Modeling dopaminergic and noradrenergic influences on working memory and behavior

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Dopamine (DA) and norepinephrine (NE) originate in the ventral tegmental area (VTA) and locus coeruleus (LC), respectively, and have been shown to significantly modulate visuospatial working memory in the dorsolateral prefrontal cortex (dPFC). When either DA or NE is too high, input to the PFC is essentially blocked. When either DA or NE is too low, working memory in the PFC becomes noisy and activity levels diminish. This produces an inverted-U dose-response profile where spatially tuned representations are held in working memory only when DA and NE are at optimal levels and degrade as DA and NE levels increase or decrease. Mechanisms for how this is occurring have been suggested, however, they have not been tested in a large-scale model with neurobiologically plausible network dynamics. Also, DA and NE levels have not been simultaneously manipulated experimentally, which is not realistic in vivo due to strong bi-directional connections between the VTA and LC. To address these issues, we built a spiking neural network model of the dPFC that included D1, α2A, and α1 receptors and contained 57,000 neurons and 30 million synapses. The model was able to match the inverted-U dose-response profiles that have been shown experimentally for differing levels of DA and NE. Furthermore, we were able to make predictions about what working memory and behavioral deficits may occur during simultaneous manipulation of DA and NE outside of their optimal levels. Specifically, we show that when NE is low and DA is high, behavioral deficits occur due to weak excitatory activation. When NE is high and DA is low, behavioral deficits occur due to weak lateral inhibition. On the other hand, when both DA and NE are high or low, behavioral deficits are not as pronounced. Our model further demonstrates the important role that GABAergic neurons play in reducing noise in both working memory and motor output layers. Specifically, we found that inhibition in working memory plays a more important role in increasing signal-to-noise ratio than recurrent excitation; and lateral inhibition in motor output layers acts to filter out noise that may accumulate in working memory in order to improve behavioral performance.