DOPAMINERGIC MODULATION OF ACTIVITY STATES IN THE PREFRONTAL CORTEX.

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The dense dopaminergic input to the prefrontal cortex influences working memory through multiple effects on intrinsic ionic and synaptic currents in cortical neurons in ways that are not fully understood. In vitro voltage-clamp studies of pharmacologically-isolated currents revealed that activation of D1-receptors shifts the voltage dependence of a persistent Na^+ current to more hyperpolarized potentials while slowing its inactivation. Moreover, D1 agonists produced a 30-40% increase in isolated $GABA_A$ IPSPs and isolated NMDA EPSCs. We have incorporated these cellular and synaptic effects of dopamine into a network model of highly realistic prefrontal cortex model neurons. Compartmental models of neurons were constructed that reproduced whole-cell patch-clamp recordings from the soma and dendrites of prefrontal cortex layer V pyramidal cells. A network model of interacting pyramidal neurons and GABAergic interneurons exhibited attractor states characterized by persistent activity following a brief external input. In a simulation of D1 activation, low activity states driven by background synaptic inputs were suppressed but high activity states driven by recurrent excitation were strongly enhanced. In the dopamine condition it was more difficult to disrupt persistent activity patterns, which were thus more stable and were sustained for longer periods of time. However, if new stimuli were presented simultaneously with a short-lasting 'D2-mediated inhibition', stability of a persistent pattern could be more easily overcome. In this manner, the network could first switch to a new pattern via D2-mediated effects, and then stabilize it via the D1-mediated effects. These simulations suggest that dopamine has state-dependent effects on network dynamics and different levels of D1- and/or D2-receptor stimulation might set the right dynamics for different cognitive operations in the prefrontal cortex. *Supported by the DAAD, NSERC and HHMI.*