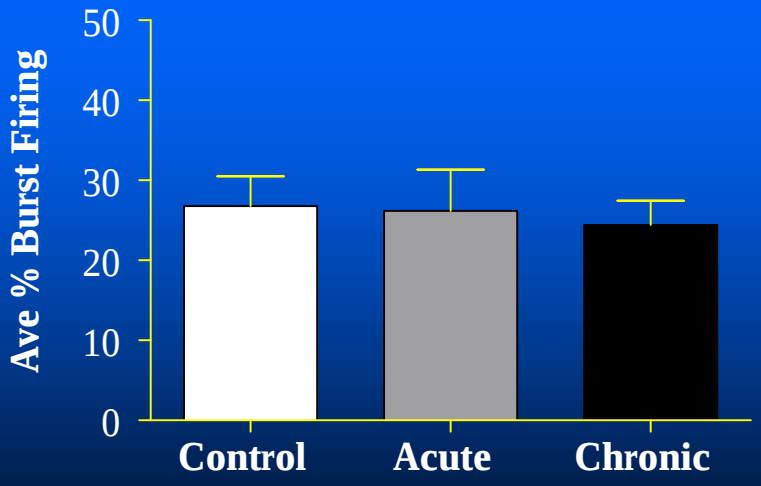
Amphetamine abuse is a risk factor for schizophrenia, and can exacerbate psychosis

Amphetamine sensitization is also a context-dependent phenomenon

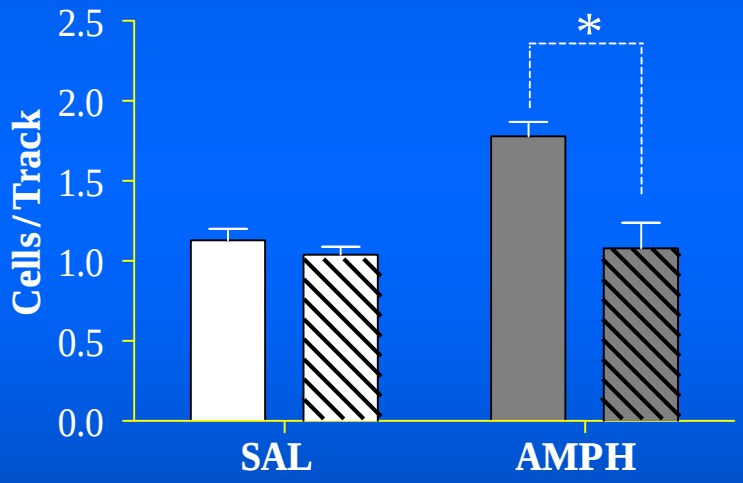
Repeated Amphetamine Treatment Increases Tonic DA Neuron Firing to Baseline

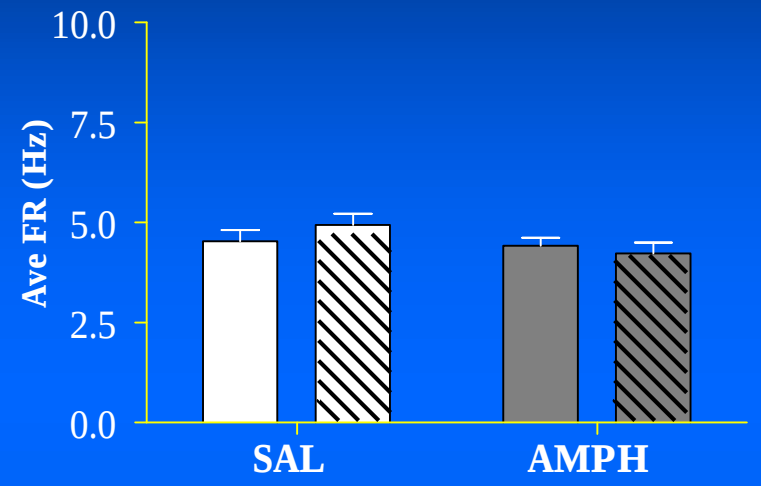


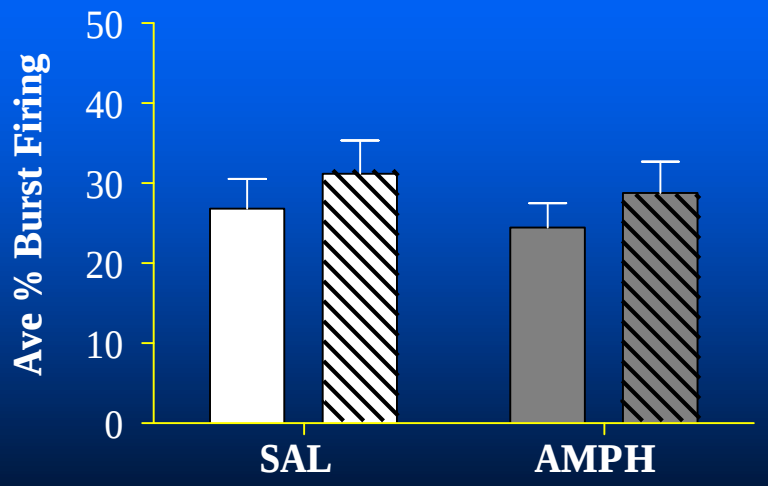




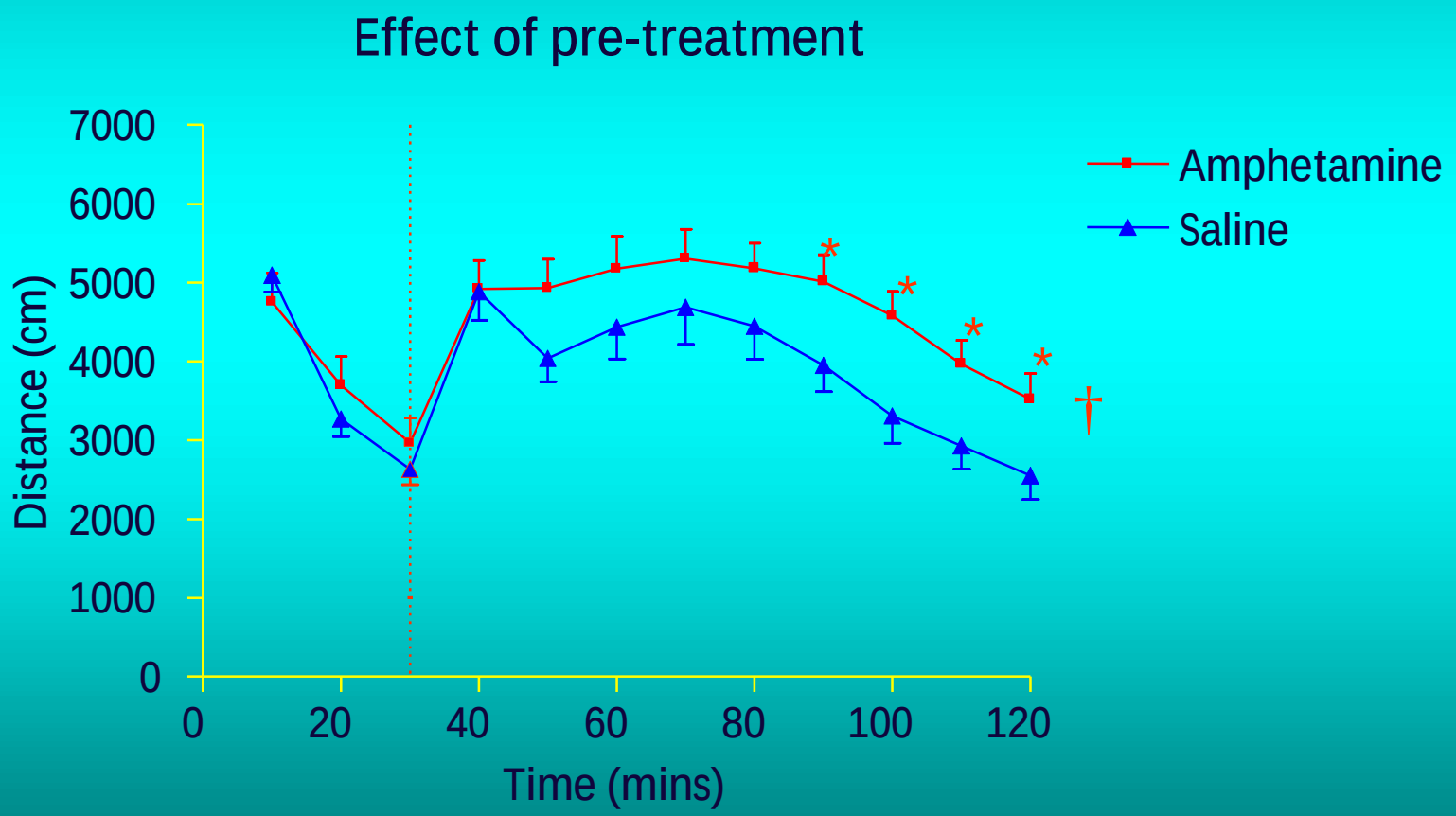
vSub Inactivation by TTX Restores Tonic DA Neuron Firing



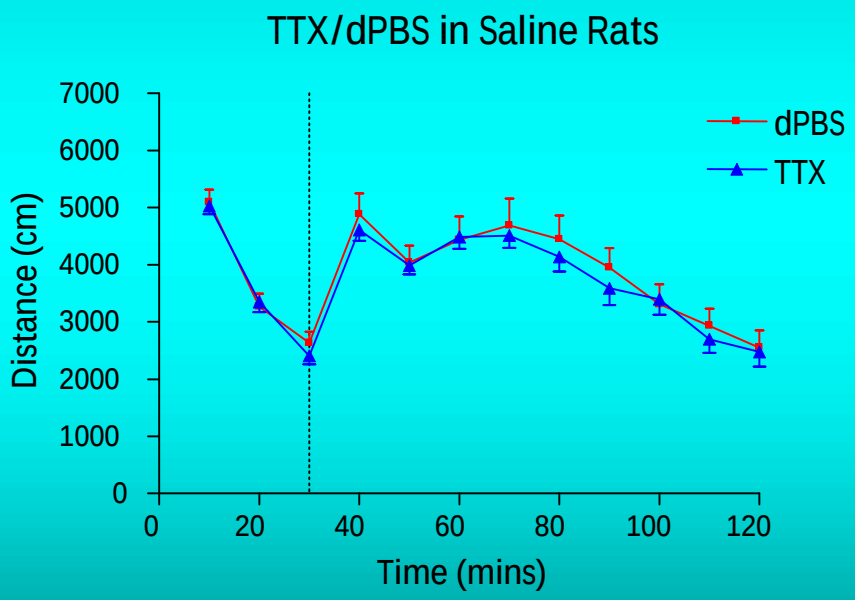


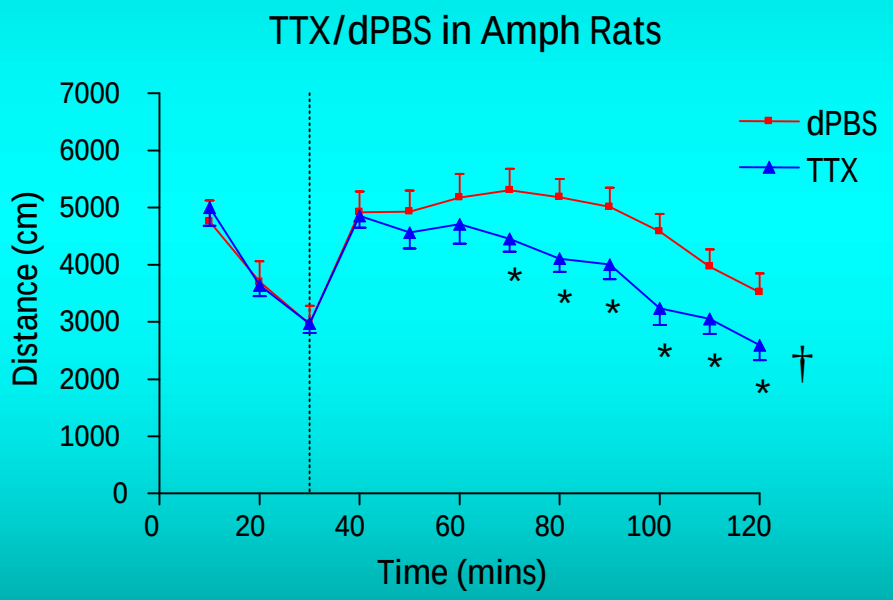


Repeated Amphetamine Induces Behavioral Sensitization



vSub Inactivation by TTX Reverses Behavioral Sensitization

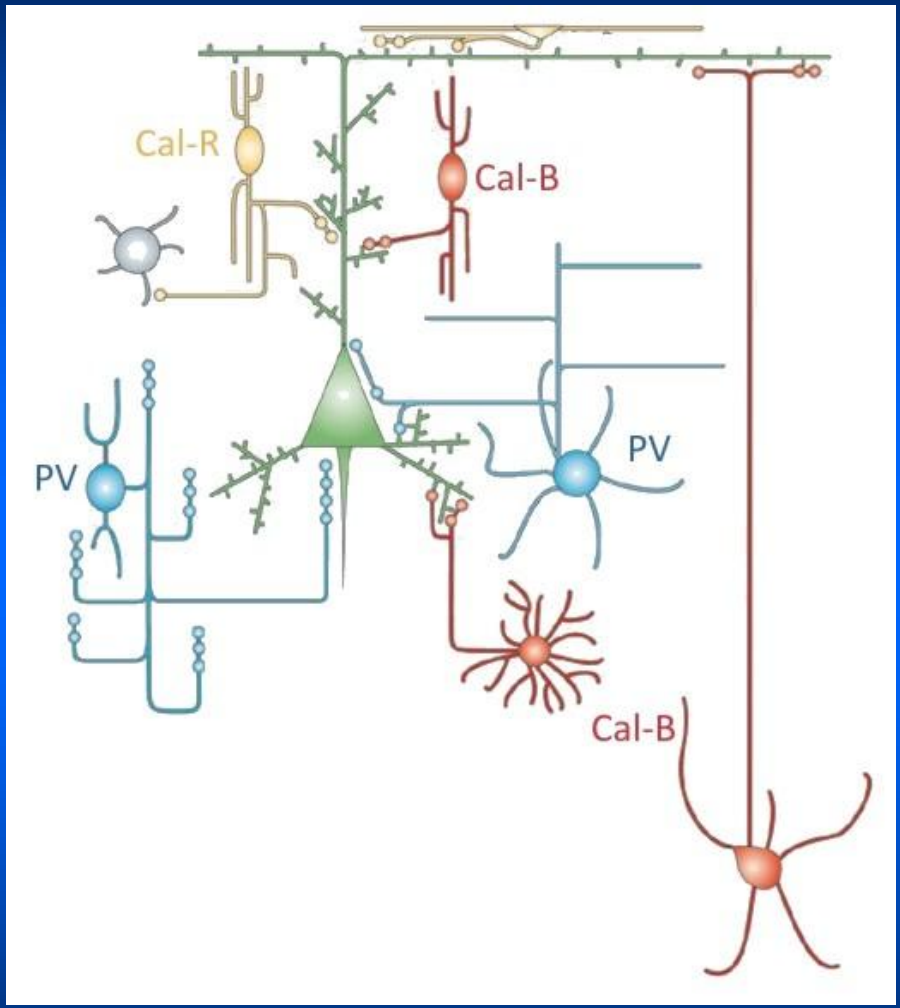




In amphetamine sensitization and other disorders in which context plays a prominent role, an abnormal hippocampal augmentation of tonic DA neuron activity may be a common pathophysiological variable

What is the source of ventral hippocampal hyperactivity in schizophrenia?

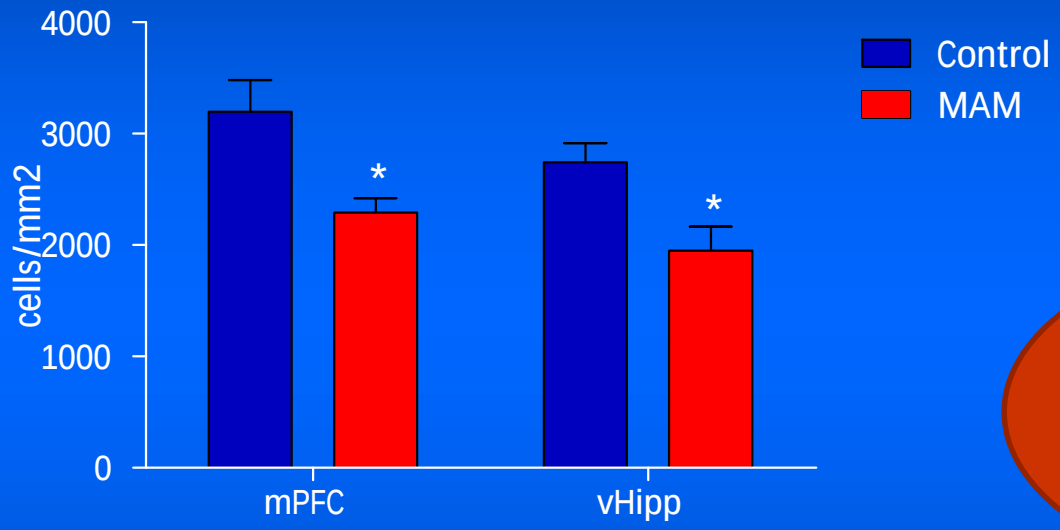
What is the source of increased vSub activity?



Parvalbumin interneurons are selectively decreased in PFC and hippocampus of SZ patients

(Adapted from Lewis et al. Nat Rev Neurosci 2005)

PV - Interneuron Cell Counts



MAM rats display a regionally selective reduction in PV interneuron number

No significant differences in dorsal hippocampus

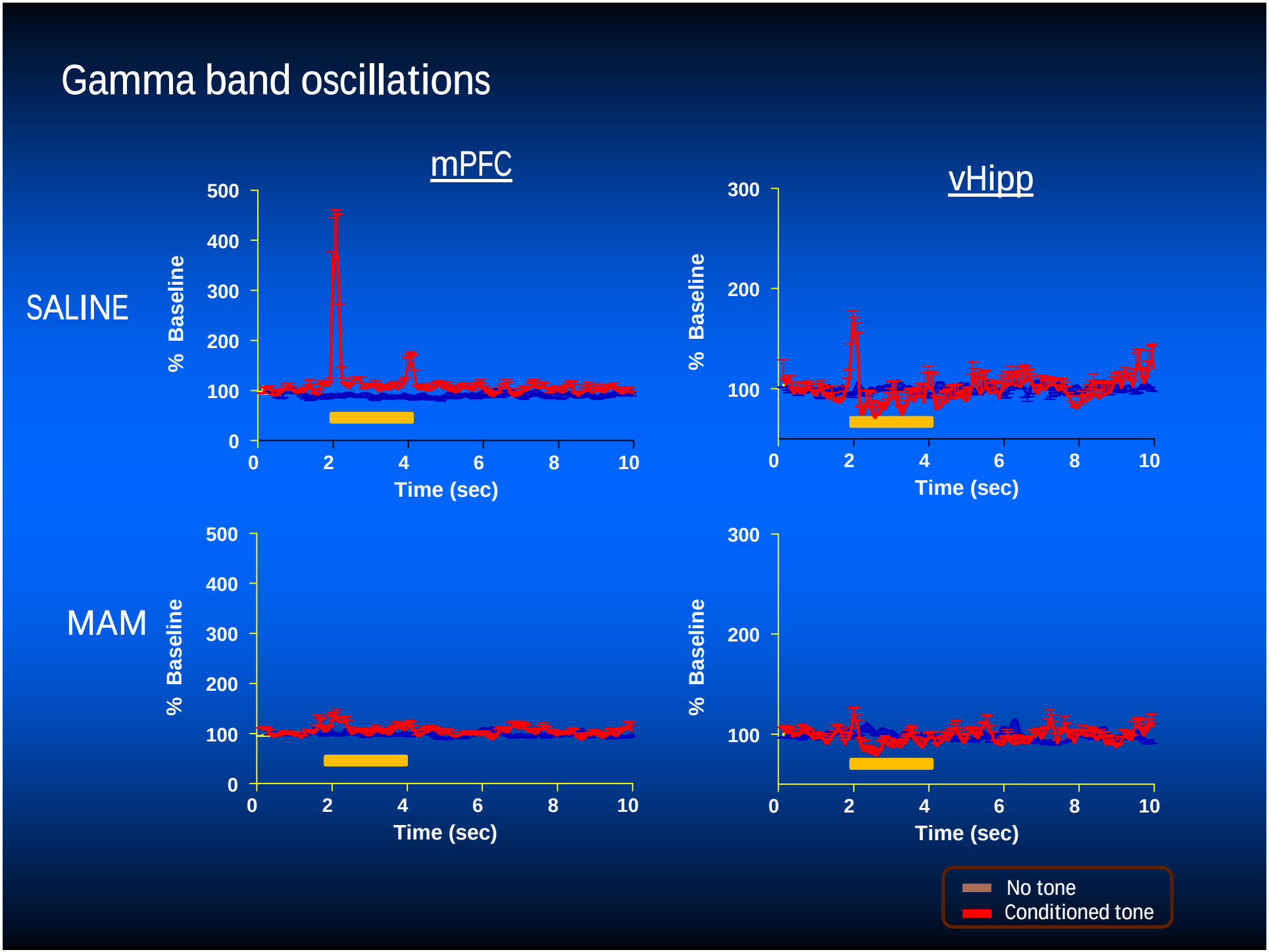
(In collaboration with Dr. Margarita Behrens, UCSD)

How does the decrease in PV interneurons affect information processing?

- PV interneurons are known to affect high frequency gamma rhythms that are known to have a role in stimulus recognition and processing

- Examine whether activity rhythms evoked by conditioned stimuli are altered in brain regions showing decreased PV interneurons

Gamma band oscillations



Conclusions:

-Evidence suggests that both in schizophrenia and in the MAM model, there is hyperactivity in the ventral hippocampus, possibly due to decreased interneuron function

-This hyperactivity could underlie the disruption of gating within PFC-accumbens circuits and disrupt activity rhythms

-Inactivation of the ventral hippocampus in the MAM model restores normal DA system function

Can this be used as a potential therapeutic approach for schizophrenia?

Therefore, in schizophrenia, in the MAM model, and in amphetamine sensitization, an abnormal hippocampal augmentation of tonic DA neuron activity may be a common pathophysiological variable, particularly in cases where context is a factor

Restoration of hippocampal activity could be an effective therapeutic strategy in the treatment of schizophrenia and other disorders

Acknowledgements

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