Introduction

• In vivo recordings in the behaving monkey show that prefrontal (PFC) cortical cells maintain an elevated state of firing during the delay period associated with working memory tasks (Goldman-Rakic, 1996). This firing depends on an appropriate level of dopamine (DA) in the PFC (Williams and Goldman-Rakic, 1995; Zahrt et al., 1997), and is related to the specific properties of the item that is remembered (Constantinidis et al., 2001).

• The effects of dopamine on cortical neurons in vitro are controversial, but it is clear that DA neuromodulation changes intrinsic and synaptic properties (Gulledge and Jaffe, 1998; Henze et al., 2000; Seamans et al., 2001).

• Modeling studies suggested that a possible mechanism for the maintaining of sustained activity relied on an increase of synaptic drive through NMDA receptors (Lisman et al., 1998) and recurrent network activity (Durstewitz et al., 2000; Brunel and Wang, 2001; Scheler and Fellous, 2001).

• We use a hybrid network made of a real rat prefrontal neuron and many simulated synapses to show that the dopamine modulation of the membrane of the real neuron coupled to the simulated modulation of synaptic transmission allows for in vivo-like sustained firing.

Methods

• In vitro: Layer V pyramidal cells in 2-3 weeks old Sprague Dawley rats. Whole cell patch technique at 31 °C. All drugs are bath applied. We use dopamine with ascorbic acid (<0.01%), DNQX (10 µM), APV (50 µM), Biccuculine (20 µM) (Fellous et al., 2001).

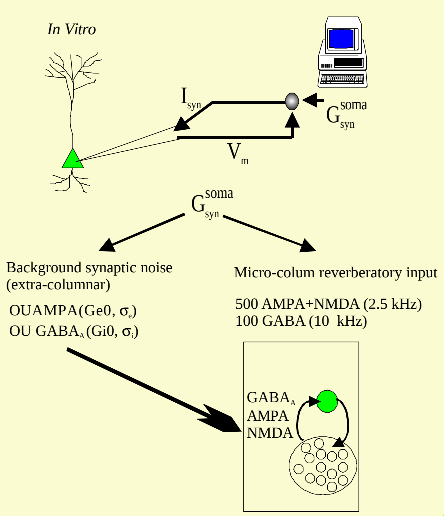
• Background conductance noise: 2 Ornstein-Ulenbeck (OU) processes with time constants 2.7 ms (AMPA), and 10.7 ms ($GABA_A$) (Destexhe et al., 2001).

$$\frac{dGe(t)}{dt} = -\frac{1}{\tau_e}\left[Ge(t) - Ge0\right] + \sqrt{D_e}\,\chi(t),$$

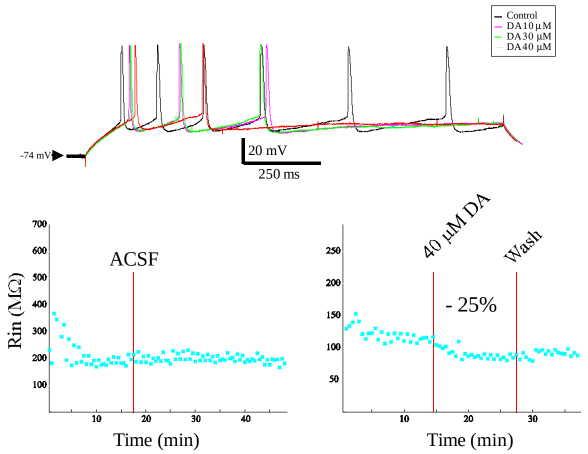
$$\sigma_e = \sqrt{D_e \tau_e / 2}$$

• Feedback conductances: Alpha functions. NMDA depends on voltage (Jahr and Stevens, 1990).

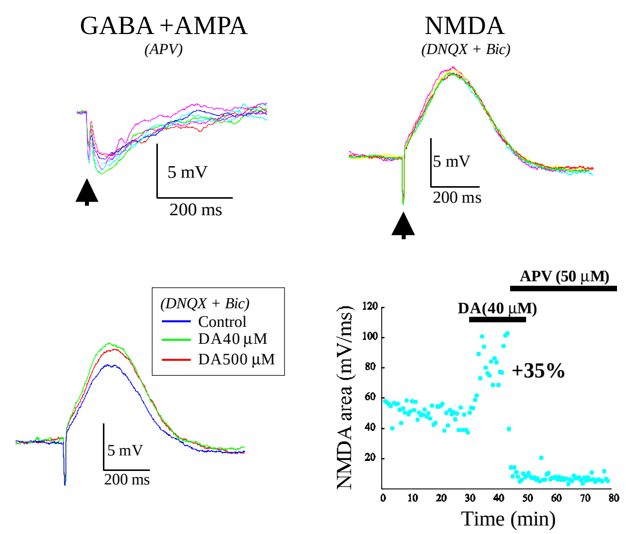
• We use the *reactive clamp* technique to inject conductances in feedback mode.



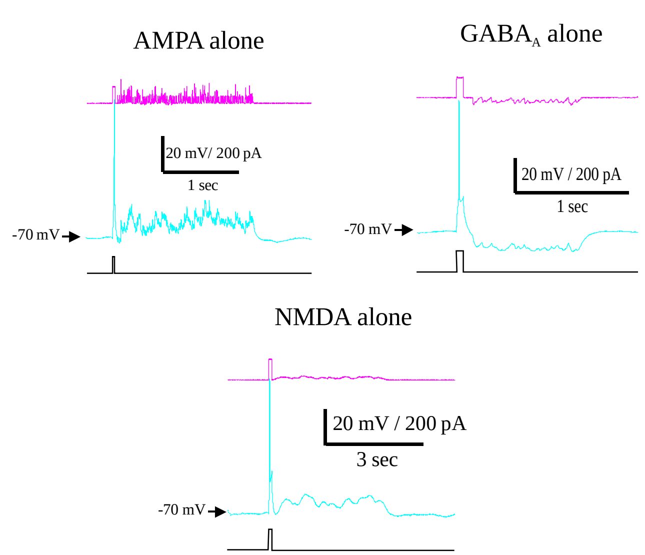
1 • DA decreases excitability



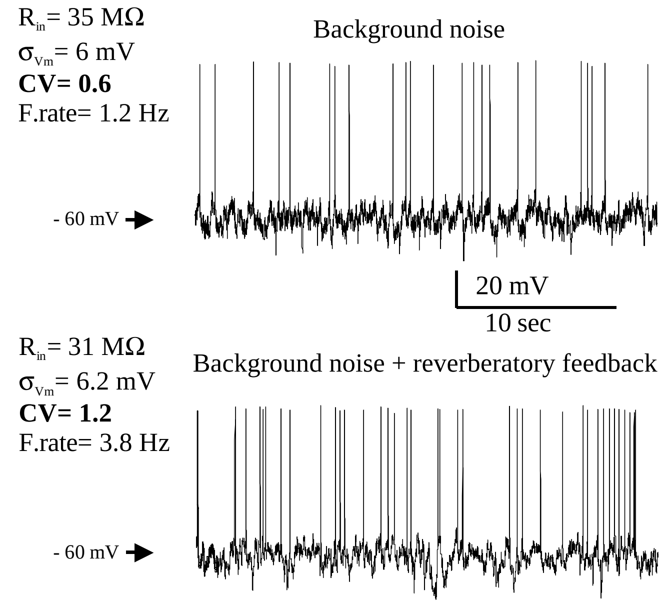
2 • DA increases the NMDA response



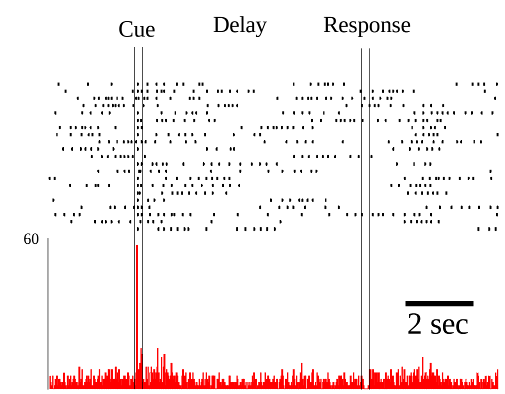
3 • Reactive Clamp



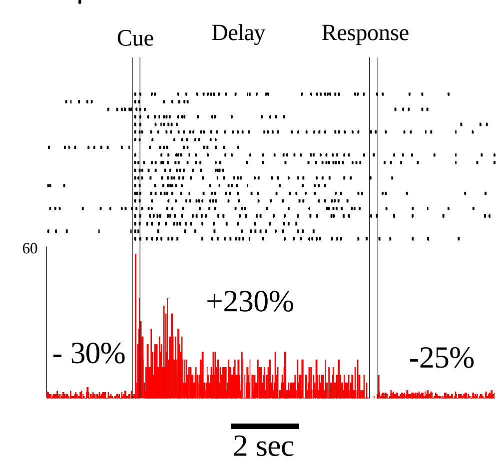
4 • Recreating *in vivo* conditions



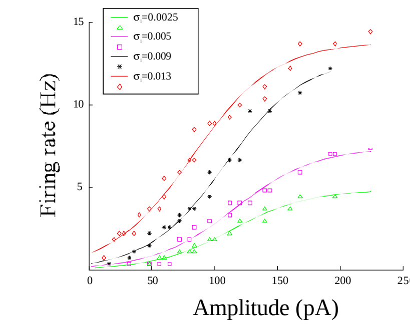
5 • DA increases the signal-to-noise ratio in a simulated working memory task



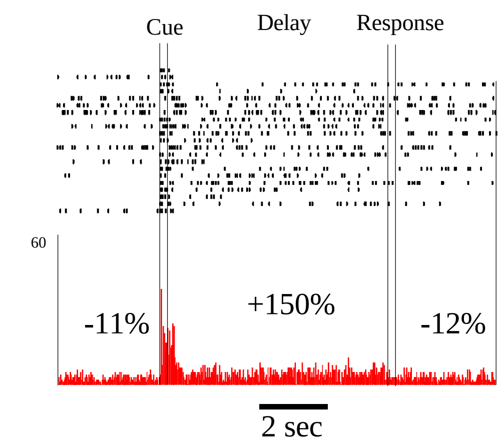
40µM DA and 30% increase in NMDA



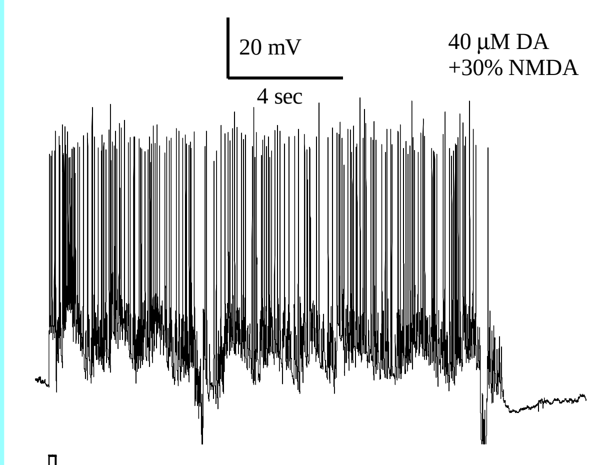
6 • The standard deviation of the background noise sets the gain. Emergence of multi-stability



40 µM DA, 30% increase in NMDA, $\sigma_i/2$



7 • Sustained activity in DA is robust to perturbations



Conclusions

• Dopamine (40 µM) decreases the excitability of rat prefrontal cortex cells in layer V and increases NMDA currents.

• Reactive clamp coupled to a stochastic model of extra-columnar background noise recreates *in vivo* membrane potential and spiking characteristics *in vitro*:
Depolarization of 15 mV, membrane fluctuations, spontaneous spiking with high CV, and low input resistance.

• Under simulated *in vivo*-like conditions, DA enables the sustained firing of prefrontal cells in response to a ‘cue’. Dopamine increases the signal-to-noise ratio.

• The standard deviation of the extra-columnar inputs sets the gain of PFC cells and regulates their firing rate during the delay period.

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