A neurocomputational hypothesis for nicotine addiction

Boris S. Gutkin†, Stanislas Dehaene‡, and Jean-Pierre Changeux§

†Recepteurs et Cognition, Unité de Recherche Associée, Centre National de la Recherche Scientifique 2184, Institut Pasteur, 75015 Paris, France; and ‡Cognitive Neuroimaging, Institut National de la Santé et de la Recherche Médicale–Commissariat à l’Energie Atomique, Unit 562, Service Hospitalier Frédéric Joliot, 91401 Orsay, France

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We present a hypothetical neurocomputational model that combines a set of neural circuits at the molecular, cellular, and system levels and accounts for several neurobiological and behavioral processes leading to nicotine addiction. We propose that combining changes in the nicotinic receptor response, expressed by mesolimbic dopaminergic neurons, with dopamine-gated learning in action-selection circuits, suffice to capture the acquisition of nicotine addiction. We show that an opponent process enhanced by persistent nicotine-taking renders self-administration rigid and habitual by inhibiting the learning process, resulting in long-term impairments in the absence of the drug. The model implicates distinct thresholds on the dosage and duration for the acquisition and persistence of nicotine addiction. Our hypothesis unites a number of prevalent ideas on nicotine action into a coherent formal network for further understanding of compulsive drug addiction.

Main Hypothesis

Nicotine effects on the VTA DA signaling initiate a cascade of molecular changes that, in turn, bias glutamatergic learning processes in the dorsal striatal structures responsible for behavioral choice, leading to the onset of stable self-administration. Nicotine, by activating and up-regulating nAChRs, dynamically changes the gain of the DA signaling: nicotine both potentiates phasic DA, in turn, directs learning at the DA gates this learning process (3, 34). Persistent nicotine-taking changes the gain of the DA signaling: nicotine both potentiates phasic DA, in turn, directs learning at the DA gates this learning process (3, 34). Persistent nicotine-taking changes the gain of the DA signaling: nicotine both potentiates phasic DA, in turn, directs learning at the DA gates this learning process (3, 34).

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Abbreviations: A-S, action-selection; DA, dopaminergic; nAChR, nicotinic acetylcholine receptor; VTA, ventral tegmental area.

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dependent renormalization in tonic DA causes the learned behavioral bias to become rigid, and nicotine self-administration progressively escapes from the DA control. Because DA adaptations lead (in time) the learning in the A-S machinery, our model implements and gives a functional meaning to the ventral–dorsal progression of long-term drug addiction (12).

Model Framework

The model consists of two modules, both affected by nicotine: a module that simulates action selection and a DA signal module governing outcome-driven learning of action choices.

DA Signaling Module. This module consists of a single neuronal population that is under the control of acetylcholine (or nicotine) binding to the nAChRs. Phasic DA activity signals action outcomes: the burst responses of the VTA DA neurons (15). In behavioral terms, the DA response relates to the reward-prediction error (5), which in some versions of reinforcement learning theory modifies the “value function”/“learned incentive” of the stimulus/action choice (6, 7). In our specific context the VTA DA signal is affected directly by nicotine binding to the nAChRs; thus, the notion of “outcome” of the action becomes implicit. For the neutral (unrewarded) action (no nicotine injection), we hypothesize no phasic activation of the DA population.

We model nicotine-injection-dependent changes in the DA module as a cascade occurring on three distinct time scales: (i) phasic nicotine effect, a short time scale activation (seconds) of nAChRs by nicotine action [nicotine activates nAChRs on the Tonic DA and

\[ + \text{Phasic DA increase above tonic and pre/postactivity increase} \Rightarrow \text{potentiate weights} \]

\[ + \text{Phasic DA increase above tonic and no pre/postactivity increase} \Rightarrow \text{decrease weights} \]

\[ \text{no Phasic DA and pre/postactivity increase} \Rightarrow \text{decrease weights} \]

Scheme 1. The differential equations are given in Methods.

DA-Governed A-S Learning. DA signal modifies responses of the action selector by gating learning in the recurrent excitatory connections, as a separate corticostriatal loop coding for an action plan. Competition between the action plans (or loops) is implemented through cross-inhibition between the units. In physiological terms, this effect can be subserved either by the GABAergic collaterals whose physiological function has been identified in the striatum (40) or as an outcome of the negative feedback between direct and indirect corticostriatal pathways. Recurrent excitation ensures that A-S occurs even in response to transient stimuli. Action choice depends on integrating the stimulus strength, the internal dynamics (self-activation and cross-inhibition), and the random inputs (see supporting information, which is published on the PNAS web site). This model generates realistic response-time distributions (41), which change as the reward history modifies the A-S connections.

Nicotine injections act at three time scales to (i) a slower positive-feedback process acts on a time scale of minutes and reflects the up-regulation of nAChRs by a repeated exposure to nicotine that persists after a long-time drug exposure; (ii) and long-term homeostatic opponency, a renormalization of the nAChR response after prolonged hyperactivation by nicotine (scale of several weeks) and settling of nAChRs into an inactivated but sensitized state/phenotype. This effect results in lower tonic DA response while preserving the phasic signals in response to nicotine.

A-S Module. We implement A-S by a competitive activation in a “winner-take-all” network representing activity in the dorsal nigrostriatocortical pathway (7, 8, 9). We identify each of the units, with its recurrent excitatory connections, as a separate corticostriatocortical loop coding for an action plan. Competition between the action plans (or loops) is implemented through cross-inhibition between the units. In physiological terms, this effect can be subserved either by the GABAergic collaterals whose physiological function has been identified in the striatum (40) or as an outcome of the negative feedback between direct and indirect corticostriatal pathways. Recurrent excitation ensures that A-S occurs even in response to transient stimuli. Action choice depends on integrating the stimulus strength, the internal dynamics (self-activation and cross-inhibition), and the random inputs (see supporting information, which is published on the PNAS web site). This model generates realistic response-time distributions (41), which change as the reward history modifies the A-S connections.

Under control conditions, a choice yielding an unexpected reward (signaled by phasic DA firing) is potentiated (weights increased) and other actions are depressed (weights decreased). Nicotine injections act at three time scales to (i) provoke, (ii) potentiate, and (iii) depress different aspects of the DA signal. Initially, this boosts the drug-armed action weight, installing the positive-feedback cycle of self-administration. In the long-term, the opponent process reducing the tonic DA would freeze the plasticity and make the previously potentiated behavior robust to changes in the rewarding quality of nicotine.

Results

Nicotine Injections Elicit Neuroadaptation in the DA Module. The model simulates the following aspects of nicotine actions. Phasic nicotine injection provokes an acute increase in nAChR activation. Under tonic nicotine injection, this increase is followed by a slower up-regulation of the nAChRs (see Fig. ). A third, much slower

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opponency acts to renormalize the average nAChR sensitivity to control levels. When nicotine is removed, this slow opponency leads to a long-term depression of the nAChR activity. Because nAChR activity controls the gain of the DA population, nicotine modifies the DA signal that may be elicited by behaviorally relevant environmental stimuli and actions. The transient or medium-term nicotine administration leads to activation, followed by up-regulation of the nAChR population, in turn increasing the gain of the DA population. The long-term opponency results in a decrease in the amount of nAChR activation. When nicotine is injected (only phasically in the model) the DA signal shows, as expected, a rapid increase due to the activation of the nAChRs (see Fig. 3 for an experimental analog); however, in the simulation, the slow opponent renormalization of the DA response to nicotine is not evident (see below for discussion).

A chronic administration of nicotine leads to rapid DA signal increase (Fig. 2, first graph) followed by a sensitized DA signal and a slower renormalization (to control levels when nicotine is present). This cascade directly corresponds to DA signaling in animals chronically administered with nicotine (44) and hints at what would happen in animals that chronically self-administer nicotine (15). In the long term, the spontaneous DA activity returns to normal levels, the DA signal for weaker stimuli is depressed, and nicotine-boosted stimuli are potentiated. Under removal of nicotine the DA level drops dramatically (see below) and recovers much later, on the time scale of the slow opponent process.

Nicotine Self-Administration Is Driven by the DA-Gated Action Learning. Injections of nicotine potentiate the DA signal to gate plasticity of the excitatory self-connections in the A-S module. Provided that the injection is contingent on a specific action choice, the excitatory weights of the corresponding neural population are increased and a bias in A-S is established, leading to self-administration of nicotine (Fig. 4; open symbols represent the neutral action choice, and filled symbols represent nicotine-armed choice).

During the initial stages of self-administration (Fig. 4A, sessions 1–4), the nicotine intake leads to a general increase in motor activity: both armed and neutral action latencies decrease. In this regime the A-S is similar to control conditions: random inputs break the symmetry in the dynamics and lead to self-initiated choices (50/50 between the two) (see supporting information for noise-driven A-S). Subsequently, the behavior becomes selective: the recurrent weight for the nicotine-administration action plan increases beyond the threshold necessary to overcome the random inputs. This action is progressively robustly selected, and the neutral choice declines. The initial latency decrease corresponds to the motor activational effects of nicotine observed experimentally (45, 46), and the differential responding for the armed vs. the neutral action choice is in direct concordance with experimental results on nicotine self-administration (7).

For transient self-administration, responding extinguishes once nicotine is withdrawn but is reacquired by the model once nicotine is reestablished (Fig. 4A), indicative of behavioral sensitization (1, 3).
We have shown that a minimal neurocomputational model, putatively result in anhedonia and possibly other somatic with-
as well as behavioral choice, a decrease of DA signal would
terminate in the brain structures associated with an hedonic state
stamped in. Because the outputs of the DA neurons from the VTA
DA leads to a pathology of learning, and the behavior becomes
effect: on learning and on the hedonic state. The drop in the tonic
withdrawal after a prolonged self-administration (15). In our
opponent process. Such decline has been reported during nicotine
long-term, the self-administration behavior becomes “routin-
ized.” independent of the hedonic or motivational value of
nicotine: it continues to be self-administered when nicotine is
withdrawn and even when paired with an aversive stimulus
(simulations not shown). This progression forms a key experi-
mental prediction of the model.

Nicotine Self-Administration Leads to Behavioral Sensitization and Withdrawal. The model shows that transient injections of suffi-
cient nicotine doses potentiate the DA activity to the levels
necessary to initiate plasticity of the self-connections in the A-S
module. The priming dose leads to a small bias in the behavior,
which is boosted to observable levels by a subsequent nicotine
dose and results in behavioral sensitization (Fig. A) (1, 15). We
note here that the sensitization of the DA responses to nicotine
injections does not necessarily lead to persistent behavioral
sensitization directly: this effect is crucially dependent on DA-
gated learning (potentiation of weights in the model). In the
model, DA may, depending on the dose, lead to transient
behavioral sensitization.

Furthermore, the model shows that persistent self-administration of nicotine leads to up-regulation of nAChRs and the recruitment
of the opponent process (simulations not shown). Subsequently, if
in simulations of long-lasting self-administration (as in Fig. B)
nicotine is withdrawn, the DA signal shows a dramatic decline that
persists for a long period (Fig. B). This decline is due to the
long-term removal of the up-regulated nAChR signal by the slow
opponent process. Such decline has been reported during nicotine
withdrawal after a prolonged self-administration (15). In our
framework the nicotine-evoked opponent process has a double
effect: on learning and on the hedonic state. The drop in the tonic
DA leads to a pathology of learning, and the behavior becomes
stamped in. Because the outputs of the DA neurons from the VTA
terminate in the brain structures associated with an hedonic state
as well as behavioral choice, a decrease of DA signal would
putatively result in anhedonia and possibly other somatic with-
drawal signals.

Discussion
We have shown that a minimal neurocomputational model, positing nicotine-elicited neuroadaptations in the VTA and
DA-modulated learning in the dorsal striatocortical A-S, suffices
to account for a number of basic experimental findings associ-
ated with nicotine addiction. The model gives a key role to the
long-lasting up-regulation of the nAChRs by nicotine with the
subsequent effects on the DA signals. Short-term nicotine
effects lead to behavioral motor activation. Provided that nic-
ocine is administered in a behaviorally contingent manner (such
as self-administration), this effect provides the initial behavioral
bias that leads to a preferential selection of actions resulting in
addiction. The long-term up-regulation of the receptors causes a
potentiation of the DA signal carrying information about the
incentive salience of actions (action-outcome contingency), in
turn leading to differential gating of synaptic plasticity in neu-
ronal populations coding for the specific action choice.

Our model also shows that a slow opponent process plays a key
role in cementing the drug-associated behavior by reducing DA
responses. When nicotine is removed, the DA levels drop below
those required for efficient learning. During the withdrawal the
animal does not unlearn drug-taking choices despite possible
negative consequences. Hence, once learned, self-administration
behavior escapes from motivational control and becomes robust
to extinction, i.e., habitual. The reduced DA responses to all
stimuli/actions lead to a general hypohedonic state. The model
predicts reduced striatal plasticity in animals chronically admin-
istered and then withdrawn from nicotine (the reduced or
withheld dose), which would then show deficits in readjusting
their behavior under new conditions. This prediction is testable
in both humans and laboratory animals and perhaps in analogy
with behavior observed in nAChR knockout mice (46).

The above results imply that distinct dose/duration thresholds
for stable acquisition and persistence of the nicotine-associated
behavior are defined by the drug ability to activate nAChRs, to
recruit nAChR up-regulation and the opponent process. The
lowest threshold is for behavioral sensitization, which does not
require learning in the A-S and is only transient. Below this
threshold, desensitization rather than sensitization would occur
and nicotine would have an aversive behavioral valence. Next is
the threshold for differential self-administration. It occurs when
the action choice weights are learned beyond the threshold
necessary to overcome the internal noise: the up-regulated
nAChRs and persistently increased DA gain ensure learning.
Further threshold for the persistence of nicotine-taking is de-
fined by recruitment of the opponent process (withdrawal, lack
of unlearning, and escape from DA control of behavior).

Our computational framework further implies that, in the course
of addiction, the persistent changes should progress from the
mesolimbic circuit to the A-S nigrostriatofrontal loops. Initial
mesolimbic changes are necessary for initiation of addictive behav-
ior, caused by the motivational, activational, and or hedonic effects
of nicotine. The subsequent A-S changes are largely independent of
the motivation valence of the drug as long as the behavioral bias has
been acquired and reinforced for a sufficiently long time scale (that
of the slowest opponent process).

We have made a number of mechanistic choices and assumptions
to subserve the functional effects, such as the nicotine→DA pathway and the identity of the opponent process.
Hence, experimental data are required to validate such choices.
For instance, the nAChR up-regulation needs to be observed in
self-administration paradigms; a subsequent opponent process, at
the level of the receptors, needs to be identified as, for
example, a down-regulation in the number of receptors or a
change in affinity/cooperativity mediated by covalent modific-
ations or changes in subunit composition (0). The crucial role
of the VTA DA signaling in the onset of self-administration implies
that wild-type animals should self-administer nicotine most robustly into the VTA directly (see ref. 9).
Recent work (1) indicates indirectly that nicotine may be self-administered into the striatum, provided that the action choice is already
sufficiently salient to evoke bursting DA activity. This require-
ment is different from other addictive drugs (like cocaine) that
target DA at the targets of the VTA afferents.

Our model is inspired by abstract reinforcement learning models (47) of instrumental conditioning. It is in line with a
recent model for cocaine addiction as a disorder of DA-signalized
reward learning (5). We also assign a central role to DA signal
and, in particular, to the phasic signaling mode. However, unlike
the previous efforts, we provide a specific biological model of
drug action at the receptor and DA-circuit level and of the tonic
DA function in the onset and progression of addictive behavior,
and we further pinpoint the role of the opponent process. We do
so without an explicit representation of value (or “incentive
value”) of the various actions, but we rely on action choice and
learning. In our model, drug-taking (self-administration) does
not result in an infinitely increasing value for the drug-seeking,
nor does it imply context-independent value encoding.

As with any modeling study, we should sound a note of caution.
Possibly, alternative neuronal mechanisms may yield the equivalent
effects. For example, the complex nicotine effect on multiple
neuromodulatory systems may perturb the delicate balance of
signals in the VTA and explain both positive and negative immediate
hedonic consequence as reported in ref. 22. Furthermore,
nicotine-modulated DA may have different roles in the nucleus
accumbens shell vs. the nucleus accumbens core (25), an issue we
further pinpoint the role of the opponent process. We do

that is independent of its “value” and robust to aversive condition-
ing (5, 54).

Finally, how nicotine-taking escapes from voluntary control of
behavior remains a key issue to investigate. A cognitive control
deficit may be the principle cause of the apparent compulsivity
and the long-term relapses to smoking. Such top-down control
may be mediated by a reciprocal prefrontal cortex–DA–striatal
link, a brain circuit postulated to contribute to the conscious
“neuronal workspace” (4, 55). One may envision that a long-
term selective depression by nicotine of this loop (k) disconnects
A-S from cognitive control and uncovers the compulsive
nonconscious aspects of nicotine addiction.

Methods
Neuronal activity in the modules is described by the firing rate
$U_i$ on $[0;1]$. Synaptic coupling is given by weights $W_i$. Plasticity is modeled as changes in $W_i$. By convention time constants, reaction
rates and random noise are marked by Greek letters. The

The $r_i$ is the effect of an action $i$ on the DA signal, from −1
(aversive) to 1 (appetitive). $N(t)$ is the nAChR activation with a
gain-modulatory effect on $U_{DA}$, $\theta_{DA}$ is the threshold setting the
minimum tonic DA. For neutral actions $r_i = 0$ and $< \theta_{DA}$.

In the A-S module, $U_{AI}$ is the unit activity for each of the action
plans. We consider a circuit of two units (two-choice task):

$$
\frac{dU_{DA}}{dt} = -U_{DA} + S_{DA}\sum_i r_i N(t) - \theta_{DA} + \sigma\xi
$$

where $S$ is a sigmoid input–output function:

$$
S_{DA} = \frac{1}{1 + \tanh(N(t)\sum_i r_i(t) - \theta_{DA})}
$$

Here, $w^i_1 \cdot w^i_{A1}$ cross-plan competition (inhibition) and self-
excitation weights $w^i_{1A} \sigma\xi$ form closed excitatory loops. $S_A$ is a
sigmoid function, identical in form to $S_{DA}$ but with $U_{DA}(t)$ taking
the gain-modulatory role. Random input $\xi$ with strength $\sigma$ plays
a crucial role: it leads to random symmetry breaking (network
chooses an action plan “at will”). $\tau_{AI}$ is the A-S time constant.
We use a threshold near 1 to mark the selection of a action and reset
units to $U_{reset}$ to start the next trial.

The learning in the action selection excitatory weights is governed by

$$
\tau_{AI} \frac{dw^i_{A1}}{dt} = L((U_{DA}), N(t))(U_{DA} - \theta_{DA})H(U_{AI} - \theta_{AI})
$$

The factors are the phasic DA activity $U_{DA}$, the activation of an
action plan $U_{AI}$ (postsynaptic signal), tonic DA activity (running
average $(U_{DA})$) and nAChR activation $L((U_{DA}), N(t)) = k(U_{DA}) + N(t)), H()$ is 0 when the argument is negative and equal to
the argument otherwise. The weights increase when both $U_{DA}$ and $U_{AI}$
are above their respective thresholds: $\theta_{DA}$, $\theta_{AI}$. We take $\theta_{DA} = (U_{DA}) + \overline{thr}$ and $\theta_{AI} = (U_{AI})$, ensuring that neural popu-
lation activity and no phasic DA lead to a decrease in the weights.

We model nAChR signal with three dynamical variables on
$[0;1]$: $r$ is the activation of the nAChRs; $s$ is the up-regulation
of the nAChRs; and $c$ is an opponent process. Key to the model are
the time scales for the different processes: \( n \) is the fastest and \( c \) is the slowest. The kinetic equations for dynamics are

\[
\frac{dn}{dt} = -\beta_n(c)n + \alpha_n(\text{drug})(1 - n),
\]

\[
\frac{ds}{dt} = -\beta_s + \alpha_s(n, \text{drug})(1 - s),
\]

and

\[
\frac{dc}{dt} = -\beta_c + \alpha_c(s, n)(1 - s).
\]

The forward (\( \alpha \)) and backward (\( \beta \)) rates are

\[
\alpha_n(\text{drug}) = \frac{1}{[1 - \tanh(\text{drug} - \theta_n)]},
\]

\[
\alpha_n(\text{drug}) = \frac{1}{[1 - \tanh(n + \text{drug} - \theta_n)]},
\]

\[
\alpha_c(s, n) = \frac{1}{[1 - \tanh(s + n - \theta_c)]},
\]

\[
\beta_n(c) = \frac{1}{[1 - \tanh(c - \theta_n)]}.
\]

The thresholds \( \theta \) are free parameters set such that in the absence of the drug \( n \) is at a small stable value and \( \theta_n \) is non-zero. The time constants are separated by orders of magnitude \( \tau_n \approx \tau_c \approx \tau_s \).

The up-regulation increases nAChR number; in the model the total nAChR signal is \( N(t) = n(t)s(t) \). Chronic nicotine injection is modeled as \( \text{drug}(t) = K \). Phasic nicotine is a double exponential:

\[
\text{drug}(t) = \text{dose} \times \sum e^{\lambda(t - \tau(\text{drug} - \theta))},
\]

where \( \tau_t \) are the armed-choice times (\( U_{AI} \) above the threshold). The doses and the time course of the nicotine are scaled to agree qualitatively with available data (e.g., the nicotine onset on the order of 1 min and the offset of several minutes).

For the chronic nicotine model ran continuously and no A-S was simulated. Simulated self-administration sessions lasted \( =60 \) min with timeout periods \( \approx 0 \) h of simulated time; no A-S was simulated. To calculate response probabilities, response latencies, and response number per session we averaged 0–40 runs.

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