Implementing Incentive-Sensitization Theory of Addiction with Nengo Neural Network Simulator

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Abstract

We present first steps towards a biologically grounded implementation of the Incentive-Sensitization Theory of addiction. We present multiple different plausible ways of mapping this theory into a computational model, and examine the resulting behaviour to see whether it accords with standard interpretations of the theory. This is the first step in a larger project to create a computationally tractible and biologically motivated model of addiction to help clarify and ground various terms in the theory.

Keywords: Addiction; Computational Modelling; Incentive Sensitization

Background

Prior to the 1980s, addiction was often viewed as a character flaw or personal failure (Frank & Nagel, 2017). This moral model of addiction assumes that drug use is voluntary: addicts consciously choose to self-administer drugs despite knowledge of adverse personal and societal costs associated with this behaviour. A growing understanding of the biological consequences of excessive drug use helped to establish the medical model of addiction, where behavioural patterns associated with maladaptive drug use (e.g., compulsion, impulsivity, craving, relapse) are driven by underlying changes in the structure and function of neural circuits mediating reward, motivation, and decision making (Koob & Volkow, 2016).

The medical model of addiction builds on positive reinforcement theories, proposing that drug-taking is reinforced by the euphoric state of drug use. These effects are mediated through the mesolimbic dopamine (DA) pathway, which projects from the ventral tegmental area to the nucleus accumbens and prefrontal cortex (Wise, 1980). Antagonizing mesolimbic DA activity reduces the reinforcing effects of both abused drugs and natural reinforcers like food or sex (Koob & Le Moal, 1997; Wise, 1980; Farooqi et al., 2007).

The medical model of addiction acknowledges that negative reinforcement also contributes to continued drug use in that drug intake alleviates negative symptoms of withdrawal, such as drowsiness, headache, or depression. With chronic use, mesolimbic DA system function is altered (Pierce & Kumaresan, 2006) such that baseline DA levels are decreased in drug-free states. As a consequence, substance abusers experience less drug-induced pleasure as addiction develops; they also increase the dose and frequency of drug intake to make up for reductions in baseline DA levels (Koob, 2020).

The Incentive-Sensitization Theory of Addiction

By the mid 1990s, it became clear that neither positive nor negative theories of reinforcement provided a full account of addictive behaviour. For example, the positive reinforcing effects of natural reinforcers, such as food or sex, are also mediated by the mesolimbic DA system but individuals are less likely to develop compulsive intake of these commodities. Negative reinforcement also fails to sufficiently explain addiction. Psychostimulants, such as cocaine, are clearly addictive but do not produce strong somatic, withdrawal symptoms. In addition, intensified withdrawal symptoms do not elicit robust drug craving (Shaham, Rajabi, & Stewart, 1996). Therefore, although both positive and negative reinforcement may contribute to continued drug use, they cannot explain fundamental aspects of addictive behaviour.

In response, Robinson and Kolb (1999) formulated the Incentive-Sensitization Theory of drug addiction which proposes that 'wanting' and 'liking' drugs are mediated by two different mechanisms. In support of this theory, 'liking' in rats, assessed as orofacial responses to presentation of a sweet solution, is unaffected by depletion of mesolimbic DA whereas the same manipulation reduces motivation to obtain a reward (i.e., 'wanting') (Berridge, Venier, & Robinson, 1989). Subsequent work confirmed a dissociation in biological systems that mediate these two processes in rodents (K. C. Berridge, 2007; Pool, Sennwald, Delplanque, Brosch, & Sander, 2016). Similarly, in human patients with reduced DA function (Parkinson's disease), ventral striatal DA changes following DA replacement therapy (levodopa) are correlated with self-reported 'wanting', but not 'liking' (Evans et al., 2006). Brain imaging studies using fMRI confirmed that the expectation (wanting) and receipt (liking) of pleasant tastes activate distinct brain areas (O'Doherty, Deichmann, Critchley, & Dolan, 2002).

The Incentive-Sensitization Theory also proposes that repeated drug use sensitizes, rather than reduces, mesolimbic DA activity. This is supported by animal studies showing enhanced locomotor responses to psychomotor stimulants with repeated injections (Wise & Bozarth, 1987; Robinson & Berridge, 1993) and increases in stereotypy and motor behavioural patterns in chronic drug abusers (Steketee & Kalivas, 2011). Sensitization of mesolimbic DA may also underlie the persistent craving and attentional bias for drugs that

develop with addiction. Neurobiologically, the mesolimbic DA system is altered with repeated drug administration, resulting in increased outflow of DA from pre-synaptic neurons and more DA D1 receptors on the post-synaptic membrane. Structurally, medium spiny neurons in the nucleus accumbens and prefrontal cortex 'grow' more dendritic branches and spines following chronic drug intake, increasing the capacity for DA transmission (Robinson & Kolb, 1997, 1999; Robinson & Berridge, 2000).

A primary characteristic of drug addiction is excessive craving triggered by drug-associated stimuli. For example, in human drug users, imagery, contextual, and social cues previously paired with drug intake can trigger drug use (Weiss et al., 2001; Norberg, Kavanagh, Olivier, & Lyras, 2016). The Incentive-Sensitization Theory explains this maladaptive response through sensitization of DA function: the association between cues predicting drug intake and drug effects are mediated by mesolimbic DA. With sensitization, cues associated with drug use become more salient predictors of drug effects, thereby eliciting craving (K. Berridge & Robinson, 2011).

The Computational Modelling Approach

With the amount of experimental evidence and possible theoretical interpretations of addiction, researchers have turned to computational tools to form and test theories. Many models described addiction as a negative reinforcement process, focusing on analyzing the role of withdraw in addiction (Zhukovsky et al., 2019). But as argued in the previous sections, neither positive nor negative reinforcement provides a full account of addiction. On a behavioral economic level, models of free decision making is often used to study the compulsive behaviour of addiction (Redish, 2004; Morris & Cushman, 2019). On a psychopharmacological level, neuroscientists examine the role of DA activation and transmission in psychiatric disorders (Enrico et al., 2016). The difficulty with these models is that results are generalized across many disorders. Therefore, they fail to identify the unique mechanism that is responsible for the formation of addiction. Levy and Colleagues developed a multiscale model of addiction, integrating cognitive, behavioural and neural psychological factors (Levy, Levy, Barto, & Meyer, 2013) to simulate the development of drinking behavior of a virtual agent. However, because the model consisted of multiple factors, including incentive sensitization, withdraw, rationality, and social influence, among others, it was difficulty to examine each factor individually and more importantly, to make informative claims about the role of each in addiction.

Method

To design an informative and applicable model, we first examined the core proposal of the Incentive-Sensitization Theory (Robinson and Berridge 2000, 2016) which include the following four statements:

'(1) Potentially addictive drugs share the ability to produce long-lasting adaptations in neural systems (i.e., addictive drugs change the brain).

(2) The brain systems that are changed include those normally involved in the process of incentive motivation and reward.

(3) The critical neuroadaptations associated with addiction render brain reward systems hypersensitive ("sensitized") to drugs and drug- associated stimuli.

(4) The brain systems that are sensitized do not mediate the pleasurable or euphoric effects of drugs (drug "liking"), but instead they mediate a subcomponent of reward we have termed incentive salience or "wanting".'

Then, we designed models with structural components that can actualize the processes described in these statements. Particularly, our model is not examining Statement(4),the disassociation of 'liking' and 'wanting'. The reason is three fold: 1) the separation of 'liking' and 'wanting' has been acknowledged, and the notion that mesolimbic DA activity is not responsible for 'liking' is now widely accepted. 2) According to the statement(1), 'wanting', not 'liking' is the essential component of addiction 3) In this model, we describe the neurological changes that are common for all drug types, which is 'wanting'. But different classes of drugs may have different hedonic effects. Therefore, our model will mainly describe the first three statements.

Our goal here is to explore various ways of building a computational implementation of the above theory. That is, we want to examine different possible methods for having biological components that create the addiction process. We used a step by step approach, starting with the smallest processing component and adding more complex features with each model.

We are also constraining our focus to substance addiction alone, excluding behavioural addictions. The goal of the study is to examine the neurological changes and mechanism of addiction. Substances have a more direct impact on neural circuits. Moreover, whether or not is behavioural addiction (such as gambling and pornographic addiction) the same as substances is still under debate (Alavi et al., 2012).

Schematic Description

The architecture of the neural network for simulating incentive sensitization is represented in the following schematic. (presented at CSBBCS conference).

Our model will build up the incentive saliency attributor component of the schematic, which is a main characteristic of the incentive sensitization model of addiction.

Nengo and the Neural Engineering Framework

Since our eventual goal is to have a biologically grounded implementation of Incentive-Sensitization Theory, we decided to implement our models using Nengo, a software package implementing the Neural Engineering Framework (NEF; Eliasmith & Anderson, 2003). This forces each component in the model to be something that can be implemented using spiking neurons.

As such, our models consist of five core features of NENGO. (1) Groups of neurons (ensembles) encode numer-

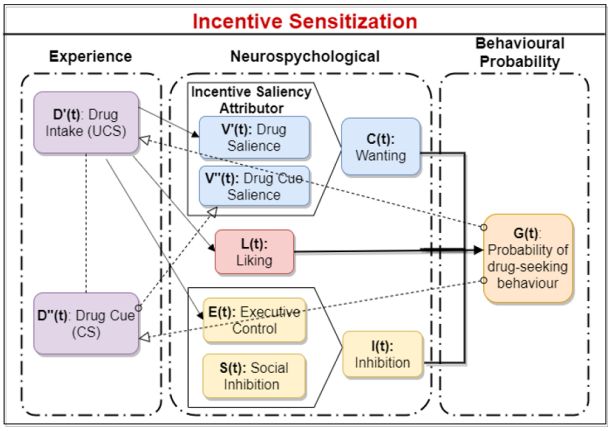

Figure 1: Schematic description of the Incentive-Sensitization Theory.

ical *vectors*, such that different patterns of activity represent different values, using a distributed population code. (2) Connections between ensembles compute functions on those vectors, allowing information to be transforms and transmitted throughout the model. (3) Recurrent connections within an ensemble allow for storage of information over time; technically, this allows the neurons to approximate arbitrary differential equations, allowing the current value represented by the neurons to be a function of both their current input and their value in the recent past. (4) Learning rules allow connection weights to be changed, effectively changing the function that is being computed. (5) Modulation of neuron parameters allows for large-scale changes to a group of parameters of the model, such as making a neuron more sensitive to firing, or scaling how quickly a learning rule changes weights.

We create approximations of the brain's response to drug and drug-associated stimuli by scaling down the duration of drug-use experience and the resulting neurological processes. For example, a drug use episode might take hours, but our models only receive the input of drug intake for several seconds. This shortened time frame allows us to examine the models' behaviour without running full-length simulations while retaining the interpretability of the results.

Models

Model I – Dopamine Activation and Mesolimbic Sensitivity

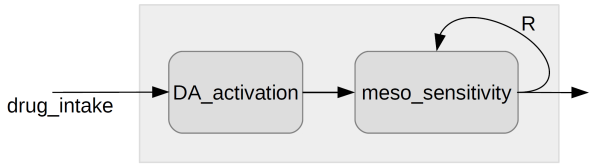

Figure 2: Structure for Model I. Rounded boxes are groups of neurons, arrows are all-to-all connections approximating functions.

Structural Design: Our first model is a direct representation of the top section of the schematic flow: the drug salience attributor. According to the Incentive-Sensitization Theory, the salience value of drugs reflects hyper-reactivity of the mesolimbic system. Stimuli with incentive value, including natural reinforcers, stimulate DA activity in the mesolimbic system. In drug addiction, intensified DA activation also changes the neurological structures responsible for DA activation, leading to a hypersensitized mesolimbic system (Robinson & Kolb, 1999). Therefore, the drug salience attributor should consist of at least two components DA activation and mesolimbic sensitivity. The output of the salience attributor integrates with other mechanisms (described in Model II and III) to form an overall wanting for drugs.

In this model, `drug_intake` is an external stimulus, with a value of 0 or 1. `DA_activation` approximates the value of `drug_intake`. Therefore,`DA_activation` increases when `drug_intake` = 1 and decreases when `drug_intake` = 0. This pattern of DA activation is normally involved in reward processing, as described in Statement(2). Additionally, chronic drug use leads to further neuroadaptations, making the mesolimbic system hypersensitive to drug intake, as described in Statement(3). To store the sensitization of the mesolimbic system, the recurrent `meso_sensitivity` component(defined in the previous section) reflects both the increased baseline synaptic DA transmission reacting to drug intake and the structural changes increasing the capacity of mesolimbic DA activity.

Model Behaviour: According to Statement(1), neuroadaptation with repeated drug use is long-lasting. Therefore, each drug intake should have significant sensitization effects on the mesolimbic system, while the decay of the sensitization during drug absence should be slower. To create simple representations of this mechanism, we computationally manipulated Model I to perform the 4 functions in Table 1.

Table 1: Model I Computational Options

Simulation	R	meso_sensitivity(t) = M(t)
Simulation1	0.9	M(t)
Simulation2	0.9	M(t)+0.1 if DA_activation=1 M(t)-0.01 if DA_activation= 0
Simulation3	0.9	M(t)+0.15 if DA_activation=1 M(t)-0.01 if DA_activation= 0
Simulation4	0.9	M(t)+0.2 if DA_activation=1 M(t)-0.01 if DA_activation= 0

In Simulation1, `meso_sensitivity` has a recurrence value of 0.9, storing 90% of the neuroadaptations made at the previous time point. Simulation2, Simulation3 and Simulation4 added a non-linear function, where `meso_sensitivity` is increased by a certain amount with spikes in DA activation and is decreased when `DA_activation` is minimal.

To examine Model I, we fed in 0.6 seconds of `drug_intake` = 1 following 0.4 seconds of drug absence.

This relatively long duration of drug administration (0.6s out of every 1s) provides a clear visual demonstration of its effect on mesolimbic DA sensitivity. `Meso_sensitivity` is recorded as the output. With six repetitions of `drug_intake`, the four simulations are compared as shown in Figure 3.

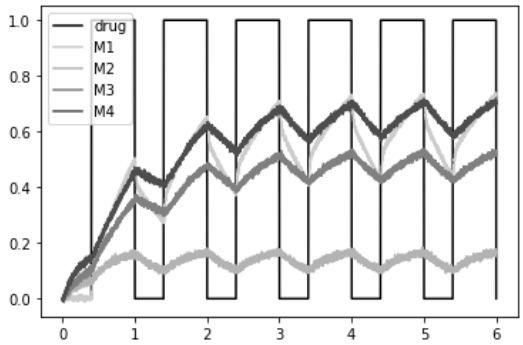

Figure 3: meso_sensitivity output of 4 variants of Model I

Model Evaluation: Simluation1 showed a significant overall growth in `meso_sensitivity` with drug intake repetition. Before plateauing, `meso_sensitivity` in Simulation1 had a greater increase during drug intake than its decrease during drug absence. Simulation2 and Simulation3 had lower overall increases of mesolimbic sensitivity compared to the other two simulations. In Simulation4, the amount of increase in `meso_sensitivity` with drug intake was 20 times greater than decreases in between drug intakes. Therefore, if the mesolimbic system achieves sensitization by implementing the nonlinear function in Model I, it must be 20 times more efficient in developing sensitization than to decay the sensitized information. Comparing Simulation1 to Simulation4, although they reached similar levels of mesolimbic sensitivity with repeated drug intake, Simulation1 had a greater spike in mesolimbic sensitivity in response to each drug intake. This characteristic of Simulation1 correlates with the hyperactivity feature of a sensitized mesolimbic system described in the Incentive-Sensitization Theory. However, it can also be argued that Simulation4 reached a higher baseline of wanting during drug absence, which also coincides with the Incentive-Sensitization Theory.

All four simulations in Model I reached a maximum level of `meso_sensitivity` within 5 representations of drug intake. In contrast, pathological drug use is often characterized by a ramping up of craving for drug (i.e., wanting) over a longer period. Thus, with the current structural design, Model I failed to describe the pattern of wanting in addiction. Therefore, other structural designs are required to achieve a continual increase in wanting with repeated drug use.

Model II - Drug Cue Salience

Structural Design: The sensitization track, from `drug_intake` to `DA_activation` to `meso_sensitivity` is the same as Model II. On top of that, we added drug-associated cue processing. Drug-associated stimuli are

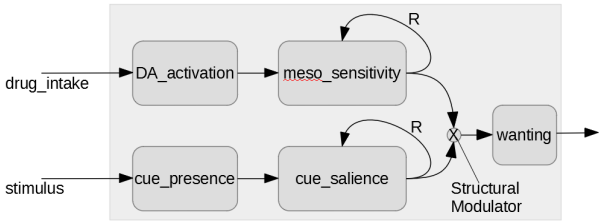

Figure 4: Structure of Model II. Circled X is a multiplicative modulation of connection strengths.

conditioned stimuli, so their representation leads to neurological representation of drug-associated effects. With repeated exposure to the drug cue, salience attributed to the drug cue will accumulate, according to Statement(2) of the Incentive-Sensitization Theory. Overall, drug intake should increase the overall baseline of wanting for drugs, while the drug cue should elicit acute increases in wanting the drug.

The structural modulator implements the two primary ways that mesolimbic sensitization and associative learning can affect each other. The learned cue salience may directly impact the mesolimbic system, triggering intensified wanting. Alternatively, the sensitized mesolimbic system may amplify cue salience, eliciting exaggerated wanting. These are done as affine transformations from 0-1 to 1-10.

Model Behaviour: To examine the model, we feed in `drug_intake`=1 every 0.65 seconds with a drug presence of 0.1 seconds, and a stimulus every 0.9 seconds, for 0.1 seconds. This set up allows the independent presence of drug and cue, as well as a combined presence of both drug intake and cue at t=3 and t=6. The value of `wanting` in Simulation1 and Simulation2 are compared in Figure 5.

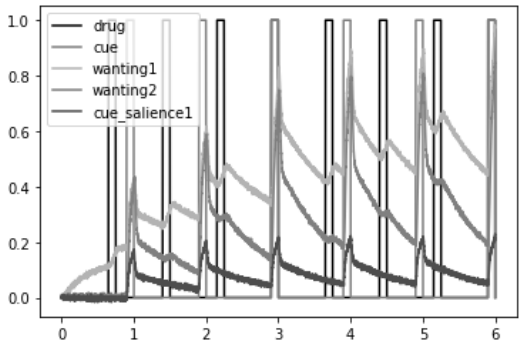

Figure 5: Wanting in simulation1 and 2 are presented in green and red respectively. cue_salience1 is the value of cue_salience in simulation 1.

Model Evaluation: Both simulations had an accumulated increase of wanting at t=6 compared to baseline at t=0. Compared to Model I, the two simulations in Model II also had a continual increase, extending beyond the plateau in Model I. However, Simulation1 had an overall steeper increase in wanting than Simulation2. While drug cue triggered similar spikes of wanting in both simulations, drug intake resulted

in a greater increase in wanting in Simulation1 than in Simulation2. Importantly, `wanting` failed to respond to the first presentation of `drug_intake`. Therefore, the computational design in Simulation2 did not generate enough increase in baseline wanting. Thus, Simulation1 is a more realistic representation of addiction formation.

`Cue_salience` in Simulation1 showed a slight increase with repeated drug cue presentation. Nonetheless, with the computational design in the `structural_mod` component, `wanting` achieved continual growth in Simulation1, compared reaching an early plateau in Model I. So far, we have adjusted the degree of change in mesolimbic sensitivity and cue salience, while leaving the two processes independent of each other. Another way to create an extraordinary level of wanting is to have sensitization and associative learning processes dependent on each other. The Incentive-Sensitization Theory of addiction emphasizes the abnormal amount of additional bias given to drug-associated cues. Therefore, it is plausible that the sensitized mesolimbic system can intensify the associative learning drug cues, triggering more craving for drugs.

Model III - Intensified Associative Learning

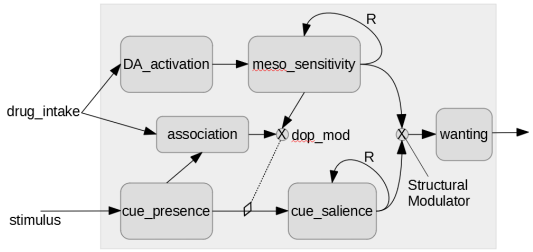

Figure 6: Structure of Model III. Dotted line is a learning signal, adjusting the strengths of the connection weights to which it is connected.

Structural Design: The main feature of this model is that mesolimbic sensitivity can accelerate the formation of drug cue salience. To implement this feature, the `association` component tracks the presentation of `drug_intake` and `cue_presence`, computing the absolute distance of the two values. The stronger the `association`, the more `cue_salience` should increase. Then, `dop_mod` scales up `association` based on `meso_sensitivity`. The integration of `association` and `meso_sensitivity` then contributes to the development of `cue_salience`. Therefore, when drug intake and stimulus are presented close together (aka, there is an association), a sensitized mesolimbic system should intensify the power of association, leading to a faster increase in cue salience.

Model Behaviour: Our primary purpose in this simulation is to test the new `association` and `dop_mod` components. To reduce uncertainty in the other processes in the model, we used the linear option for `meso_sensitivity`, with a recurrence value of 0.95. We fed the model with `drug_intake`=1 every 0.65 seconds with a drug presence of 0.1 seconds, and stimulus every 0.9 seconds, for 0.1 seconds. With ten repetitions of the inputs, results are shown as below:

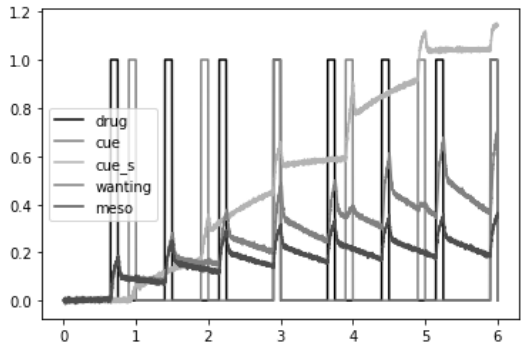

Figure 7: Cue_salience is presented as cue_s in green. Wanting is in red, and meso_sensitivity is meso in purple.

Model Evaluation: Model III simulation generated overall increases in mesolimbic sensitivity, wanting and cue salience. Cue salience in Model III increased with a significantly steeper slope than the `cue_salience` curve in Model II Simluation1 (Figure 5). In Model II, `cue_salience` did not increase as drug intake, and drug cue built an association. In contrast, the new structural design in Model III helped the simulation achieve an overall growth in `cue_salience`. Moreover, the spike in `cue_salience` following drug cue presentation also increased as drug cue presentation repeated. The success of associative learning is also evident in the pattern of wanting. Importantly, at the first two cue presentation, wanting showed minimal increases. At t = 3, drug intake and drug cue occurred together, forming a strong association. Subsequently, at t=4 and t=5, cue presentation elicited a noticeable increase in wanting. In other words, in accordance with the Incentive-Sensitization Theory, Model III simulation demonstrated sensitization in mesolimbic reactivity, drug cue related response, and overall wanting for drugs.

Discussion

Overall, our study took a structuralist computational approach, rebuilding the neurological process of addiction according to the blueprint provided by the Incentive-Sensitization Theory of addiction. Here, we discuss the implications of our model simulations in relation to the first three statements of the Incentive-Sensitization Theory, the limitations to our models, and future directions for studies on drug addiction. Implementing Statement(1), the long-lasting sensitization: In this paper, we explored both linear and non-linear options of implementing the long-lasting effect of sensitization. Simulations in Model I demonstrated that both linear and non-linear functions are computationally plausible to describe mesolimbic sensitization.

The incentive sensitization did not propose a computational guideline that specifies the degree of long-lasting effect. To determine the exact value of recurrence strength in the linear function, or the variables in the non-linear func-

tion, we need a realistic data set. Ideally, this would contain the speed of sensation formation and decay, represented by quantifiable units (e.g., the duration of time, or the number of drug use repetitions required to produce sensitization). Then we can perform data fitting and select the model with the best fit.

Implementing Statement(2), brain areas responsible for motivation: While we can pinpoint the mesolimbic system as the centre for processing rewards, it is difficult to determine the brain area responsible for cue salience attribution. We have an adaptive bias towards natural rewards such as food. But according to the Incentive-Sensitization Theory, chronic drug use will produce an abnormal attentional bias towards drug-associated cues (Robbinson and Berridge, 2003). Therefore, other than sensitization in the mesolimbic system, there must be a neural activation pattern that is dedicated to directing sensitization towards drug-associated cues. When implementing `cue_salience` in our models, we did not specify the neurological areas corresponding to this computational component. The `structural_modulator` in Model II and III was also not implemented as a neurological component. This is because current literature of incentive sensitization does not account for the neurological mechanism of how drug cue salience triggers wanting in incentive sensitization.

Implementing Statement(3), drug salience and cue salience associative learning: Incorporating the cue association process, Model II generated more realistic simulations compared to Model I. Model II extended the system's capacity for growth of wanting, allowing for the continual increase in wanting beyond the plateaus produced in Model I. Furthermore, Model I simulated two possible mechanisms of combining mesolimbic sensitization and drug cue associative learning. The results supported the hypothesis that intensified drug cue salience affects the sensitized mesolimbic system, triggering spikes in wanting rather than the other way around. Nonetheless, there are limitations to the current model. Crucially, neither Model II nor III included a complete process of the development of drug cue associative learning. For example, our simulations registered a successful pairing of drug and drug cue only when `drug_intake` and stimulus are presented simultaneously. In reality, associative strength is strongest when the conditioned stimulus is presented slightly after the unconditioned stimulus. Future studies can utilize mature computational models of associative learning to complete the model further.

Models in this paper are shortened approximations of real-life neurological processes. The assumption is that if the models' time scale is scaled up to match actual drug-use experiences, the qualitative brain changes should be the same. However, this assumption requires validation with human data and more extended simulations that run for weeks, if not months. Extensive simulations might also reveal a faster rate of Incentive-Sensitization formation and a slower rate of its recovery. This is because, in our current models, the ratio of drug intake duration to drug absence duration is significantly higher than in reality. For instance, Model I Simulation 4 had drug intakes of 0.6 seconds and drug absences of 0.4 seconds – the length of drug absence is 2/3 of drug intake. In reality, drug absence can last days, weeks, even months. Drug users with longer abstinence in between drug repetitions still present a high level of wanting for drugs. Moreover, the duration of drug intake is usually shorter than drug absence. Importantly, the neuropharmacological effects of addictive drugs can occur within minutes after drug intake. This means that the Incentive-Sensitization of the mesolimbic DA system can form within minutes of drug use and remain robust after drug absence periods longer than in the models. In Model I Simulation 4, the recurrent strength of the mesolimbic DA system is set to 0.9. The increase of mesolimbic sensitivity during drug intake is 20 times larger than its decrease during drug absence. Given the analysis above, the computational difference between mesolimbic sensitivity increase and decrease is likely to be more significant with more realistic simulations. Overall, it is likely that the strength of Incentive-Sensitization as a result of addictive drug use is more robust than the models present.

In sum, our paper informs future studies in that 1) the rate of mesolimbic sensitization can be determined with data fitting from clinical studies, 2) the process of associative learning indispensable to drug addiction formation, 3) the Incentive-Sensitization Theory needs to identifying the neurological area responsible for storing associated salience to drug cues, and 4) the methodology of computationally structuring virtual neural circuits can be very useful for examining theories of neurological mechanisms and simulating those processes.

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