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Constructing dopaminergic signals in response to transient inputs in the ventral tegmental area

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Midbrain dopaminergic (DA) neurons signal motivational properties of natural reinforcers and addictive drugs important for the acquisition of conditioned behavior. The phasic DA response has been suggested to signal the discrepancy between the predicted and received reward, signaling a crucial learning term for reinforcement learning. The relevant dopaminergic neurons are found in two nuclei, the substantia nigra pars compacta and the ventral tegmental area (VTA). Electrophysiological recordings have demonstrated that transient inputs to the VTA, e.g. glutamatergic and cholinergic, convey salient information about the environment such as novel stimuli, received rewards, and reward predictive sensory cues. However, how transient inputs to the VTA are converted into DA output is poorly understood. In particular, the mechanism and location of the difference computation between expected and received rewards remain elusive. Furthermore, how addictive drugs such as nicotine modulate the VTA response to afferent inputs is not know. We address those questions using a biologically realistic model of the local VTA circuitry that includes both the neuronal dynamics and the kinetics of the relevant cholinergic receptors.

We implement the neuronal microcircuit of the VTA in a network model accounting for the local VTA connectivity, the afferent projections to the VTA, the location of the nicotinic acetylcholine receptors (nAChRs) and their subtype-specific activation and desensitization properties. The VTA contains DAergic and GABAergic neurons receiving cholinergic (ACh) and glutamatergic (Glu) afferent input from subcortical and cortical structures. The DA response to endogenous acetylcholine is mediated by various nAChR subtypes expressed on: (i) DA neurons, (ii) GABAergic neurons, and (iii) presynaptic Glu terminals. The very same nAChRs are responsible for the impact of exogenous nicotine on DA signaling. The glutamatergic input activates synapses located on DA and GABAergic neurons. We first constrain our model by requiring it to account for both in vivo and in vitro experimental data obtained from recordings during nicotine exposures. In particular, we use the data to pin down the specific distribution of nAChRs.

We then investigate how the VTA DA neurons respond to transient afferent inputs. We show that glutamatergic inputs phasically increase DA output. The impact of transient ACh inputs depends crucially on the the distribution of alpha4 beta2 subunit containing nAChRs in the VTA. Transient cholinergic inputs decrease DA output if alpha4 beta2 nAChRs are predominantly expressed by GABAergic cells. In this case, the VTA DA signal reflects the difference between the Glu and ACh inputs. This leads us to speculate that the "no reward" prediction signal from the habenula may be mediated via the cholinergic projections to the VTA. Finally, we show how nicotine subverts those signaling pathways by removing the impact of ACh signals on DA activity. Our investigations suggest biological mechanisms explaining how salient stimuli encoded in

transient inputs to the VTA are translated into dopamine output.