Computational Approaches to the Neurobiology of Drug Addiction

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Abstract

To increase our understanding of drug addiction – notably its pharmacological and neurobiological determinants – researchers have begun to formulate computational models of drug self-administration. Currently, one can roughly distinguish between three classes of models which all have in common to attribute to brain dopamine signaling a key role in addiction. The first class of models contains quantitative pharmacological models that describe the influence of pharmacokinetic and pharmacodynamic factors on drug self-administration. These models fail, however, to explain how the drug self-administration behavior is acquired and how it eventually becomes rigid and compulsive with extended drug use. Models belonging to the second class circumvent some of these limitations by modeling how drug use usurps the function of dopamine in reinforcement learning and action selection. However, despite their behavioral plausibility, these latter models lack neurobiological plausibility and ignore the potential role of opponent processes in addiction. The third class of models attempts to surmount these pitfalls by providing a more realistic picture of the midbrain dopamine circuitry and of the complex action of drugs of abuse in the output of this circuitry. Here we provide a brief overview of these di erent models to illustrate the potential contribution of mathematical modeling to our understanding of the neurobiology of drug addiction.

Intrigued by the apparent irrational behavior of drug addicts, researchers from a diversity of scientific domains have formulated a great number of theoretical schemes over the years to understand addiction. However, most of these models are qualitative in nature and are formulated using terms that are often ill-defined. As a result, the validity of these models has been di cult to test empirically, which has served to generate more controversy than clarity. In this context, as in other scientific fields, mathematical analysis and computational modeling may contribute to the development of more testable and rigorous models of addiction. Recently, several researchers have begun to simulate drug self-administration behavior in an attempt to better understand the pharmacological and neurobiological determinants of drug addiction. This brief overview describes a few examples of mathematical models of drug self-administration that illustrate the potential contribution of mathematical modeling to our understanding of drug self-administration paradigms. It should be mentioned that a number of powerful mathematical models have been developed over the years by economists to predict the influence of economic variables on drug consumption. For sake of brevity we will not discuss these in the present manuscript.

Currently, three classes of models have been advanced. Importantly, all of these models have in common to attribute to midbrain dopamine neurons a key, though significantly di erent, role in the development of addiction (see below). These di erent classes include in order of increasing neurobiological plausibility: 1) quantitative pharmacological models of dopamine function in reward modulation that explain the influence of pharmacokinetic and pharmacodynamic factors on drug self-administration; 2) abstract, computational models of dopamine function in reinforcement learning and action selection that predict the progression toward preferential drug choice with repeated drug use; and, finally, 3) neurophysiologically plausible models of midbrain dopamine circuitry and drug opponent processes that explain the transition to compul-

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sive and rigid drug use. Below, we describe the strength and limitations of each of these models and formulate several big challenges for future computational research on the neurobiology of drug addiction.

Pharmacological Models of Drug Intake Regulation

After acquisition and escalation of drug self-administration, the level of drug use becomes remarkably stable over time, a phenomenon that is documented in both humans and laboratory animals. This day-to-day stabilization of drug intake is generally associated with a daily regular distribution of drug injections, characterized by an initial, brief drug loading period followed by a maintenance period [75,69]. These findings suggest that both animals and humans learn to regulate drug intake. This interpretation is strengthened by many studies showing that both rats and humans adjust, more or less precisely depending on the class of drugs, the rate of self-administration to the unit dose available, presumably in an attempt to maintain drug reward around some ideal level, called variously the hedonic set point [4], the trigger point [74] or the satiety threshold [71]. Environmental (e.g., chronic stress) and/or drug-induced alterations in this self-regulatory behavior were recently hypothesized to contribute to the shift from controlled drug use to addiction [36].

Inspired by the seminal work of Yokel and Pickens [75], several quantitative models of acquired cocaine self-administration have recently been advanced [5,51,68]. All of these models postulate that acquired cocaine self-administration is "all or nothing" and is determined by a particular level of drug e ects. Depending on the model, this specific level of drug e ects either would serve as a goal that drives the self-administration behavior (negative-feedback loop model [5]) or it would define the pharmacological switch where the e ects of cocaine shift from being excitatory to being inhibitory (positive-feedback loop model – [51]).

According to the positive-feedback loop model formulated by Andrew Norman and Vladimir Tsibulsky [51], cocaine self-administration is not goal directed but is automatically induced when brain cocaine levels are within a specific range, called the compulsion zone because cocaine-induced responding is deemed out of control (i.e., insensitive to the positive or negative consequences of responding). The compulsion zone has a lower limit (the priming threshold) below which drug levels are too low to induce a response and an upper limit (the satiety threshold) above which cocaine levels inhibit self-administration behavior. Support for the positive-feedback loop model comes from a very elegant study showing that when cocaine levels were artificially maintained between the lower and upper limits of the compulsion zone by experimenter-programmed intravenous cocaine injections, animals responded for hours without receiving any response-contingent cocaine injection [51]. One specific prediction from this model is that cocaine should be able to elicit or to release specific actions, without deliberation and/or consideration of their future consequences.

According to the negative-feedback loop model, called hereafter the set-point model, drug self-administration is conceptualized as a goal-directed behavior ([5]. Under this paradigm, the goal of the cocaine user is to adjust the sensitivity of the brain reward system to a set level, presumably by increasing tonic dopamine signaling. Though still incompletely defined, the brain reward system is thought to include the neural circuitry involving the extended amygdala and its connections with the prefrontal cortex and the lateral hypothalamus. Thus, cocaine would not directly activate the reward system but would facilitate its activation by sensory stimulation via dopamine. This hypothesis is consistent with the role of dopamine transmission in the modulation of brain stimulation reward [31] and with the ability of cocaine to increase the reinforcing e ects of a range of brain stimulation intensities [7]. The set-point model predicts that the demand for drugs should be a function of both the basal level of dopamine signaling, which controls basal sensitivity to reinforcement, and the ambient level of reinforcing stimulation. Thus, individuals with low sensitivity to reinforcement and access to a poor array of alternative reinforcers should be at increased risk for drug use and addiction. Inversely, individuals with high sensitivity to reinforcement and access to a rich array of alternative reinforcers should be protected from developing drug use and addiction [2,38].

The set-point model satisfactorily simulates several features of intravenous cocaine self-administration as observed in laboratory rodents, including 1) the within-session dynamics of cocaine self-administration (initial loading, post-loading pause, and maintenance) and 2) the function relating the dose to the rate of injections [5]. In this model, an upward shift in the dose-injection function is induced by simulating a decrease in basal sensitivity to brain stimulation reinforcement similar to that seen in rats with escalated levels of cocaine intake [4,3]. This decrease in sensitivity – which was also reported recently in rats with prolonged access to heroin self-administration [34] – seems to result from both chronic counter-adaptations within the mesostriatal dopamine pathway [6,45] and sustained overactivation of brain reward-opponent neurotransmitter systems [36]. Thus, according to the set-point model, addiction is a vicious cycle whereby increased drug use, in the attempt to acutely normalize brain reward system, leads instead to its chronic alteration.

Both positive- and negative-feedback loop models of drug self-administration predict that the dose-injection function should be discontinuous at a threshold dose, with a descending limb, but no initial, gradual ascending limb. The term "threshold" refers here to an all-or-none increase in drug self-administration at a specific dose. This prediction was recently confirmed in a large sample of cocaine-trained rats. In each subject individually, below the threshold, there was no evidence of cocaine self-administration; at and above the threshold, the rate of injection spiked to its maximum and then decreased in a dose-dependent manner, a decrease that reflected cocaine titration. In all subjects, this critical transition in behavior occurred over a dose interval of less than 0.008 mg [52,76].

Finally, one should briefly mention that a non-quantitative alternative of the positive- and negative-feedback loop models of drug self-administration was recently proposed [54]. According to this novel model, animals would stop self-administering the drug when the drug e ect increases above a certain level because the drug is no longer reinforcing, "possibly due to the reinforcement system reaching full capacity." Thus, this specific drug level would act as an interoceptive discriminative stimulus, "signaling when additional drug will be reinforcing and when it will not" [54]. One specific prediction from this model is that the targeted extinction of this interoceptive discriminative stimulus should perturb the regularity of cocaine self-administration.

Despite these strengths, however, the validity and usefulness of pharmacological models of drug self-administration are limited by a number of important weaknesses. First, the neurobiological

plausibility of these models is obviously very poor. For instance, in the set-point model of drug intake regulation, the action of the drug on brain dopamine signaling is postulated but not modeled. Second, these models do not explain the initial acquisition and subsequent escalation of drug self-administration; they merely assume that these di erent stages have been experienced before the stabilization of drug intake. Third and most importantly, contrary to other computational models (see below), they do not conceptualize behavior as choice. As a result, they fail to incorporate action selection and decision rules that are important to understand the development of compulsive drug use [59]. Thus, an obvious challenge for research is to develop computational models of addiction with increased behavioral and neurobiological plausibility.

Abstract Computational Models of Drug Addiction

This challenge was taken up previously by a model borrowed from the machine learning techniques. Redish [59] presented an abstract computational model of cocaine addiction. The model is a straightforward application of the temporal-di erence reinforcement learning algorithm (TDRL) to action selection (see, for example, McClure et al. [46] for an overview). Briefly, within this framework, the agent is assumed to choose an action (e.g., pressing a lever to obtain a fixed drug dose) in function of its value relative to the values of other available actions (for an accessible and entertaining presentation of TDRL, see Niv and Schoenbaum [50]). The goal of TDRL is to learn the value of taking each available action. This goal is achieved by generating a dopamine signal proportional to the error of prediction (δ) between the expected and observed change in the reward associated with the selected action. Eventually, once the agent correctly predicts the reward following each action, there is no longer a dopamine signal and thus no further changes in value. The pattern of choice between available actions then becomes stable and is proportional to their expected values.

The key to Redish's model is that the value of the action leading to cocaine reward increases without bound with repeated drug choice because cocaine consumption constantly produces a dopamine surge – and thus a positive, false δ – through blockade of the function of the dopamine transporter. More specifically, the error of prediction generated during cocaine receipt has two separate terms, a normal reward term, called R(S), that is compensated during learning, as with any other nondrug rewards, and a relatively small, pharmacologically-induced dopamine signal term, called D(S), that is not cognitively compensable. In Redish's model, the normal reward term R(S) explains initial drug use while the neuropharmacological term D(S) would explain the subsequent overvaluation of the actions leading to cocaine reward. This model makes two specific predictions with great relevance to addiction. With repeated drug experience, drug choice should become 1) more inelastic to costs and 2) less sensitive to alternative nondrug reinforcers. The first prediction was recently confirmed in rats following escalation of heroin self-administration [37] but the other prediction is currently less well supported [37, 38].

Despite its obvious strengths, Redish's model has some important limitations. First, as recognized by Redish himself, the unbounded increase in the value of drug-related actions is behaviorally and neurobiologically implausible. Second, the model postulates that the normal reward term R(S) of the error of prediction following cocaine receipt is independent from the neuropharmacological term D(S). This implies that cocaine reward per se does not depend on cocaine action on the dopamine transporter and thus on the resulting surge of dopamine – which is obviously highly unlikely [70]. In fact, the initial basis of the reward term R(S) is currently obscure. Furthermore, the model assumes that the size of this term is much greater than the size of the term D(S) which is again highly unlikely (e.g., 37). How the output of the model changes when the sizes of these two terms approach is currently unclear. Third, one of the key assumptions of the model – that the dopamine surge following cocaine receipt does not accommodate – is also probably incorrect (see, for instance, 73; 45; 6). Fourth, because of weaknesses that are inherent to TDRL, the computational model of cocaine addiction proposed by Redish [59] does not make any specific prediction about the e ects of drug exposure on the subsequent extinction of drug use (see below). Finally and most significantly, Redish's [59] model is very abstract in nature which considerably weakens its neurobiological plausibility. As discussed above, it postulates that cocaine has intrinsic rewarding e ects but does not model the detailed neurophysiological mechanisms that confer to cocaine its abuse liability. These key questions are being addressed by an alternative approach, based on neurodynamical approaches at the systems and circuit level.

Neuro-Dynamical Models for Drug Addiction

Large Scale Framework for Nicotine Addiction

Gutkin and colleagues [29] have recently introduced a neurocomputational framework for nicotine addiction that integrates nicotine e ects on the dopaminergic (DA) neuron population at the receptor level (signaling the reward-related information), together with a simple model of action-selection (**Fig. 1**). This model also incorporates a novel dopamine-dependent learning rule that gives distinct roles to the phasic and tonic dopamine neurotransmission. The authors try to tease out the relative roles of the positive (rewarding) and opponent processes in the acquisition and maintenance of drug taking behavior, and the development of such behavior into a rigid habit.

The major hypothesis for the approach is that the nicotine e ects on dopamine (DA) signaling in the ventral tegmental area (VTA) initiate a cascade of molecular changes that in turn bias glutamatergic (Glu) learning processes in the dorsal striatum-related structures that are responsible for behavioral choice, leading to the onset of stable self-administration. Gutkin et al. [29] specifically hypothesized that nicotine, through activation and up-regulation of nicotinic acetylcholine receptors (nAChRs) in the VTA (e.g., 55; 11), dynamically changes the gain of the dopaminergic signaling. Hence, nicotine both potentiates the phasic DA response to rewarding stimuli and evokes such signal by itself [12, 17, 55]. Note that this is rather di erent than in the model of Redish [59] discussed above where the pharmacological and reward signals are independent. In the neurodynamical framework, the reward signal is in fact modulated by the pharmacological e ect of the drug. The phasic DA in turn instructs the learning and plasticity in the action-selection neural machinery that is modeled as a stochastic winner-take-all network [13, 74] and reflecting activity in the dorsal nigro-striatal-cortical loops [8, 21]. Since both DA and nicotine potentiate Glu plasticity in the dorsal striatum [61], the authors propose a specific Hebbian

learning rule for the excitatory (cortico-striatal-cortical) synapses gated by the tonic DA. Persistent nicotine-dependent depression in tonic DA then causes the learned behavioral bias to become rigid. Here Gutkin et al. [29] hypothesize a slow-onset opponent process that is recruited and that in turn disrupts DA neurotransmission to the point that extinction learning or response unlearning is impaired; hence, progressively, nicotine self-administration escapes from the control of the DA signal. This e ectively models the ventral-dorsal progression of long-term addiction hypothesized by Di Chiara (1999). Further supporting data for the framework is discussed in Gutkin et al. (2006).

The general framework is applied to simulating self-administration of nicotine. In the computational framework, nicotine a ects the DA response through a three-time scale model of drug action on the DA neuron population; the phasic nicotine dependent activation of nicotinic-ACh receptors, slower nicotine dependent upregulation or increase in number of receptors (modeled as a multiplicative term in the model) and subsequent upregulation-evoked opponent homeostatic down-regulation of nAChRs (and hence their responses to nicotine).

Injections of nicotine in su cient doses potentiate the DA signal so as to gate plasticity in the action-selection machinery. Since nicotine is contingent on a specific action choice (encoded in the model as activity of a specific neuronal population), the excitatory synaptic weights of the corresponding neural population increase and bias the action-selection towards the self-administration of nicotine. With prolonged self-administration, the influence of the DA signal diminishes due to the opponent process (consequence of the receptor down-regulation) – the behavioral bias for the action leading to nicotine becomes "stamped in". Drug seeking behavior becomes routinized, and inelastic to the motivational value of nicotine or the cost and is associated with hypodopaminergic withdrawal [57].

Simulations of the above framework, showed that positing drug induced neuro-adaptations in the ventral DA "critic" and drug-modulated learning in the dorsal cortico-striatal "actor," is sufficient to account for the development and maintenance of self-administration. Importantly, the positive rewarding e ect of the drug is translated into biased action selection and choice making, whereas the slow opponent process plays a key role in cementing the drug-associated behavior by removing the DA signal from the range where learning (and unlearning) can take place. Hence, the model predicts that in the long-term the self-administration behavior would tend to become progressively more di cult to extinguish. The model speculates that this e ect on action-selection learning may be the reason why nicotine has reportedly high addictive liability despite its limited hedonic impact.

As all computational models, the framework of Gutkin and colleagues [29] has a number of strengths and shortcomings. The major strength of the model framework is that it neatly integrates the various processes involved in nicotine self-administration identifying the various functional e ects with biological mechanisms and brain structures. This framework can be viewed as a "knowledge repository model" [9] synthesizing a host of known e ects at multiple levels of organization. For example providing links from receptor level e ects to behavior. The modular structure of the framework makes it easy to potentially incorporate additional structures and mechanisms to test their e ects. The model further makes a number of interesting predictions. An important prediction of the model is that plasticity in the dorsal striatum of animals that are chronically exposed to nicotine should be reduced. These animals should show deficits in re-adjusting their behavior under new conditions (see [28] for possible experimental equivalent). The above framework implies a hierarchy of thresholds for the progressive stages of addiction. This is an outcome of the distinct roles of the direct motivational (rewarding), and opponent processes in drug addiction such that the dose and duration of the exposure to nicotine for the initial sensitization by the drug is below that for the acquisition of the self-administration, followed by higher thresholds for the stabilization of the self-administration and for the transfer to habit-like rigidity. The proposed computational framework implies that the sensitization of behavior by nicotine through DA-dependent processes may be disassocisted(por)57(om7(ion suc)15.6(h0(u)

process. Hence, the acquisition of self-administration would be under motivational control. The behavioral choices will be selected probabilistically in agreement with their relative value. The development of rigidity in actions is a major point of the neuro-computational framework proposed by Gutkin et al. [29]. The model suggests how, in the long run, processes that oppose the primary reward ingrain the drug-related behavior making it independent of the motivation state and value of various action choices and di cult to modify in the face of changing contingencies. This further implies that drug-related behaviors would be extremely di cult to unlearn, even when the environment is enriched by new rewarding stimuli.

On the other hand, a potential shortcoming of the neurodynamical approach, is that of course like all models this framework rests on a number of assumptions to be confirmed and leaves questions that are not directly addressed. For example, explaining why nicotine self-administration can be di cult to acquire remains a challenge. One clue may come from the hypothesized multiplicative role of nicotine on dopaminergic signaling: at low doses nicotine may not boost the phasic dopamine signal su - ciently to lead to learned self-administration, yet when the dopamine burst is evoked by another rewarding stimulus, the multiplicative e ect of nicotine would boost such DA response nonlinearly, subsequently leading to a preference for drug-related behavior. A more general challenge for the neurodynamical approach is how to integrate it with the reinforcement learning style models, and how to apply it to situations that are more complex than the simple two choice self-administration task. For example it is not clear if the framework as phrased in Gutkin et al. [29] can account for accommodation of the phasic DA signal as the animal learns to predict a natural reward and/or the temporal shift in the DA signal from the reward delivery to the time of the stimulus that is predictive of that reward. Hence additional mechanisms may need to be introduced into the framework in order to remedy this shortcoming. At the more mechanistic level, the global framework is rather vague on the specific identity of the opponency: Gutkin and colleagues [29] assigned it to homeostatic down-regulation of receptors, however it may be due to influence of a further non-dopaminergic process. In addition, the global model does not pin-point the specific local mechanisms by which nicotine may bias the DA signaling. We are pursuing these issues by building circuit level models of dopaminergic circuitry (see below).

Circuit level approach to nicotinic control of dopaminergic signaling

The above computational framework laid out the general lines of thinking about the global e ects of nicotine on DA-dependent learning in the action selection machinery. However the work above pointed out a key missing link in our understanding of the addictive nature of nicotine, and possibly for all other addictive drugs that act primarily through dopamine: how does the drug alter dopaminergic signaling? In particular, how does nicotine modify the machinery that constructs the phasic DAergic signal which is known to modulate synaptic plasticity [53], and which has been suggested to signal the occurrence of unexpected rewards [65]. If we were able to tease out the specific e ects of nicotine, we might be able to understand how this drug modulates the rewarding properties of environmental stimuli, creates associations between the drug taking and such stimuli and hence creates a cycle of addiction. In order to answer this question, we sought to develop a biologically more detailed understanding of how precisely does nicotine a ect the input integration performed by the VTA. We hence developed a model of the VTA circuitry taking into account the interaction of nicotine with DA signaling pathways.

The circuit model of the VTA presented here accounts for a erent inputs to the VTA, local circuitry and the location as well as activation/desensitization properties of nAChRs. VTA DAergic and GABAergic cells receive major excitatory glutamatergic (Glu) inputs from the prefrontal cortex (PFC) and the tegmental nuclei in the brainstem [14,15]. On the other hand, cholinergic inputs from tegmental nuclei to VTA selectively target GABA neurons [26]. GABAergic neurons in the VTA furnish local inhibitory connections and e erents to various structures including the brainstem [32,66]. Further inhibitory connections to the VTA emerge form the ventral palladium and the nucleus accumbens [33]. Thus the VTA is an intricate neuronal circuit generating DA signal in response to cortical and subcortical inputs as well as in response to nicotine (see **Fig. 2A**).

Various nAChR subtypes are expressed on DA neurons, GABAergic neurons and on glutamatergic terminals in the VTA [42]. Behaviorally relevant stimuli evoke ACh release into the VTA, causing nearly synchronous activation of nAChRs (Dani et al. 2001). The rapid delivery and breakdown of ACh precludes significant nAChR desensitization. In contrast, nicotine concentrations remain elevated (~500 nM) for about 10 min in the blood of smokers [30]. This activates and desensitizes nAChRs within seconds to minutes [56]. Considering the impact of nicotine at the circuit level requires a detailed examination of the receptor responses to nicotine and acetylcholine. The various subtypes of nAChRs have distinct activation/desensitization properties and expression targets : The high a nity α4β2 subunit containing nAChRs desensitize slowly; low a nity α7 nAChRs desensitize rapidly [55]. DA neurons express both α4– and α6-containing nAChRs. The GABA neurons express mostly α4β2 nAChRs. The α7 nAChRs are found on terminals of glutamatergic projections to the VTA [35]. Although nAChRs are found in many brain regions, those located in the VTA dominantly mediate the rewarding e ects of nicotine [16].

We developed a mean-field model of the VTA reflecting average activities of the DA and GABAergic neuron populations with respect to the local connectivity, a erent inputs as well as the localization and activation/desensitization kinetics of nAChR subtypes. We accounted for the two main classes of nAChRs responsible for nicotine evoked responses in the VTA, *i.e.* high a nity slowly desensitizing (α4β2-type), and low a nity rapidly desensitizing nAChRs (α7-type) [40,11,27]. Based on these properties of nAChRs subtypes, we investigated the dynamical response of DA and GABAergic neurons to nicotine exposures and we identified the signaling pathways that are su cient to explain key experimental data (see **Fig. 2B**).

In particular, we used the model to address the disparity in the literature related to the site of action of nicotine. *In vitro* recordings from DA neurons conclude that DA increase is due to disinhibition [40,41]. Here nicotine transiently boosts GABA transmission to DA cells, followed by α4β2 nAChR desensitization that removes excitatory drive to the GABA cells, *i.e.* disinhibits DA cells. In contrast, *in vivo* studies emphasize the importance of β2-containing nAChRs on DA neurons [39], suggesting that these receptors provide direct nicotine mediated excitation to DA cells increasing DA activity.

Our explorations of the model showed that *In vitro* and *in vivo* data can be reconciled by taking into the account the di erence

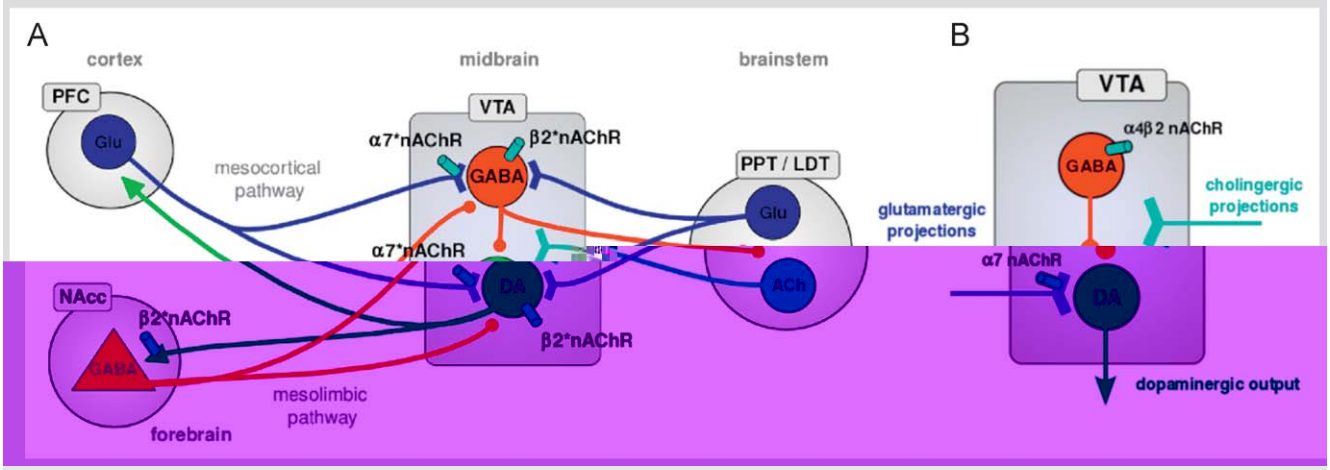

Fig. 2 Afferents and efferents of the VTA. **A,** Embedding of the VTA with respect to its related structures. Main input and output pathways to and from the VTA and the location of specific nAChR subtypes in the VTA are schematized (blue-Glu pathways, green-DA pathways, red-GABAergic pathways, cyan-ACh pathways; PFC-prefrontal cortex, NAcc-nucleus accumbens, LDT-laterodorsal tegmental nucleus, PPT-pedunculopontine tegmental nucleus). **B,** The minimal components of the VTA circuit necessary to account for data on nicotine exposures *in vitro* and *in vivo* are depicted.

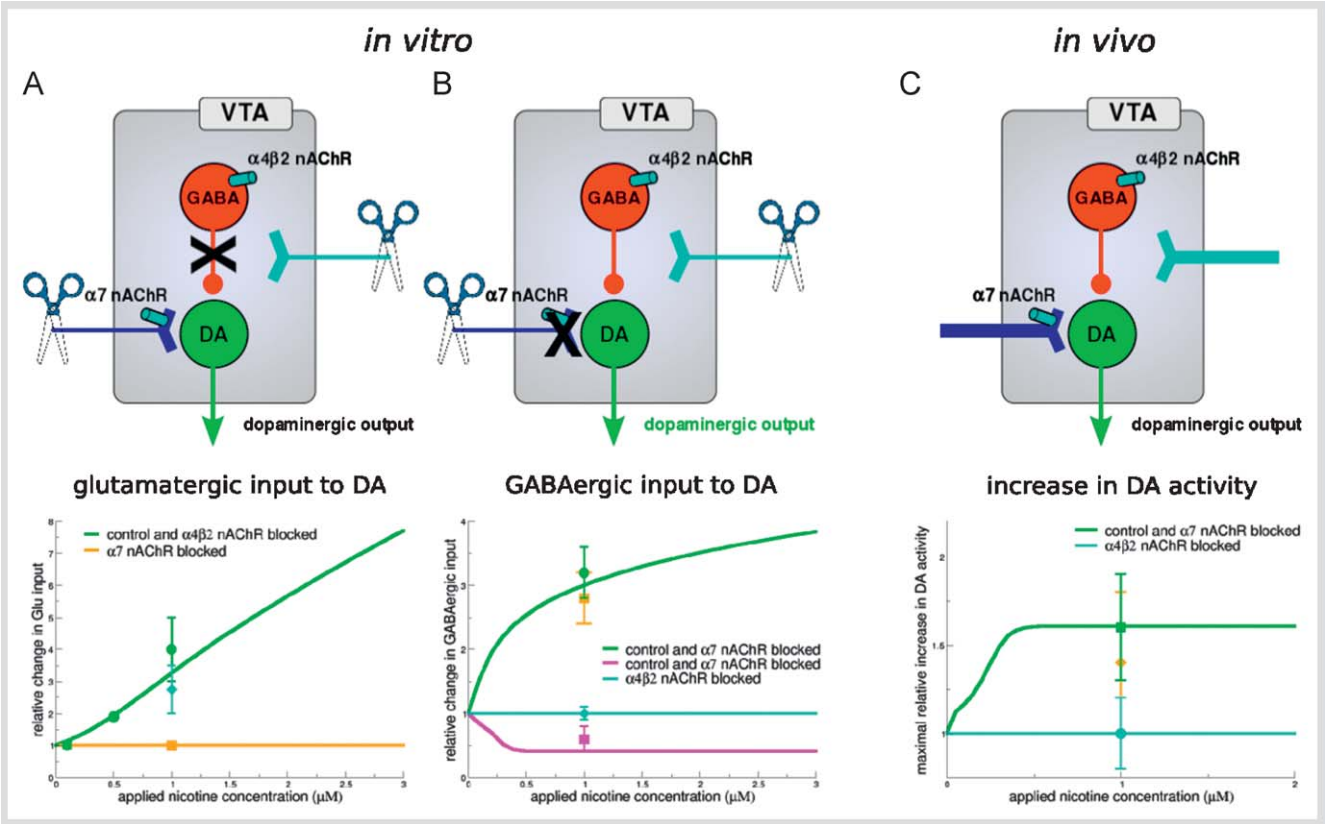

Fig. 3 Minimal model reproduces VTA DA responses to nicotine exposures *in vitro* (**A** & **B**) and *in vivo* (**C**). The respective situation is illustrated in the top panels, *i.e.* low (high) afferent input strength for *in vitro* (*in vivo*) conditions. **A & B,** Input changes to DA cells during a 2 min exposure to 1 μm nicotine under *in vitro* conditions. The Glu input increase (green line) is mediated by α7 nAChRs (A). The increase (green line) and subsequent decrease (magenta line) of GABAergic input is abolished by α4β2 nAChR blockade (B). Note that GABAergic transmission in A (glutamatergic transmission in B) is blocked in experiments and simulations. **C,** Increase of DA activity (green line) following nicotine exposure under high afferent input levels. The increase is abolished in the absence of α4β2 nAChRs (cyan line). In all panels, lines correspond to model results, and points to data adapted from Mansvelder *et al*. 2000 – panel A; Mansvelder *et al*. 2002 – panel B; Mameli-Engvall *et al*. 2006 – panel C). Green and magenta represent control conditions, cyan - with α4β2 nAChRs blocked, and orange - with α7 nAChRs blocked.

in a erent input strengths to the VTA. The cortical glutamatergic and subcortical cholinergic input levels are low *In vitro*, whereas such input levels are high *in vivo*. ▶ **Fig. 3** shows a summary of our results. Note that the circuitry of the VTA is left exactly the same in *In vitro* and *in vivo* situations.

In vitro, the increase of Glu input to the DA cells during nicotine exposure is mediated by α7-containing nAChRs ([40], see

Fig. 3A). In these experiments GABAergic transmission is blocked. The model accounts qualitatively for this increase when the a erent Glu activity is low (**Fig. 3A**). With blocked Glu transmission, changes in the GABAergic input to the DA cells are predominantly mediated by α4β2 nAChRs (**Fig. 3B**; [41]). The initial increase of GABAergic input is followed by a drop below baseline after removal of nicotine. The model exhibits a similar time course and profile for the GABAergic input to DA cells, provided the ACh input to the VTA is low (**Fig. 3B**). The model makes it clear that the undershoot stems from desensitization of α4β2 nAChRs. Hence, the di erential activation/desensitization kinetics of the two nAChR types combined with low a erent input explain the mechanism of nicotine action *In vitro.*

We found that exactly the same circuit model accounts for the *in vivo* data by changing only the a erent input strength. *In vivo* nicotine boosts DA activity. This e ect remains in α7-knockout mice but is absent in α4 knockout animals [39]. In our model with strong Glu and ACh inputs, the high a nity α4β2 nAChR expressed on the GABA neurons are already significantly activated before drug exposure. Nicotine then mainly drives these receptors into the desensitized state. This reduces GABAergic activity and disinhibits DA cells thereby boosting the DA output. We furthermore found that removing selectively the two classes of nAChRs in the model reproduces the *in vivo* knock-out studies (see **Fig. 3C**).

The combination of a population activity model of the VTA with a detailed model of nAChR kinetics enabled us to understand the mechanisms of nicotine action on the DA machinery. Our approach confirms the hypothesis that α4β2 nAChRs on GABA cells predominantly mediate nicotine action. Identifying the specific functional targets of nicotine action has potential direct implication for developing nicotine treatments, e.g. for designing replacement drugs. Hence a clear advantage of this approach is its potential applicability to translational research. However, the model as briefly described above is far from being complete. We have focused only on a erent input and the local circuitry of the VTA and did not address the possible recurrent involvement of other neuronal structures involved in DA-signaling, such as the nucleus accumbens (**Fig 2A**). Treating a dynamical situation, where inputs signal behaviorally relevant features, remains a key challenge to the local circuit modeling approach. There are two possible complementary directions to address this challenge. First is to understand how the VTA circuit model would respond to transient inputs, *i.e.* signaling reward delivery, expectation of reward or appearance of a behaviorally relevant stimuli. Posing the question in more functional terms: what might be the computations that the VTA circuitry performs on its inputs, and are such compatible with the reinforcement learning accounts of DA signaling? Second and complementary approach is to incorporate the local circuit model of the VTA in a computational framework capable of simulating behavior, and examine if the specific mechanisms we propose are likely to lead to the behavioral outcomes observed under the influence of nicotine. Finally, a more general challenge to the circuit model is whether the model generalizes to drugs of addiction other than nicotine? These are the topics that are being actively pursued.

Long-term Future Developments

Computational modeling of drug addiction is still in its infancy. Nevertheless, as reviewed here, important aspects of drug self-administration and drug addiction have already been simulated with some success, including the initial acquisition of drug self-administration, the regulation of drug intake, the progression toward preferential drug choice and the transition to rigid drug habits. However, there remain many big challenges for future computational research on the neurobiology of drug addiction. First, some important behavioral aspects of addiction are still totally untouched. For instance, current computational models fail to model one of the most significant behavioral e ects of drugs of abuse on addicted individuals, that is, their ability to directly prime craving and/or drug seeking. In addition, another behavioral aspect that remains to be explicitly modeled is how drug use escapes "voluntary control" to become a rigid habit. To address this problem will probably require incorporating higher-order modules of decision making and cognitive control into existing computational or circuit models of addiction. Second, another big challenge will thus be to determine how to realize this incorporation of the higher level of cognitive control and decision making with the neuronal circuit and molecular levels directly impacted by the drug. This would necessarily involve building mesoscopic computational models that treat addiction in a systematic fashion, and may potentially account not only for the drug e ects at the di erent and disparate levels of neurobiological organization but also for various time scales. Finally, a last but not least large scale challenge will be to construct computational models that span genetic and biophysical and behavioral domains so as to inform us about the ultimate basis for the individual variability in the vulnerability to drug addiction.

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