Supplementary Materials:
1. Materials and Methods
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Title: A computational hypothesis for allostasis: delineation of substance dependence, conventional therapies, and alternative treatments

Authors: Yariv Z. Levy1*, Dino J. Levy2,3, Andrew G. Barto1,5, Jerrold S. Meyer4,5

Affiliations:
1 School of Computer Science, University of Massachusetts Amherst, Amherst, MA 01003.
2 Recanati Faculty of Management, Tel-Aviv University, Tel-Aviv, Israel.
3 Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel.
4 Department of Psychology, University of Massachusetts Amherst, Amherst, MA 01003.
5 Neuroscience and Behavior Program, University of Massachusetts Amherst, Amherst, MA 01003.
*Correspondence to: ylevy@cs.umass.edu

1. Materials and Methods
Herein are reported the definitions of the computational framework in Figure 1.

1.1 Notations
Different time scales are used: $t$ represents time in minutes, and $t^*$ represents time in hours.

When used as a conditional term, the sum $\sum_{s=0}^{t} Z(s)$ is abbreviated with $\sum Z$ and denotes the total number of drug intakes since the beginning of the simulation.

The inequality $t \geq t_{GO}$ indicates that the current time $t$ is equal or greater than the time of the first drug intake $t_{GO}$. The presented simulations use $t_{GO} = 5$ [day].

The bounding function $\sigma$ is defined as $\sigma(x) = \begin{cases} 0 & \text{if } x < 0 \\ x & \text{if } x \in [0,1] \\ 1 & \text{if } x > 1 \end{cases}$.

The parameter $\nu$, with $\nu \in [-0.05, 0.05]$, denotes the uniform noise that is different for every process and changes at each time step.
1.2 Expanded PK/PD

**(Equation S1) Mood - M**

\[ M(t) = rc(t) + cd(t), \]

where

*rc(t)* is the rush/comedown effect of the drug, defined below, and

*cd(t)* is the cognitive dissonance, defined below.

**(Equation S2) Rush/comedown effect of the drug - rc**

\[ rc(t) = \sum_{s=0} Z(s) \cdot \left( \alpha - \beta \cdot \left( \frac{t-s}{\Delta} \right)^2 \cdot e^{\frac{t-s}{2\Delta}} \right), \]

where

*Z(t)* is the occurrence of drug intakes, defined below, and

*α, β, and Δ* are constants \( \in \mathbb{R} \) (e.g., \( α = 40, β = 60, \) and \( Δ = 10 \)).

**(Equation S3) Cognitive distortion - cd**

\[ cd(t+1) = \begin{cases} 
-T(t) + γ_M \cdot ΔTSO(t*) - ΔTSO(t* - 1) & \text{if } \sum Z \geq 1 \\
0 & \text{otherwise},
\end{cases} \]

where

*γ_M* is a constant \( \in \mathbb{R} \) (e.g., \( γ_M = 0.3 \)),

*T(t)* is the lowering effect on reward threshold, defined below,

\( ΔTSO(t*) = T_5(t*) - T_0(t*) \), where \( T_5(t*) \) is the reward set point, and \( T_0(t*) \) is the baseline reward threshold, both defined below, and

\( \sum Z \) is defined above.

**(Equation S4) Drug intakes - Z**

\[ Z(t) = \begin{cases} 
1 & \text{if } T(t) - T_5(t*) > 0 \text{ and } ΔZ \geq α \text{ and } t \geq t_{GO} \\
0 & \text{otherwise},
\end{cases} \]

where

*T(t)* is the lowering effect on reward threshold, defined below,

\( T_5(t*) \) is the reward set point, defined below,

\( ΔZ \) represents the number of minutes elapsed since the last drug intake, and

*α* is a constant \( \in \mathbb{N} \) (e.g., \( α = 30 \) [minute]).

**(Equation S5) Lowering effect on reward threshold - T**

\[ T(t) = T_0(t*) - \frac{T_{max} \cdot C(t)}{T_{50} + C(t)}, \]

where

\( T_0(t*) \) is the baseline reward threshold, defined below,

\( T_{max} \) is the maximum effect of the drug (e.g., \( T_{max} = 120 \)),

\( T_{50} \) is the index of drug potency (e.g., \( T_{50} = 588.6 \) [nM]), and

\( C(t) \) is the drug concentration in the brain, defined below.
(Equation S6) Drug concentration in the brain - C

\[ C(t) = D \cdot \frac{k_{12}}{V_b(\alpha - \beta)} \cdot \sum_{s=0} Z(s) \cdot \left( e^{-\beta(t-s)} - e^{-\alpha(t-s)} \right), \]

where

- \( D \) is the drug unit dose (e.g., \( D = 250 \) [µg]),
- \( k_{12} \) is the compartment rate constant (e.g., \( k_{12} = 0.0054 \)),
- \( V_b \) is the apparent volume of distribution in the brain (e.g, \( V_b = 1.67 [45] \)),
- \( \alpha \) and \( \beta \) are the aggregate rate constants as discussed in [8], and
- \( Z(t) \) is the occurrence of drug intakes, defined above.

(Equation S7) Reward set point - \( T_S \)

\[ T_S(t^* + 1) = \begin{cases} \lambda \cdot (1 - e^{-\beta d}) + T_S(t_c) & \text{if } G(t^*) \geq 0 \text{ and } \sum Z \geq 1 \\ T_S(t_c) \cdot e^{-\gamma d} & \text{if } G(t^*) < 0 \text{ and } \sum Z \geq 1 \\ T_S(t^*) & \text{otherwise}, \end{cases} \]

where

- \( T_S(0) \) is a constant (e.g. \( T_S(0) = 75 \)),
- \( \beta, \gamma, \text{ and } \lambda \) are constants \( \in \mathbb{R}_+ \) (e.g., \( \beta = 0.05, \gamma = 0.05, \lambda = 100 \)),
- \( d \) is a time-steps counter, reset to 0 when the sign of \( G(t^*) \) changes,
- \( t_c \) is the time \( t^* \) of last change of sign of \( G(t^*) \),
- \( G(t^*) \) is the tendency of drug-seeking behavior, defined below, and
- \( \sum Z \) is defined above.

(Equation S8) Baseline reward threshold - \( T_0 \)

\[ T_0(t^* + 1) = \begin{cases} T_0(t^*) + \delta_{T_0} \cdot (-2 \cdot H(t^*) + 1) \cdot \left( \omega_S(t^*) - \omega_P(t^*) + \omega_D(t^*) \right) & \text{if } \sum Z \geq \alpha \\ T_0(t^*) & \text{otherwise}, \end{cases} \]

where

- \( T_0(0) \) is a constant (e.g. \( T_0(0) = 100 \)),
- \( \delta_{T_0} \) is a constant \( \in \mathbb{R}_+ \) (e.g., \( \delta_{T_0} = 0.03 \)),
- \( H(t^*) \) is the healing intervention process, defined below,
- \( \omega_S(t^*), \omega_P(t^*), \text{ and } \omega_D(t^*) \) are the cognitive time-dependent weights, defined below,
- \( \alpha \) is a constant \( \in \mathbb{N}_+ \) (e.g., \( \alpha = 20 \) [intakes]); similar to stage 4 in [47], and
- \( \sum Z \) is defined above.
1.3 Cognitive scale

**(Equation S9) Rationality density - rd**

\[ rd(t^*) = -\omega_S(t^*) \cdot S(t^*) + \omega_P(t^*) \cdot P(t^*) - \omega_D(t^*) \cdot D(t^*) - \omega_Q \cdot AQ(t^*) + \omega_A \cdot \left[ AS(t^*) + AP(t^*) + AD(t^*) \right] + \omega_H \cdot H(t^*), \]

where

\( \omega_S(t^*), \omega_P(t^*), \) and \( \omega_D(t^*) \) are the cognitive time-dependent weights, defined below,

\( S(t^*), P(t^*), \) and \( D(t^*) \) are the internal processes, defined below,

\( AS(t^*), AP(t^*), AD(t^*) \) and \( AQ(t^*) \) are the external processes, defined below, and

\( H(t^*) \) is the healing intervention process, defined below.

**(Equation S10) Cognitive weights - \( \omega_S, \omega_P, \omega_D, \omega_Q, \omega_A, \omega_H \)**

- For \( i \in \{ Q, A, H \} \):

\[ \omega = c \]

where
c is a constant \( \in \mathbb{R}^+ \) (e.g., \( \omega_Q = 0.28, \omega_H = 0.35, \omega_H = 0.8 \)).

- For \( i \in \{ S, P, D \} \):

\[ \omega_i(t^*) = \max \left( \alpha_i(t^* - 1) + \theta_i \cdot H(t^*), 0 \right), \]

with

\[ \alpha_i(t^* + 1) = \begin{cases} 
\alpha_i(t^*) + \theta_i & \text{if } A \\
\alpha_i(t^*) - \eta_i & \text{if } B \\
\alpha_i(t^*) + \theta_i - \eta_i & \text{if } A \text{ and } B \\
\alpha_i(t^*) & \text{otherwise,} \end{cases} \]

where

\( \alpha_i(0) \) is a constant (e.g., \( \alpha_S(0) = 0.7, \alpha_P(0) = 1.2, \alpha_D(0) = 1 \)),

Conditions \( A \) and \( B \) are conditional terms defined as:

\( A : \text{if } H(\Theta(t^*)) = 1 \text{ and } p_A(t^*) < P(H\eta_i), \)

[for some probability, and if \( H \) is active, and at last time-step of activation]

where \( \Theta(t^*) \) is defined below

\( B : \text{if } \sum_{s=t^*}^{t^*+1} Z(s) > 0 \text{ and } p_B(t^*) < P(Z\eta_i) \text{ and } \sum Z \leq \beta, \)

[for the first number of drug intakes, and for a certain probability, and if in the past hour there was at least one drug intake]

where \( \beta \) is a constant \( \in \mathbb{N}^+ \) (e.g., \( \beta = 15 \) [intakes]), similar to stage 3 in [47]

\( p_A(t^*) \) and \( p_B(t^*) \) are values sampled from a standard uniform distribution at each time-step \( t^* \),

\( P(H\eta_i) \) and \( P(Z\eta_i) \) are constants \( \in [0,1] \) which denote, respectively, the probabilities of permanent changes in cognitive weights \( \omega_S(t^*), \omega_P(t^*), \) and \( \omega_D(t^*) \) after a healing intervention or after a drug intake, with

<table>
<thead>
<tr>
<th>(e.g.)</th>
<th>( P(H\eta_i) )</th>
<th>( P(H\eta S) = 0.7 )</th>
<th>( P(H\eta P) = 0.9 )</th>
<th>( P(H\eta D) = 0.6 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P(Z\eta_i) )</td>
<td>( P(Z\eta S) = 0.2 )</td>
<td>( P(Z\eta P) = 0.1 )</td>
<td>( P(Z\eta D) = 0.05 )</td>
<td></td>
</tr>
</tbody>
</table>
$H(t^*)$ is the healing intervention process, defined below, and $\vartheta_i$ and $\eta_i$ are constants in the following domains:

<table>
<thead>
<tr>
<th></th>
<th>$S$</th>
<th>$P$</th>
<th>$D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\vartheta_i$</td>
<td>$\in \mathbb{R}^-$ (e.g., $\vartheta_S = -0.26$)</td>
<td>$\in \mathbb{R}^+$ (e.g., $\vartheta_P = -0.42$)</td>
<td>$\in \mathbb{R}^-$ (e.g., $\vartheta_S = -0.32$)</td>
</tr>
<tr>
<td>$\eta_i$</td>
<td>$\in \mathbb{R}^-$ (e.g., $\eta_S = -0.1$)</td>
<td>$\in \mathbb{R}^+$ (e.g., $\eta_S = 0.05$)</td>
<td>$\in \mathbb{R}^-$ (e.g., $\eta_S = -0.15$)</td>
</tr>
</tbody>
</table>

(Equation S11) Cognitive state - $cs$

$$cs(t^*) = \frac{1}{2} \tanh(\alpha \cdot cs(t^* - 1) + \beta \cdot rd(t^*) + \gamma) + \frac{1}{2}$$

where $\alpha$ and $\beta$ are constants $\in \mathbb{R}^+$ (e.g., $\alpha = 0.25$, $\beta = 0.25$) $\gamma$ is a constant $\in \mathbb{R}$ (e.g., $\gamma = -0.4052$); this constant can also be computed using the following equation, as described in [56]:

$$\gamma = \frac{1}{2} \left[ \alpha - \beta \cdot \left( \omega_S(0) - \omega_P(0) + \omega_D(0) + \omega_Q + \omega_A \right) \right],$$

where $\omega_S(0)$, $\omega_P(0)$, and $\omega_D(0)$ are the values of the cognitive time-dependent weights at time $t^* = 0$.

$\alpha$ and $\beta$ are the same constants used for $cs(t^*)$.

1.4 Healing scale

(Equation S12) Healing intervention - $H$

$$H(t^*) = \begin{cases} 
1 & \text{if } p(t^*) < P(nr) \text{ or if } d \in [1, \Theta(t^*)] \\
0 & \text{otherwise},
\end{cases}$$

where $P(nr)$ is the probability of an healing intervention, $P(nr) \in [0,1]$; this probability can be based on data as in [12], $p(t^*)$ is a value sampled from a standard uniform distribution at each time-step $t^*$; in the simulations presented in this article, $H$ processes are triggered at specific times, $d$ is a time step counter reset at every instance of $H$, and $\Theta(t^*)$ is the activation time of $H$, which increases for consecutive instances:

$$\Theta(t^*) = \begin{cases} 
\Theta(t^*) + \delta_t & \text{if } p(t^*) < P(nr) \\
\Theta(t^* - 1) & \text{if } d \in [1, \Theta(t^* - 1)] \\
\max (0, \Theta(t^*) - \delta_d) & \text{otherwise},
\end{cases}$$

where $\delta_t$ and $\delta_d$ are constants $\in \mathbb{N}^+$, (e.g., $\delta_t = 15$, $\delta_d = 1 \text{ [hour]}$).
1.5 Neuropsychological scale

The internal processes are $S$, $P$, $D$, and $Q$. The external triggers are $AS$, $AP$, $AD$, and $AQ$.

(Equation S13) Stress - $S$

$$S(t^*) = \begin{cases} 
\sigma \left(1 - (1 - S_0) \cdot e^{-\beta d} + \nu\right) & \text{if } G(t^*) > 0 \\
\sigma \left(S(t^* - 1) + \nu\right) & \text{if } G(t^*) = 0 \\
\sigma \left(S_0 \cdot e^{-\gamma d} + \nu\right) & \text{if } G(t^*) < 0,
\end{cases}$$

where $S_0$ is the value $S(t_c)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, $\beta$ and $\gamma$ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.002$, $\gamma = 0.002$), $d$ is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes, $G(t^*)$ is the tendency of drug-seeking behavior, defined below, and $\nu$ and $\sigma(x)$ are defined above.

(Equation S14) Pain - $P$

$$P(t^*) = \begin{cases} 
\sigma \left(P_0 \cdot e^{-\beta d} + \nu\right) & \text{if } G(t^*) > 0 \\
\sigma \left(P(t^* - 1) + \nu\right) & \text{if } G(t^*) = 0 \\
\sigma \left(1 - (1 - P_0) \cdot e^{-\gamma d} + \nu\right) & \text{if } G(t^*) < 0,
\end{cases}$$

where $P_0$ is the value $P(t_c)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, $\beta$ and $\gamma$ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.0002$, $\gamma = 0.01$), $d$ is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes, $G(t^*)$ is the tendency of drug-seeking behavior, defined below, and $\nu$ and $\sigma(x)$ are defined above.

(Equation S15) Drug craving - $D$

$$D(t^*) = \begin{cases} 
\sigma \left(1 - (1 - D_0) \cdot e^{-\beta d} + \nu\right) & \text{if } G(t^*) > 0 \text{ and } d \in [1, \tau] \\
\sigma \left(D' \cdot e^{-\beta d} + \nu\right) & \text{if } G(t^*) > 0 \text{ and } d > \tau \\
\sigma \left(D(t^* - 1) + \nu\right) & \text{if } G(t^*) = 0 \\
\sigma \left(1 - (1 - D_0) \cdot e^{-\gamma d} + \nu\right) & \text{if } G(t^*) < 0,
\end{cases}$$

where $D_0$ is the value $D(t_c)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, $D'_0$ is the value $D(t_c + \tau)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, and $\tau$ is a constant $\in \mathbb{N}^+$ (e.g., $\tau = 20$ [hour]), $\beta$ and $\gamma$ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.00002$, $\gamma = 0.002$), $d$ is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes, $G(t^*)$ is the tendency of drug-seeking behavior, defined below, and $\nu$ and $\sigma(x)$ are defined above.
(Equation S16) Saliency to drug cues - $Q$

$$Q(t^*) = \begin{cases} 
\sigma(Q(t^*-1)+\nu) & \text{if } G(t^*) > 0 \text{ and } d \in [1, \tau] \text{ or if } G(t^*) = 0 \\
\sigma(Q_0^* \cdot e^{-\beta d} + \nu) & \text{if } G(t^*) > 0 \text{ and } d > \tau \\
\sigma(1-(1-Q_0^*) \cdot e^{-\gamma d} + \nu) & \text{if } G(t^*) < 0,
\end{cases}$$

where $Q_0$ is the value $Q(t_c)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, $Q_0^*$ is the value $Q(t_c+\tau)$, where $t_c$ is the time $t^*$ of last change of sign of $G(t^*)$, and $\tau$ is a constant $\in \mathbb{N}^+$ (e.g., $\tau = 10$ [hour]),

$\beta$ and $\gamma$ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.002$, $\gamma = 0.0005$),

d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,

$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and

$\nu$ and $\sigma(x)$ are defined above.

(Equation S17) Acute shock - $AS$

$$AS(t^*) = \begin{cases} 
S_0 & \text{if } G(t^*) > 0 \text{ and } p(t^*) < P(AS) \text{ or if } d \in [1, \tau_1] \\
\rho \cdot AS(t^*-1) & \text{if } d \in [\tau_1, \tau_2] \\
0 & \text{otherwise},
\end{cases}$$

where $S_0$ and $\rho$ are constants $\in \mathbb{R}^+$ (e.g., $S_0 = 0.75$, $\rho = 0.9$),

$G(t^*)$ is the tendency of drug-seeking behavior, defined below,

$\rho(t^*)$ is a value sampled from a standard uniform distribution at each time-step $t^*$,

$P(AS)$ is the probability of an acute shock (e.g., $P(AS) = 0.01$),

d is a time-steps counter, reset to 0 when a new $AS(t^*)$ arises, and

$\tau_1$ and $\tau_2$ are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 20$, $\tau_2 = 60$ [hour]).

(Equation S18) Acute trauma - $AP$

$$AP(t^*) = \begin{cases} 
P_0 & \text{if } G(t^*) < 0 \text{ and } p(t^*) < P(AP) \text{ or if } d \in [1, \tau_1] \\
\rho \cdot AP(t^*-1) & \text{if } d \in [\tau_1, \tau_2] \\
0 & \text{otherwise},
\end{cases}$$

where $P_0$ and $\rho$ are constants $\in \mathbb{R}^+$ (e.g., $P_0 = 0.45$, $\rho = 0.4$),

$G(t^*)$ is the tendency of drug-seeking behavior, defined below,

$\rho(t^*)$ is a value sampled from a standard uniform distribution at each time-step $t^*$,

$P(AP)$ is the probability of an acute shock (e.g., $P(AP) = 0.03$),

d is a time-steps counter, reset to 0 when a new $AP(t^*)$ arises, and

$\tau_1$ and $\tau_2$ are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 15$, $\tau_2 = 50$ [hour]).
(Equation S19) Acute drug priming - AD

\[
AD(t^*) = \begin{cases} 
D_0 & \text{if } G(t^*) > 0 \text{ and } p(t^*) < P(AD) \text{ or if } d \in [1, \tau_1] \\
\rho \cdot AD(t^* - 1) & \text{if } d \in [\tau_1, \tau_2] \\
0 & \text{otherwise},
\end{cases}
\]

where

\(D_0\) and \(r\) are constants \(\in \mathbb{R}^+\) (e.g., \(D_0 = 0.75, r = 0.9\)),
\(G(t^*)\) is the tendency of drug-seeking behavior, defined below,
\(p(t^*)\) is a value sampled from a standard uniform distribution at each time-step \(t^*\),
\(P(AD)\) is the probability of an acute shock (e.g., \(P(AD) = 0.03\)),
d is a time-steps counter, reset to 0 when a new \(AD(t^*)\) arises, and
\(\tau_1\) and \(\tau_2\) are constants \(\in \mathbb{N}^+\) with \(\tau_2 > \tau_1\) (e.g., \(\tau_1 = 5, \tau_2 = 30 \text{ [hour]}\)).

(Equation S20) Acute drug cue - AQ

\[
AQ(t^*) = \begin{cases} 
Q(t^*) & \text{if } p(t^*) < P(AQ) \\
AQ(t^* - 1) & \text{if } d \in [1, \tau_1] \\
\rho \cdot AQ(t^* - 1) & \text{if } d \in [\tau_1, \tau_2] \\
0 & \text{otherwise},
\end{cases}
\]

where

\(Q(t^*)\) is the saliency to drug cues, defined above,
\(\rho\) is a constants \(\in \mathbb{R}^+\) (e.g., \(\rho = 0.9\)),
\(p(t^*)\) is a value sampled from a standard uniform distribution at each time-step \(t^*\),
\(P(AQ)\) is the probability of an acute shock (e.g., \(P(AQ) = 0.02\)),
d is a time-steps counter, reset to 0 when a new \(AQ(t^*)\) arises, and
\(\tau_1\) and \(\tau_2\) are constants \(\in \mathbb{N}^+\) with \(\tau_2 > \tau_1\) (e.g., \(\tau_1 = 20, \tau_2 = 40 \text{ [hour]}\)).

1.6 Behavioral scale

(Equation S21) Tendency of drug-seeking behavior - G

\[
G(t^*) = I \cdot cs(t^*) - C \cdot (1 - cs(t^*))
\]

where

\(I\) and \(C\) are a constant (e.g., \(I = 1, C = 1\)),
\(cs(t^*)\) is the cognitive state, defined above.
### 2. SUPPLEMENTARY TABLE

**Table S1:** Values of the parameters as used in Figures 2-7 and Figures S1-S34.

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<thead>
<tr>
<th>Eq.</th>
<th>Parameter</th>
<th>Value</th>
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<td>N/A</td>
</tr>
<tr>
<td>S2</td>
<td>α</td>
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<tr>
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<tr>
<td></td>
<td>Δ</td>
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</tr>
<tr>
<td>S3</td>
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<tr>
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3. SUPPLEMENTARY FIGURES S1-S34
Figure S1: Details of Case Study 1 presented in Figures 2 and 3. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_S$ and $T_0$ as time-dependent processes. $T_S$ is constant and $T_0$ time-dependent in Evaluation 2, $T_S$ is time-dependent and $T_0$ constant in Evaluation 3. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S2: Details of Case Study 1 presented in Figures 2 and 3. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_s$ and $T_o$ as time-dependent processes. $T_s$ is constant and $T_o$ time-dependent in Evaluation 2, $T_s$ is time-dependent and $T_o$ constant in Evaluation 3. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S3: Comparison of different probabilities defining the associative learning between the drug and its pleasurable effect. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of $\omega_S$, $\omega_P$, and $\omega_D$ facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z\eta i)$, with $i \in \{S, P, D\}$ are tested: [0.05, 0.025, 0.0125], [0.2, 0.1, 0.05], and [0.8, 0.4, 0.2]. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T$ (blue), $T_0$ (red), and $T_3$ (black); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
Figure S4: Comparison of different probabilities defining the associative learning between the drug and its pleasurable effect. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of $\omega_S$, $\omega_P$, and $\omega_D$ facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z\eta_i)$, with $i \in \{S, P, D\}$ are tested: $[0.05, 0.025, 0.0125]$, $[0.2, 0.1, 0.05]$, and $[0.8, 0.4, 0.2]$. Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C. Maladaptive behavior is facilitated for higher probabilities. Simulations using lower probabilities terminate with the virtual subject exhibiting an average consumption of ~30 intakes/day and a abstinence index of ~30%. Higher probabilities lead these predicted measures to ~45 intakes/day and ~2% abstinence. The downslope of M becomes stronger as the probabilities become larger.
Figure S5: Details of simulations presented in Figures S3 and S4. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of $\omega_S$, $\omega_P$, and $\omega_D$ facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z \eta i)$, with $i \in \{S, P, D\}$ are tested: [0.05, 0.025, 0.0125], [0.2, 0.1, 0.05], and [0.8, 0.4, 0.2]. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S6: Details of simulations presented in Figures S3 and S4. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of $\omega_S$, $\omega_P$, and $\omega_D$ facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z \eta_i)$, with $i \in \{S, P, D\}$ are tested: [0.05, 0.025, 0.0125], [0.2, 0.1, 0.05], and [0.8, 0.4, 0.2]. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S7: Details of Case Study 2 presented in Figures 4 and 5. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_S$ and $T_0$ as time-dependent processes. $T_S$ is constant and $T_0$ time-dependent in Evaluation 2, $T_S$ is time-dependent and $T_0$ constant in Evaluation 3. In all Evaluations, the recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S8: Details of Case Study 2 presented in Figures 4 and 5. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_S$ and $T_0$ as time-dependent processes. $T_S$ is constant and $T_0$ is time-dependent in Evaluation 2, $T_S$ is time-dependent and $T_0$ constant in Evaluation 3. In all Evaluations, the recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation’s time-steps: hours in columns A-C, minutes in columns D and E.
Figure S9: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with both $T_S$ and $T_0$ time-dependent. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 1000 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T_0$ (red), $T_S$ (black), and $T_S$ (black); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.

\[
\begin{align*}
P(H\eta_S) = 0.2 & \\
P(H\eta_P) = 0.175 & \\
P(H\eta_D) = 0.15 & \\
\end{align*}
\]  

\[
\begin{align*}
P(H\eta_S) = 0.4 & \\
P(H\eta_P) = 0.35 & \\
P(H\eta_D) = 0.3 & \\
\end{align*}
\]  

\[
\begin{align*}
P(H\eta_S) = 0.8 & \\
P(H\eta_P) = 0.7 & \\
P(H\eta_D) = 0.6 & \\
\end{align*}
\]  

[same as Fig. 4 and 5 Evaluation 1]
Figure S10: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with both $T_S$ and $T_D$ time-dependent. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ becomes permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days for columns B and C. The trial employing the lowest probabilities terminates at advanced stage 4 (~25 intakes/day and ~41% abstinence), whereas the highest set of probabilities leads to stage 1 or intermediate stage 2 (~3.5 intakes/day and ~88% abstinence).

$P(H\eta_S) = 0.2$
$P(H\eta_P) = 0.175$
$P(H\eta_D) = 0.15$

$P(H\eta_S) = 0.4$
$P(H\eta_P) = 0.35$
$P(H\eta_D) = 0.3$

$P(H\eta_S) = 0.8$
$P(H\eta_P) = 0.7$
$P(H\eta_D) = 0.6$
Figure S11: Details of simulations presented in Figures S9 and S10. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H|\eta_i)$, with $i \in \{S, P, D\}$, are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S12: Details of simulations presented in Figures S9 and S10. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H|\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S13: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with $T_S$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ becomes permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T$ (blue), $T_0$ (red), and $T_S$ (black); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to $95\%$ simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
Figure S14: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with $T_S$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C.

$P(H\eta_S) = 0.2$
$P(H\eta_P) = 0.175$
$P(H\eta_D) = 0.15$

$P(H\eta_S) = 0.4$
$P(H\eta_P) = 0.35$
$P(H\eta_D) = 0.3$

[same as Fig. 4 and 5 Evaluation 2]

$P(H\eta_S) = 0.8$
$P(H\eta_P) = 0.7$
$P(H\eta_D) = 0.6$
Figure S15: Details of simulations presented in Figures S13 and S14. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S16: Details of simulations presented in Figures S13 and S14. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H|\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S17: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with $T_0$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T$ (blue), $T_0$ (red), and $T_S$ (black); column C the virtual subject’s mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
Figure S18: Comparison of different probabilities defining the durability of $H$ for conventional therapies, with $T_0$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_0$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H \eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C.
Figure S19: Details of simulations presented in Figures S17 and S18. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_g$. At the end of each therapeutic session, the positive influence that $H$ exerts on $ω_S$, $ω_P$, and $ω_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H^i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S20: Details of simulations presented in Figures S17 and S18. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figures S5 and S6 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(Hi)$, with $i \in \{S, P, D\}$, are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S21: Details of Case Study 3 presented in Figures 6 and 7. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_S$ and $T_0$ as time-dependent processes. $T_S$ is constant and $T_0$ time-dependent in Evaluation 2, $T_S$ is time-dependent and $T_0$ constant in Evaluation 3. In all Evaluations, the recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S22: Details of Case Study 3 presented in Figures 6 and 7. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both $T_S$ and $T_0$ as time-dependent processes. $T_S$ is constant and $T_0$ time-dependent in Evaluation 2, $T_S$ is time-dependent and $T_0$ constant in Evaluation 3. In all Evaluations, the recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S23: Comparison of different probabilities defining the durability of $H$ for alternative treatments, with both $T_5$ and $T_0$ time-dependent.

Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T_5$ (blue), $T_0$ (red), and $T_S$ (black); column C the virtual subject’s mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
\[ P(H\eta S) = 0.2 \]
\[ P(H\eta P) = 0.175 \]
\[ P(H\eta D) = 0.15 \]

\[ P(H\eta S) = 0.4 \]
\[ P(H\eta P) = 0.35 \]
\[ P(H\eta D) = 0.3 \]

\[ P(H\eta S) = 0.8 \]
\[ P(H\eta P) = 0.7 \]
\[ P(H\eta D) = 0.6 \]

Figure S24: Comparison of different probabilities defining the durability of \( H \) for alternative treatments, with both \( T_S \) and \( T_D \) time-dependent. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process \( H \) is activated at \( t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\} \) [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that \( H \) exerts on \( \omega_S \), \( \omega_P \), and \( \omega_D \) become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities \( P(H\eta i) \), with \( i \in \{S, P, D\} \), are tested: \( [0.2, 0.175, 0.15] \), \( [0.4, 0.35, 0.3] \), and \( [0.8, 0.7, 0.6] \). Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C.
Figure S25: Details of simulations presented in Figures S23 and S24. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H|\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S26: Details of simulations presented in Figures S23 and S24. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H|\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/come down effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
P(H\eta S) = 0.2
P(H\eta P) = 0.175
P(H\eta D) = 0.15

P(H\eta S) = 0.4
P(H\eta P) = 0.35
P(H\eta D) = 0.3

[same as Fig. 6 and 7 Evaluation 2]

P(H\eta S) = 0.8
P(H\eta P) = 0.7
P(H\eta D) = 0.6

Figure S27: Comparison of different probabilities defining the durability of H for alternative treatments, with T_S constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at \( t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\} \) [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on \( \omega_S \), \( \omega_P \), and \( \omega_D \) become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities \( P(H\eta_i) \), with \( i \in \{S, P, D\} \), are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Rows A1-A3 report the evolution of cognitive weights \( \omega_S \) (red), \( \omega_P \) (blue), and \( \omega_D \) (black); rows B1-B3 the progression of \( T \) (blue), \( T_0 \) (red), and \( T_S \) (black); column C the virtual subject’s mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
**Figure S28: Comparison of different probabilities defining the durability of H for alternative treatments, with T5 constant.** Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at \( t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\} \) [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant \( T_5 \). At the end of each therapeutic session, the positive influence that \( H \) exerts on \( \omega_S, \omega_P, \) and \( \omega_D \) become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities \( P(H \eta_i) \), with \( i \in \{S, P, D\} \), are tested: \([0.2, 0.175, 0.15]\), \([0.4, 0.35, 0.3]\), and \([0.8, 0.7, 0.6]\). Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C.

**Legend:**
- **A:** Mood scale
- **B:** Average drug intakes scale
- **C:** Abstinence index scale

**Probabilities:**
- \( P(H \eta_S) = 0.2 \)
- \( P(H \eta_P) = 0.175 \)
- \( P(H \eta_D) = 0.15 \)
- \( P(H \eta_S) = 0.4 \)
- \( P(H \eta_P) = 0.35 \)
- \( P(H \eta_D) = 0.3 \)
- \( P(H \eta_S) = 0.8 \)
- \( P(H \eta_P) = 0.7 \)
- \( P(H \eta_D) = 0.6 \)
Figure S29: Details of simulations presented in Figures S27 and S28. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant $T_S$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior $G$; columns B-D the progression of internal processes stress $S$ (red), pain $P$ (blue), and drug craving $D$ (black); columns E-F the external trigger acute drug cue $AQ$ (blue) and the internal process of saliency to drug cues $Q$ (red). The shades correspond to 95% simulation envelopes.
Figure S30: Details of simulations presented in Figures S27 and S28. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process \( H \) is activated at \( t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\} \) [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant \( T_S \). At the end of each therapeutic session, the positive influence that \( H \) exerts on \( \omega_S, \omega_P, \) and \( \omega_D \) become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities \( P(H\eta_i) \), with \( i \in \{S, P, D\} \), are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Columns A-C report the external triggers of acute shock \( AS \) (red), acute trauma \( AP \) (blue), and acute drug priming \( AD \) (black); column D the rush/comedown effect \( rc \) of drug intakes; and column E the cognitive distortion \( cd \). The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.
Figure S31: Comparison of different probabilities defining the durability of $H$ for alternative treatments, with $T_0$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant $T_0$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta_i)$, with $i \in \{S, P, D\}$, are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Rows A1-A3 report the evolution of cognitive weights $\omega_S$ (red), $\omega_P$ (blue), and $\omega_D$ (black); rows B1-B3 the progression of $T$ (blue), $T_0$ (red), and $T_S$ (black); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the abstinence index (blue) over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: hours for rows A1-A3, and minutes for rows B1-B3.
Figure S32: Comparison of different probabilities defining the durability of $H$ for alternative treatments, with $T_0$ constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant $T_0$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ becomes permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H \eta_i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the virtual subject's mood; column B the average number of drug intakes, and column C the abstinence index over time. The shades correspond to 95% simulation envelopes. The simulation time-scales are multiple: minutes for column A, days columns B and C.
Figure S33: Details of simulations presented in Figures S31 and S32. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process \( H \) is activated at \( t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\} \) [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant \( T_0 \). At the end of each therapeutic session, the positive influence that \( H \) exerts on \( \omega_S \), \( \omega_P \), and \( \omega_D \) become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities \( P(H|\eta_i) \), with \( i \in \{S, P, D\} \), are tested: \([0.2, 0.175, 0.15]\), \([0.4, 0.35, 0.3]\), and \([0.8, 0.7, 0.6]\). Column A reports the evolution of drug-seeking behavior \( G \); columns B-D the progression of internal processes stress \( S \) (red), pain \( P \) (blue), and drug craving \( D \) (black); columns E-F the external trigger acute drug cue \( AQ \) (blue) and the internal process of saliency to drug cues \( Q \) (red). The shades correspond to 95% simulation envelopes.
Figure S34: Details of simulations presented in Figures S31 and S32. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process $H$ is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figures S12 and S13 but have constant $T_0$. At the end of each therapeutic session, the positive influence that $H$ exerts on $\omega_S$, $\omega_P$, and $\omega_D$ become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H \eta i)$, with $i \in \{S, P, D\}$, are tested: [0.2, 0.175, 0.15], [0.4, 0.35, 0.3], and [0.8, 0.7, 0.6]. Columns A-C report the external triggers of acute shock $AS$ (red), acute trauma $AP$ (blue), and acute drug priming $AD$ (black); column D the rush/comedown effect $rc$ of drug intakes; and column E the cognitive distortion $cd$. The shades correspond to 95% simulation envelopes. The abscissas correspond to the simulation's time-steps: hours in columns A-C, minutes in columns D and E.