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‘Ups downs and sideways of dopamine in drug addiction

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Under the title “Dopamine ‘ups and downs in addiction revisited”, Samaha *et al* discuss the alteration of dopamine signaling evoked by repeated cocaine exposure, which may underlie addictive behavior [1]. Focusing on the commonality of addictive drugs, the pharmacologically evoked dopamine transients in the nucleus accumbens NAc), two contrasting views on adaptive changes in dopamine transmission become apparent. On the one hand, prolonged exposure to cocaine can blunt dopamine elevations a.k.a. tolerance), which the individual would try to overcome by taking more drugs. On the other hand, when a subject is exposed intermittently, dopamine levels in response to the drug and drug cues may become larger, thereby strongly driving the ‘wanting of drugs. In discussing the various behavioral paradigms, such as a clever intermittent cocaine self-administration model, the authors conclude in favor of the ‘up hypothesis of incentive saliency that also better ts human intake patterns.

Here, we expand this view by putting the emphasis neither on the ‘up nor the ‘down , but on the ‘sideways . We review the key arguments for dopamine s function as a modulator of glutamate and GABA transmission to be the neural substrate of long-lasting drug adaptive behavior.

Our view has its roots in much cell biological literature that has examined the function of dopamine receptor transduction in the context of addictive drugs. While dopamine can modulate excitatory transmission acutely via modi cation of AMPAR and NMDAR function, drug-evoked dopamine surges also evoke long-lasting changes that outlast the presence of the drug in the brain. For example, D1Rs, which in the NAc couple to G_{olf}- a member of the Gs alpha family) initiates a crosstalk with glutamate receptors to activate intracellular ERK-MAPK signaling [2], eventually increasing the number of AMPA receptors in the postsynaptic membrane. All addictive drugs are able to activate this pathway, speci cally in D1R-medium spiny neurons MSNs) [3].

Temporal coincidence of dopamine and glutamate release potentiates NMDARs function, which lowers the threshold for long-term potentiation LTP). Conversely D2Rs, which couple to Gio, prevent the induction of LTP when activated by dopamine. As recently demonstrated [4], brief dips of dopamine relieve the D2R signaling to unleash protein kinase A PKA) activation, which in turn favors strengthening of glutamate afferents. Taken together, surges and dips in dopamine are associated with distinct plasticity rules, depending on whether the cells express D1R or D2Rs, which tells us how dopamine modulates glutamate afferents Figure 1) [5]. For GABA transmission, the dopamine affects presynaptic release, again involving D1Rs signaling for potentiation and D2Rs for depression.

In the NAc, with as little as one injection of cocaine, D1R intracellular cascade is activated, leading to several lasting alterations, such as postsynaptic potentiation of excitatory cortical and hippocampal afferents. As a result, the second injection of cocaine reveals striking differences in the two major accumbal cell populations: D1R-MSNs and D2R-MSNs. Monitoring the activity of MSNs with calcium imaging reveals that, at the same time, more D1R-MSNs are activated and more D2R-MSNs are silenced, thus enhancing the dichotomy of the two populations [6].

While not suf cient to induce addiction, such a reductionist approach offers the possibility to establish stringent links of causality between plasticity at identi ed synapses and simple drug-adaptive behavior. For example, a second injection of cocaine leads to an enhanced locomotor response, reflecting sensitization. Optogenetic inhibition of D1R-MSNs or blocking intracellular receptor signaling precludes the induction of sensitization as well as the plasticity of excitatory synapses onto MSNs [7,8]. Moreover, once induced, it suf ces to depotentiate the afferents onto D1R-MSNs to abolish sensitization [9]. We and others used these results to understand how such neural building blocks could add up to generate more complex behavior. In fact, ‘reversal therapy also works after short- and long-access cocaine self-administration to reduce cue-associated seeking [10] and some other addiction-like behaviors discussed by Samaha *et al*. [1].

The model that is emerging is that dopamine, through its respective receptors, induces long-lasting alterations of afferent transmission onto D1R-MSNs, thus altering circuit function. This change is largely independent of the acute modulation of neural activity by dopamine transients but relies on circuit activity modi cations by synaptic plasticity. The effects on the circuits downstream of D2R-MSN is less clear, particularly because some D1R-MSNs also send their axons to the ventral pallidum VP), where distinct behavioral correlates can by tied to the contrasting afferents. D2R MSNs projection may, to some extent, reflect negative reinforcement.

Current research now uses exposure paradigms that more closely mimic human addiction along with high-density behavioral observations. The goal is to build a circuit model integrating both positive and negative reinforcement, which together are responsible for the transition to compulsion that de nes addiction [11]. Integrating drug-evoked changes in synaptic weight

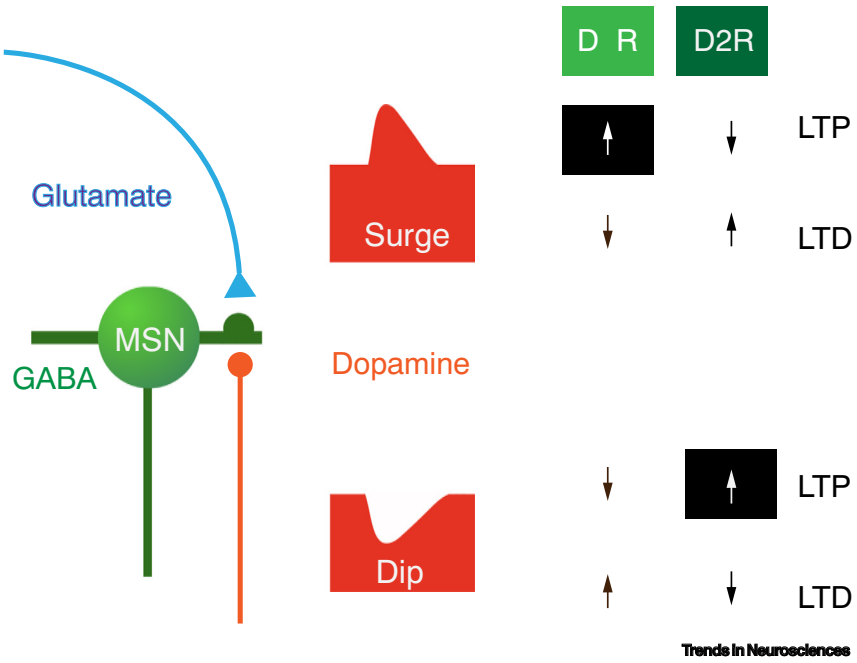

Figure 1. Dopamine modulation of synaptic plasticity in the nucleus accumbens NAc). The tripartite synapse between glutamate and dopamine afferents onto medium spiny neurons MSNs) undergoes long-term potentiation LTP) and long-term depression LTD), depending on the receptor being expressed. Dopamine surges favor LTP onto D1R-MSNs, whereas dopamine dips favor LTP onto D2R-MSNs. For details, see main text.

into a comprehensive wiring diagram will also enable predicting the effects on dopamine neuron ring. If excitatory efferents onto D1R-MSN are strengthened and their output onto local GABA interneurons enhanced, disinhibition of dopamine neurons could result [12], thus linking the 'sideways to the 'ups , as proposed by Samaha and colleagues [1]. It is therefore plausible that drug-evoked synaptic plasticity and ensuing altered circuit function can also lead to enhanced dopamine transients, which in turn would further modulate transmission and induce early adaptive behavior. Sensitized dopamine levels alone may therefore be insuf cient for driving the transition to addiction. In this context, it will be interesting to identify the speci city of intermittent drug exposure proposed by Samaha *et al*. [1] on drug-evoked synaptic plasticity.

What is clear already, is that the neuromodulatory role of dopamine on synaptic transmission, the 'sideways of dopamine, represents a compelling unitary neural substrate underlying drug-adaptive behavior and, eventually, addiction.

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