COMPUTATIONAL IMPLEMENTATION OF THE INCENTIVE - SENSITIZATION THEORY OF ADDICTION

by

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Abstract

In the mid-1990s, the disease model of addiction replaced the moral model, emphasizing the underlying neurological mechanism of addiction. In accord with this view, the Incentive-Sensitization theory provides an account of compulsivity in addiction by emphasizing neural changes that accompany chronic drug use. This thesis presents the first steps towards a biologically grounded implementation of the Incentive-Sensitization theory of addiction. First, this project proposes an update of computational model structure with a learning perspective of addiction, focusing on the Incentive-Sensitization process. This project then presents multiple different plausible ways of mapping this theory onto a computational model, and examines the resulting behaviour to see whether it accords with standard interpretations of the theory. Results showed that, while repeated drug use can lead to a sensitized mesolimbic dopamine system, associative learning hyperreactivity to drug cues is crucial for the development of chronic drug use. Analyses of the computational models also revealed important ambiguities and limitations to the Incentive-Sensitization theory. This is the first step in a larger project to create a computationally tractable and biologically motivated computational model of addiction to help clarify and ground various terms in the theory.

Co-Authorship

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Chapter 1

Introduction

1.1 Overview

Up until the early to mid-1990s, addiction was viewed as a moral failure (Frank & Nagel, 2017). This moral model of addiction assumes that addicts have a choice and that they consciously choose to participate in drug use activity. The moralization of addiction leads to social marginalization of addicts (Ahern et al., 2007), social disapproval among the general public (Room, 2005), as well as a punitive attitude in health providers towards addicts (Deehan et al., 1998). In addition to the negative views it promotes, a moral model of addiction alone cannot explain why addicts would repeatedly consume drugs in the face of reduced pleasure from drugs and destructive consequences to their daily lives.

A reaction against the moral model of substance abuse supported biological explanations of this disorder. As early as the 1980s, researchers found a strong genetic factor to alcoholism (e.g., Cloninger, 1987) that helped to alleviate some blame on drug addicts. Furthermore, findings that drugs themselves change brain structures in chronic abusers (T. E. Robinson et al., 2001) led to a brain disease view of addiction. Today, the National Institute on Drug Abuse (NIDA) defines addiction as a 'chronic disease characterized by drug seeking and use that is compulsive, or difficult to control, despite harmful consequences' (NIDA, 2018).

This disease model of addiction assumes that addictive behaviours are compulsive and out of the addicts' control (Leshner, 1997). Following this notion, addicts' rational judgements are not responsible for addictive behaviours. The disease model also acknowledges neuroscience evidence of brain changes as a result of drug use (Leshner, 1997). Clinical research confirms a causal relationship between drug-use and brain changes in humans and animal models (e.g., (Kalivas & Stewart, 1991). Whereas the moral model of addiction does not provide effective treatments, the disease model generates therapeutic and pharmacological treatment options (Kiefer, 2007). Overall, the disease model effectively reduces the moralization of addiction, and encourages new scientific solutions, instead of simply blaming the addictive behaviour on the addicts (Buchman & Reiner, 2009). This disease model of addiction continues to be the most adopted perspective of researchers, therapists, and practitioners (Ahern et al., 2007).

The brain disease model of addiction evolved further in the 21st century. Around 2010, many researchers identified faults of the brain disease model, and proposed other potential mechanisms of addiction. For example, Pickard and colleagues (2015) put together an E-book with articles that critically evaluated how the brain disease model is incompatible with recent data and theories, pointing out that addictive behaviour is at least partially subject to voluntary choice. Other researchers, such as Marc Lewis and Maia Szalavitz, drew from their personal experience and argued that addiction is a learning process, rather than a brain disease (Lewis, 2017; Szalavitz, 2016). These new models do not support either the moral model of addiction or the brain disease model; collectively, they will be referred to as alternative models of addiction. These alternative models provide different arguments against the brain disease model although they all point out common weaknesses. Specifically, whereas the disease model denies addicts' ability to perform deliberate choices, alternative models suggest addiction is better predicted and treated when addicts' choices are acknowledged. The disease model proposes that drugs alter normal brain processing. In contrast, alternative models suggest that such brain changes are not qualitatively different from normal brain plasticity and, most importantly, are reversible. The disease model has an absolute definition of addiction – the brain is either addicted or it is not- whereas alternative models propose a dimensional view of substance abuse. Whereas the disease model studies addiction as a final product (an addicted brain), the alternative models focus on the development of the disorder. This thesis incorporates perspectives of the alternative models of addiction, specifically adopting a learning process of these models.

At the same time that the alterative models of addiction were being proposed, advances in computational modeling and artificial intelligence were impacting research in neuroscience, psychology, and medicine. In terms of addiction, most of the computational models are based on outdated theories and have not incorporated recent progress in understanding this disorder, such as the learning perspective of addiction. For my Master Thesis, I propose to unify the alternative models, and to develop a computational model of addiction based on a learning perspective.

1.2 The Brain Disease Model

The brain disease model of addiction emphasizes the destructive and chronic nature of brain changes that result from drug use. The most agreed upon alterations in brain mechanisms include hyperactivation of dopaminergic pathways, which is responsible for learning what is desired, and a shift from prefrontal cortex (PFC) to striatal activity, which accounts for the inability to perform rational decision making (e.g., Everitt & Robbins, 2005). By stressing that these two changes are not in the addicts’ control, the brain disease model informed the public on why addicts have the desire for drugs and why they cannot simply stop their drug use. A common expression ‘hijacked brain’ was coined and widely used after a psychiatrist wrote ‘The war on drugs is a war between the hijacked reward pathways that push the person to want to use, and the frontal lobes, which try to keep the beast at bay” (*Doctor’s Orders*, 2009).

Research based on the brain disease model usually focuses on the result: an addicted brain. By emphasizing how the brain has fundamentally changed, the brain disease model avoids discussing addicts’ personal choices, and whether or not these choices influence the development of addiction. In other words, the brain disease model links drug use directly with the most extreme case: a destructively changed brain, without much attention to the incremental nature of these brain changes.

Overall, the benefits of the disease model are twofold. First, it opened up avenues for neuroscience findings. Incorporating falsifiable theories, behavioural and neurological data, and clinical experiments, the brain disease model is a more scientific account of addiction than the moral model. Second, the brain disease model alleviated blame on the individual addict by removing the responsibility for choice of drug use over abstinence. As a result, the media started to portray a more empathy-worthy image of addicts, and more humanistic addiction treatments were developed, and social advocacy groups argued against institutional confinement of addicts.

1.3 Alternative Models of Addiction

Although the removal of ‘choice’ in the brain disease model of addiction relieves addicts of moral judgement, it creates other problems for understanding this disorder. For example, Heyman (2013) argued that the recovery of an addict is better predicted when the model contains choice factors. Choice, as a result of temporal bargaining, also explains impulsivity in addiction (Ainslie, 2013). In response, Pickard (2015) proposed a Response Without Blame model of addiction, in which addicts are making a choice, but are not to be blamed for such choices. One of the advantages of acknowledging choice in addictive behaviours, is that it provides a sense of control which may counter the feeling of helplessness that often occurs in addiction. For example, self-efficacy is associated with the effectiveness of addiction treatment (Rollnick & Heather, 1982). After 30 years of practice in addiction treatment, Snoek (2017) concluded that addicts can overcome the disease-like duress of addiction by 'learning more self-control techniques' and 'building on their self-concept and belief in self-efficacy'. Therefore, although the disease model has had a positive impact on society's view of addiction by removing responsibility and blame from addicts, a model that deprives addicts of choice is ineffective in predicting and treating addiction.

It is undeniable that drug use will lead to changes in brain wiring. But many argue that these changes are neither abnormal nor chronic. According to Marc Lewis, brain changes in addiction are not fundamentally different from those occurring in normal neural plasticity and learning. For example, the most documented brain change in addiction is the shift in neural systems that control behavioral responses, from the ventral to the dorsal striatal areas (Volkow et al., 2016). This change is common in the development of habits (Everitt & Robbins, 2005; Lewis, 2017), defined as behavioural responses that occur in response to environmental stimuli. Habitual responding is often described as 'automatic' or 'unconscious' and is characterized by gradual changes in behaviour with repeated stimulus-response associations. The fact that brain changes in habit learning and addiction overlap suggests that this brain change, itself, cannot define addiction as a brain disease.

The brain changes that accompany chronic drug use do not always lead to relapsing addictive behaviour. In fact, most addicts eventually recover voluntarily without professional help (Lopez-Quintero et al., 2011). Figure 1 (Figure 1 in Lopez-Quintero et al., 2011) shows the remission rate as a function of years since meeting the criteria of substance dependence according to the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association, 2013). The cumulative probabilities of remission after ten years of use were 18.4% for nicotine (n=6,937), 37.4% for alcohol (n=4,781), 66.2% for cannabis (n=530) and 75.8% for cocaine (n=408). Half of the cases of cocaine reached a remission after five years of use. Heyman (2013) further argued that considering the average onset age of illicit drug use is 20, most addicts remit by the age of 30. Therefore, these new data contradict the brain disease model's claim that addiction is a chronic, relapsing disease.

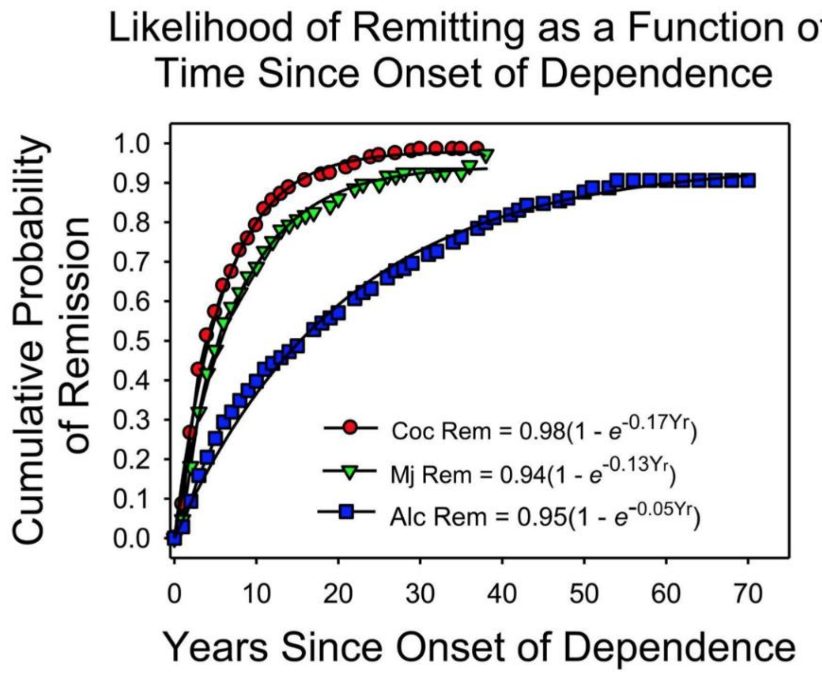

Figure 1: The cumulative frequency of remission as a function of time since the onset of dependence. Based on Lopez-Quintero et al.'s (2011) report.

These alternative models of addiction propose that rewiring of the brain with chronic drug use is not destructive and irreversible. In that sense, addiction resembles habit learning more than a chronic disease. Heyman (2013) pointed out four convergent study results supporting this contention: 1) rats that had consumed cocaine still preferred saccharin (Lenoir et al., 2007), indicating a spontaneous cessation of cocaine use; 2) As shown in Figure 1, remission rates stay constant over time suggesting that the length of time an addict has been addicted does not predict his or her likelihood to quit; 3) in a longitudinal study, the likelihood of quitting cocaine does not increase or decrease over time (Vaillant, 1973); and 4) rats' likelihood to switch from cocaine to saccharin intake in a two-choice operant paradigm was not correlated with previous cocaine use (Cantin et al., 2010). Heyman then concluded that the brain changes resulting from substance use do not decrease the probability of remission. In other words, the brain still has the plasticity to be trained out of addiction, regardless of the duration of substance use.

Compared to the disease model of addiction, alternative models focus on how addiction develops, rather than the addictive state itself. For example, (Lewis, 2017) proposed that the development of addiction is a subset of learning based on two assumptions. First, as discussed previously, brain changes during addiction can be described as brain plasticity. Second, addiction does not arise from brain changes alone. More specifically, an individual's experiences, combined with feedback from actions that lead to drug intake, all play a role in the development of addiction. This reliance on external feedback is also a characteristic of learning.

1.3.1 Biological Basis of Learning in Addiction

Following the discovery of pleasure centers in the brain (Olds, 1956), positive reinforcement accounts of addiction guided research in addiction. These theories propose that drug-seeking behaviour is reinforced by the euphoric state induced by drug intake. The rewarding effects of abused drugs, like those of natural reinforcers, is mediated through the mesolimbic dopamine (DA) pathway, projecting from the ventral tegmental area (VTA) to the nucleus accumbens (Nacc) and PFC (R. A. Wise, 1980). Antagonizing the mesolimbic DA system blocks the positive reinforcement effect of drug use (Koob & Le Moal, 1997; R. A. Wise & Bozarth, 1987). In fact, many researchers considered DA a reinforcement signal, anticipatory, or error prediction signal, sustaining responding for drugs of abuse as well as natural reinforcers through the mesolimbic DA pathway (Farooqi et al., 2007; Schultz, 1998; Suri & Schultz, 1999).

Negative reinforcement also contributes to addiction when drug intake alleviates the negative symptoms of withdrawal, such as drowsiness, headache, or depression. Repeated drug use leads to neurobiological adaptations that alter mesolimbic DA system function (Pierce & Kumaresan, 2006). As a result, baseline DA levels are decreased in drug-free states, which may explain why substance users experience less pleasure from drug use as addiction develops. In other words, substance abusers must increase the dose and frequency of drug intake to make up for reductions in DA levels following excessive drug intake (Ahmed & Koob, 2005).

Despite the similarities between addiction and habit learning described above, drug use is more difficult to quit than other behavioural patterns. This can be explained by the Incentive-Sensitization theory (T. E. Robinson & Berridge, 1993), which regards addiction as a neuroadaptation resulting from drug intake. In line with learning models of addiction, the Incentive-Sensitization model theorizes that drug intake induces sensitization of the neural system that attributes value/incentive salience to the action of drug taking. Therefore, as drug use behaviour repeats, the drug-associated context and the act of drug taking itself become more attractive, and hence, drug users will experience greater 'wanting' of the drug. At the same time, as drug intake continues, each dose will induce less subjective pleasure, resulting in less 'liking' of the substance. As a result, as the two mechanisms have simultaneous effects, drug users will experience less liking of the substances but increased wanting to take drugs (Ternes et al., 1985).

1.3.2 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 et al., 1996). Therefore, although both positive and negative reinforcement may contribute to continued drug use, neither alone can explain fundamental aspects of addictive behaviour.

In response, Robinson and Berridge (1993) formulated the Incentive-Sensitization theory of drug addiction which proposes that 'wanting' and 'liking' of 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 et al., 1989). Subsequent work confirmed a dissociation in biological systems that mediate these two processes in rodents (Berridge, 2007; Pool et al., 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 et al., 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 (T. E. Robinson & Berridge, 1993; R. A. Wise & Bozarth, 1987) 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 Nacc and PFC ‘grow’ more dendritic branches and spines following chronic drug intake, increasing the capacity for DA transmission (T. E. Robinson et al., 2001; T. E. Robinson & Kolb, 1997, 1999).

A primary characteristic of drug addiction is excessive craving that is triggered by drug-associated stimuli. For example, in human drug users, imagery as well as contextual and social cues previously paired with drug intake can trigger drug use (Norberg et al., 2016; Weiss et al., 2001). 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 (Berridge & Robinson, 2011).

Although the Incentive-Sensitization theory describes neurological processes, it is consistent with the learning perspective of addiction. The brain disease model adopts a categorical definition of addiction, many alternative approaches suggest addiction is common in individuals not diagnosed with substance use disorder. For example, (Dill & Holton, 2014), building on (T. E. Robinson & Berridge, 1993) Incentive-sensitization view of addiction, suggest that the temptations addicts and non-addicts face are not qualitatively different – most individuals experience wanting something that does not produce pleasure or has no adaptive value.

Since its original formulation, the Incentive-Sensitization theory has generated over 7 000 citations (Google scholar), attesting to its impact in understanding the etiology and treatment of addiction. These theories have been applied to a variety of substances (e.g., psychostimulants, alcohol, opioids) (Wyvell & Berridge, 2001), palatable food (Joyner et al., 2017), and behavioral addictions (Rømer Thomsen et al., 2014, 2014). Despite its strengths, the Incentive-Sensitization theory does not provide a complete account of addiction in that it cannot explain evidence of decreased DA levels that accompany chronic drug use (Diana, 2011). A goal of this study is to build a computational framework that recreates neurobiological changes in incentive sensitization, providing information on the mechanisms underlying excessive drug use and, potentially, informing the development of pharmacological treatments for addiction.

1.4 The Computational Modelling Approach

Based on experimental evidence and theoretical interpretations of addiction, a number of researchers have turned to computational tools that provide a means to formulate and test theories of addiction. A number of these theories describe addiction as a negative reinforcement process, focusing on analyzing the role of withdrawal in continued drug use (e.g., Zhukovsky et al., 2019). As argued previously, however, neither positive nor negative reinforcement provides a full account of addiction. From a behavioral economic perspective, models of free decision making are often used to study the compulsive behaviour of addiction (Morris & Cushman, 2019; Redish, 2004), within a broader context of understanding psychopharmacological processes (e.g., DA activation and transmission) that characterize psychiatric disorders (Enrico et al., 2016). The difficulty with these models is that results are generalized across many disorders, resulting in an inability to identify mechanism that are unique to the development of addiction. One multiscale model that focused on addiction integrated cognitive, behavioural, and neural processes to simulate the development of drinking behavior by a virtual agent (Figure 2; Figure 1 in Levy et al., 2009).

In this model, the development of addiction is divided into three sections: the behavioural section, the cognitive section and the neuropsychology section. The neuropsychology section includes the internal state of the drug user that can increase the chances of drug pursuit. External triggers, such as acute pain (Ap(t)) and acute drug presence (Ad(t)), are also categorized under the neuropsychology section. The combination of internal states and external cues then affects the rationality (R(t)) component in the cognitive section. The more intense the internal cues and external triggers, the less rational the subject becomes. In the behaviour section, compulsivity (C(t)) results from Incentive-Sensitization, which increases with repeated drug intake. The over compulsivity level consists of compulsivity to consume drugs during drug presence (c'(t)) and drug cue presence (c''(t)). The inhibition component (I(t)) includes neurological inhibition from the prefrontal cortex (i'(t)) and social inhibition (i''(t)), such as restrictions from families, the society values and peer influences. The final output in this model is the probability of drug-seeking behaviour (G(t)). The value of this output is the integration of rationality (r(t)), compulsion (C(t)) and inhibition (I(t)). Rationality and inhibition decrease the probability of drug-seeking behaviour (G(t)), while compulsion increases such probability.

This project is one of the few computational models that simulate the process of addiction formation, based on an influential theory of this disorder (Incentive-Sensitization). Although a significant development in the field, this model has some drawbacks. First, the classification of the components into the three sections is debatable. For example, the process of Incentive-Sensitization (compulsion) is structured under the behaviour section when it is a neurological process. Similarly, neural inhibition (i'(t)) is also included in the behaviour section. Second, some processes are vaguely defined. For example, the cognitive process of rationality (r(t)) is complex and debatable. This project did not choose a clear definition or theory of rationality to construct the model. The roles of dopamine craving (D(t)) and Compulsion (C(t)) are also not clearly differentiated. Finally, because the model consisted of multiple factors, including incentive sensitization, withdrawal, rationality, and social influences, among others, it was difficult to examine each factor individually and, more importantly, to make informative claims about the role of each factor in addiction.

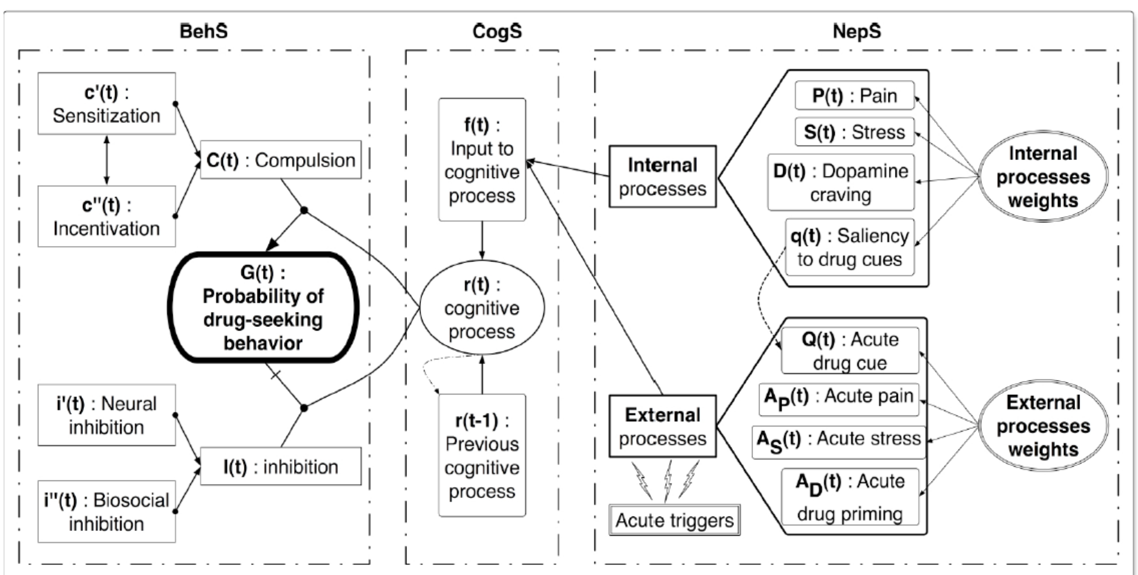

Figure 2: The descriptive model of addiction developed by Levy and colleagues (2009). This model divides the development of addiction into three section: the behavioural section, the cognitive section and the neuropsychological section

1.4.1 Reconstructing the Incentive-Sensitization Theory with a Learning Perspective

As discussed above, researchers arguing against the brain disease model often share similar beliefs about addiction. These include the following: 1) addiction is a behavioural pattern acquired through learning; 2) long-term relapsing addiction is rare; 3) self-efficacy to choose is critical to remission; 4) on a neurobiological level, incentive-sensitization is unique to addiction; and 5) brain plasticity is capable of reversing neural states that develop with addiction. This thesis attempts to unify these accounts by proposing a learning model of addiction that defines addiction as a developmentally acquired neurological state that attributes disproportional desire to drugs and results in continued drug use.

By defining addiction as a type of learning, the disorder can be re-conceptualized based on what we know about learning. Marc Lewis's 2017 paper suggested that, in learning, individuals first have *experience*, which will lead to corresponding *brain changes*. Those brain changes will alter the probability of performing certain *behaviours*. The performance of the behaviours will then cause changes in experience. This loop of learning can describe addiction in the same fashion. Since learning is a universal mechanism, our model has the capacity to describe extreme cases of addiction (the focus of the brain disease model), but also dimensional aspects of addiction development. As Marc Lewis repeatedly argues, 'The brain changes seen in addiction are just the biological underpinnings of this natural learning progression.' (Lewis, 2017). To test this learning model, this thesis will take advantage of computational tools. To fit the learning model to computational language, addiction will be described as a dynamic learning process that uses drug intake as well as external stimuli as input. Neurological changes act as a mediator in the model, leading to alternations in behavioural probabilities as the output.

Reconstructing Figure 2 based on the learning perspective and focusing on the Incentive-Sensitization mechanism, the schematic flow of addiction can be updated as shown in Figure 3. The three components in Figure 2 are *Behaviour*, *Cognitive* and *Neuropsychological.* A potential issue with this design is that the *Cognitive* and *Neuropsychological* component are likely to have overlapping subcomponents. Also, the *r (rationality)* cognitive subcomponent is difficult to describe with neurological mechanisms. Informed by the learning perspective of addiction, the model's components are replaced with *Experience*, *Neuropsychological Process* and *Behavioural Probability*.

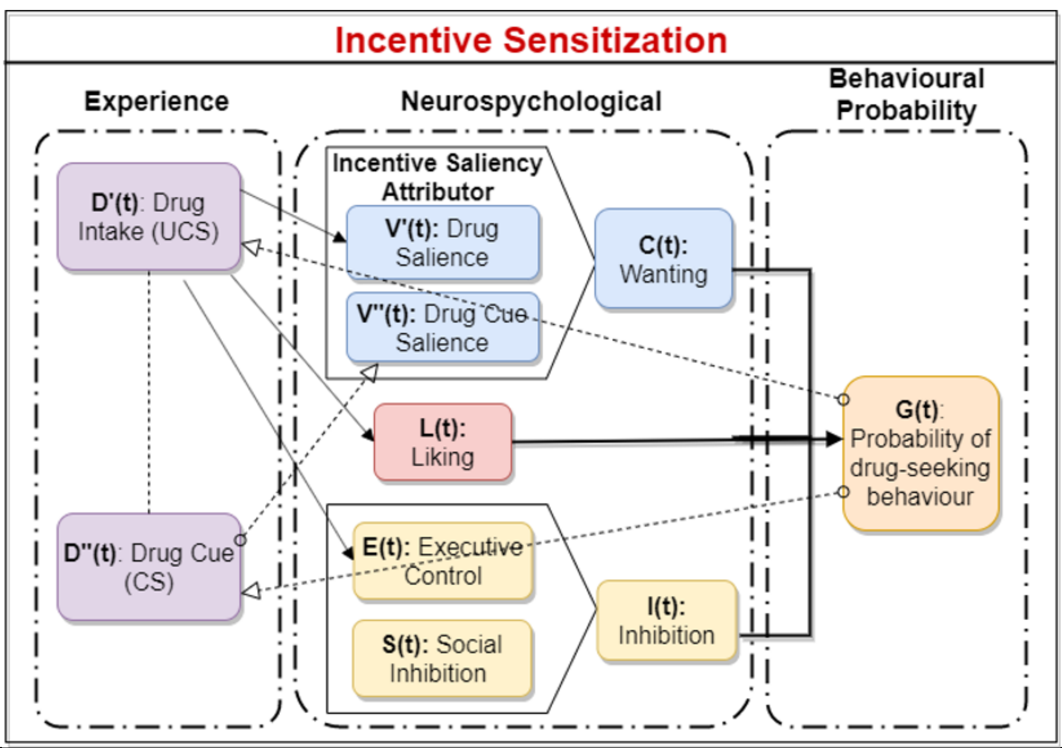

Figure 3: This schematic chart shows the architecture of the neural network for simulating Incentive Sensitization. This structure takes a learning perspective, dividing the development of addiction into sections representing experience, neuropsychology and behavioural probability. Each component in the model is defined in the main text

In Figure 3, subjects experience drug intake (D'(t) and drug cue presentation (D''(t)) as external stimulations. To create a clear demonstration of the addiction process, we focus on only the presence or absence of drugs and drug-associated cues, instead of evaluating the effects of dosages. Therefore, the value of *drug intake* and *drug cue* is either 0 or 1. Borrowing Robinson and Berridge's term, the *incentive saliency attributor* reflects the function of the mesolimbic DA system hyperreactivity to drug and drug-associated cues. In other words, the mesolimbic DA system can be seen as a centre that learns to attribute salience value to drugs and drug-associated cues. According to the Inventive-Sensitization theory, these salience values are reflected by reactivity of the mesolimbic DA system in response to drug or drug-associated cues. The salience for drug (V'(t)) and salience for drug cue (V''(t)) form an overall level of wanting (C(t)). Liking(L(t)), on the other hand, is the subjective euphoric experience as a result of drug intake, which is disassociated from wanting the drug. Inhibition (I(t)) reduces the motivation to pursue drug intake. Similar to Ivey's model (Figure 2), the inhibition component consists of both neurological inhibition, characterized by the executive control function of the prefrontal cortex, and social inhibition, which may include family influences, geographical barriers, financial status etc. The final output is the probability of drug taking behaviour (G) which is a value between 0 and 1 to reflect the probability of drug intake at any given moment.

Prior to drug use, the *incentive saliency attributor* is not active (V'(0) = V''(0) = 0). *Executive Control*(E) is not impaired by drugs; thus, it is at a maximum value and able to inhibit G. G (∈ 0-1) is small but non-zero to reflect risk seeking and curiosity. With drug use (D' = 1), *drug salience, drug cue salience*, and *liking* activate and increase. *Executive Control*(E) starts to decline, followed by a reduction in *Inhibition*(I). *Wanting* and *liking* increase G, while *inhibition* reduces G. As drug use continues, *drug salience* and *cue salience* significantly increase with each drug intake. Initially, *drug_salience* is a greater value than *cue salience* (V'(0)>V''(0)). With continual exposure to drug and drug associated cues, salience to drug cue surpasses salience to drug (V''(n)>V'(n)). *Wanting*(C) will exponentially increase while *liking*(L) will achieve a plateau. As *Executive Control*(E) reduces, *Inhibition*(I) will continue to reduce, resulting in less inhibited G growth.

To set up computational examinations, we first summarized the central claims of the Incentive-Sensitization theory into falsifiable statements. We then selected the most fundamental processes of the theory and built a basic computational model. Next, we examined the behaviour of the model, and compared it to addictive behavioural patterns that are characterized and described in clinical reports, and are predicted by the Incentive-Sensitization theory. On top of the initial model, we added new components and functions described in the Incentive-Sensitization theory, discussing what each component of the model represents. According to Michael Frank, “the brain is like a massive LEGO set, where each of the individual pieces is quite simple (like a single LEGO piece), and all the power comes from the nearly infinite ways that these simple pieces can be recombined to do different things.” In this study, we are building up the incentive saliency attributor component of the schematic, which is a main characteristic of the Incentive-Sensitization model of addiction.

Overall, the goal of this study is to identify the neurological processes that are critical to addiction formation, according to the Incentive-Sensitization theory of addiction (Robinson and Berridge, 1993). We focused on the Incentive-Sensitization theory because it was formulated, specifically, to explain the neurological foundations of addiction, and has had an enormous impact on the field. Therefore, computational models of this theory can examine its explanatory power. The results of this project, therefore, may contribute to the discourse of the fundamental neurological mechanism of addiction. In the long-term, the methodology in this project can be used to examine other competing theories (such as the dopamine depletion and the allostasis theory of addiction). This current project also sets up a foundation for future data-fitting examinations to test the computational models, train the models to generate a behaviour pattern that is close to clinical data on addiction, and determine the key parameter values required to achieve realistic simulations.

Chapter 2

Method

2.1 Procedure

To design an informative and applicable model, we first examined the core proposals 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 with chronic drug use 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 mediate a subcomponent of reward, termed incentive salience or “wanting”. It is the psychological process of incentive salience, specifically, that is responsible for instrumental drug-seeking and drug-taking behavior (drug “wanting”).'

Then, we designed models with structural components that can actualize the processes described in these statements. The specific processes will be organized into statements or hypotheses of how brain mechanisms are altered during addiction. In this way, the theory will be both implementable and falsifiable. Although it is a critical part of the Incentive-Sensitization theory (see Statement(4) above), our model does not examine the disassociation of 'liking' and 'wanting’ for three reasons: 1) mesolimbic DA activity is not responsible for the ‘liking’ process of addiction; 2) ‘wanting’, not 'liking' is the essential process of addiction; and 3) our model attempts to describe neurological changes that are common to drug addiction: the psychological and neural mechanisms of ‘wanting’, but not ‘liking’, are similar across drug classes. Finally, we restrict our model to substance addiction, while acknowledging that our findings may eventually be applicable to behavioural and food addictions. We focus on drugs because these substances directly impact the neural circuits we propose to model. Moreover, the relationship between maladaptive use of drugs and non-drug activities remains controversial.

2.2 Nengo and the Neural Engineering Framework

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 processes that create the addiction process. To do this, we make use of the Neural Engineering Framework (NEF; Eliasmith & Anderson, 2004) as implemented in the Python software toolkit Nengo. We chose Nengo as the computational tool for the following reasons. First, Nengo contains pre-existing elements that encode information as neuron spikes. Researchers can specify an algorithm and a particular neuron model, and the software finds the optimal way of organizing neurons of that type to approximate that algorithm. Second, Nengo allows parallel processing of multiple model components, simulating how brain circuits activate simultaneously, instead of in a step-by-step, hierarchical fashion. Third, Nengo excels at translating neurological responses to behavioural outputs. Future steps of this project involve combining subjects' internal wanting and external inhibition to form an overall level of probability of drug-seeking behaviour. Therefore, Nengo opens up avenues for further development of this project.

2.2.1 Neuron ensemble:

A group of neurons in the NEF is referred to as an "ensemble". Consistent with the general idea of population coding in the brain, each ensemble forms a distributed representation of a numerical vector. For example, one might use 100 neurons to represent a two-dimensional value, such as the x, y location of an object in the visual field. Each different location would correspond to a different pattern of neural activity, meaning that each individual neuron has a different (randomly chosen) tuning curve in that space. This is equivalent to having a single hidden layer of 100 neurons in a traditional artificial neural network with a randomly chosen set of weights between the 2-dimensional input and the hidden layer.

2.2.2 Connection:

If different ensembles (groups) of neurons represent numerical vectors, then connections between those ensembles compute functions on those vectors. For example, if ensemble A represents a two-dimensional vector and ensemble B represents a one-dimensional vector, then we can connect the neurons in A to the neurons in B such that some computation is performed. For example, if A represents an x, y location in the visual field and we want B to represent the visual angle to that location, we would want $B = tan^{-1}(A_2/A_1)$. In the Neural Engineering Framework, we approximate this function by finding the connection weights between all the neurons in A and all the neurons in B that best approximates this desired function. In general, with enough neurons and enough variety in the initial randomly chosen tuning curves, any function and be approximated to any degree of accuracy. However, if we include biologically realistic constraints on the neural tuning curves and the number of synapses for a particular neuron, then the accuracy with which we can approximate functions is more limited. In general, these connections are good at approximating *smooth* functions (that is, functions that are well-approximated by low-degree polynomials). See (Eliasmith & Anderson, 2004) for more details.

2.2.3 Recurrence:

If an ensemble of neurons is connected back to itself, then we can also get neurons to approximate algorithms that contain differential equations. That is, rather than just using feed-forward connections that approximate $B = f(A)$, we can also do $\frac{dB}{dt} = f(B) + g(A)$ to reflect incremental changes where g(x) is the feed-forward function from A to B. While this can be applied to complex non-linear differential equations and chaotic attractors (Eliasmith & Anderson, 2004), a more common situation to approximate a *linear* differential equation. For example, an equation like $\frac{dB}{dt} = -0.1B + 0.1A$ would result in the ensemble B representing a value that is a smoothed version of the value in A, as this is the equation for a low-pass filter with a time constant of 10 seconds. Interestingly, implementing a low-pass filter with a time constant of τ involves the same connection weights as computing a feed-forward linear function $B = (1 - \frac{\tau_s}{\tau})A$, where τ_s is the time constant of the synapses involved in the connection. This means that neurons are very good at approximating such functions, and that the time scale over which this information is stored can be very long. We use this approach here to store active memories of past information (such as associations between drug cues and actions).

2.2.4 Changing connections:

Using recurrent connections within one ensemble of neurons is one way for neurons to store information over time. Another method is to change the connection weights themselves. In biology, this would correspond to changing the effective strength of synapses, either by increasing the number of neurotransmitter receptors, or decreasing the vesicle release failure rate. While a variety of learning rules have been proposed, one common type is an *error-driven* rule; that is, one where there is a separate input that modulates the learning rule itself. The rule that we use here is known as the Prescribed Error Sensitivity rule (PES; (Eliasmith & Anderson, 2004)) where this separate modulatory input has been mapped onto dopamine. The actual connection weight change is as follows, where α is a learning rate, a_i is the activity of a pre-synaptic neuron, a_k is the activity of a modulatory neuron, ω_{ij} is the connection weight that is being learned between pre-synaptic neuron i and post-synaptic neuron j, and ω_{kj} is the connection weights for the modulatory inputs. Given a rule of this form, one can solve for the connection weights ω_{kj} in the same manner as discussed above such that the overall learning rule is the same as the standard Delta learning rule that is widely used in artificial neural networks $\omega_{ij} = \alpha a_i e_i$, where e_i is the error signal indicating how incorrect the current output of the network is $\omega_{ij} = \alpha a_i (\sum a_k \omega_{kj})$. In the work presented here, we use this learning rule to model the learning of an association between a cue and that cue's salience (see Model IV).

2.2.5 Modulation:

One particular challenge with developing biological models of addiction is that many addictive substances directly affect the neural systems themselves. Furthermore, there are a wide variety of mechanisms by which they do so, and those mechanisms are not often modelled in large-scale neural modelling software such as Nengo. Since our goal in this work is to produce a fairly generic model of addiction, here we make as few assumptions as possible and model these mechanisms by making large-scale adjustments to the neuron model while the model is running. For example, in Model III and IV we implement the effects of the presence of a drug by scaling up all of the connection weight strengths ω_{kj} in the learning rule above. Mathematically, this is identical to scaling up the learning rate, allowing us to implement a model where associations are formed much more quickly when under the influence of the drug.

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.

Chapter 3

Simulations and Results

3.1 Building Nengo Neural Network Models

To this point, we have abstracted the theory of Incentive-Sensitization into three core claims and drew a schematic flow chart representing Incentive-Sensitization. We would then implement the Incentive-Sensitization process with the Nengo Neural Network system. For each of our models, we tried to implement and examine specific claims of the Incentive-Sensitization theory and added more features to the previous model.

Statement (1) of the Incentive-Sensitization model claims that addictive drugs can produce long-lasting adaptations in neural systems. Computationally, this would mean that the increase in mesolimbic DA sensitivity when drugs are present, is greater than the decay of information when drugs are absent. In Nengo, this feature can be implemented by adjusting two vectors. The first one is the function of mesolimbic DA sensitivity itself. The mesolimbic DA sensitivity component can perform a non-linear function, which increases by a large amount when there is drug presence and decreases by a small amount during drug absence. Another vector that can be manipulated is the *recurrence* element. As introduced in the previous section, the *recurrence* element is a storage unit that contains the information over time. When the *recurrence* value is 1, the mesolimbic DA sensitivity component possesses the same value as the previous timepoint, which means it does not decay over time. When the recurrence value is 0.5, the rate of information decay is the same as information cumulations. Therefore, we can adjust the recurrence value to achieve the long-lasting effect of Incentive-Sensitization.

Model I and II demonstrated two ways of implementing Statement 2 of the Incentive-Sensitization theory -- the primary brain system that is changed with chronic drug use is the mesolimbic DA system. The structural design of Model I follows the intuitive design in the schematic chart, with an external stimulus of drug intake impacting mesolimbic DA sensitivity, affecting the overall level of wanting. To complete the process, Model II, added a dopamine activation component in between drug intake and mesolimbic DA sensitivity. This way, drug intake will first affect dopamine activation levels in the mesolimbic DA pathway. This activation then leads to the long-term effect of mesolimbic DA sensitization.

Models III and IV built on the previous models and implemented the third statement of the Incentive-Sensitization theory, which is: (3) The critical neuroadaptations associated with addiction render brain reward systems hypersensitive (“sensitized”) to drugs and drug-associated stimuli. This third claim of the Incentive-

Sensitization theory of addiction emphasizes the importance of drug-associated stimuli to the development of addiction. With repeated drug use, the mesolimbic DA system becomes sensitive, not only to drugs, but also to drug cues. This cue-associated learning follows the classical conditioning principle. It is not clear, however, what the 'critical neuroadaptations' in the statement refers to. Particularly, we now have two processes in the model's system, the mesolimbic DA sensitization process and the drug cue associative learning process. Model III demonstrated two ways in which a sensitized mesolimbic DA system and drug cue salience can integrate together to form an overall level of wanting. On top of that, Model IV had the two processes depend on each other, with a sensitized mesolimbic DA system increasing the speed of associative learning of drug cue salience.

Another parameter required by the Nengo element of *ensemble* is the number of neurons. This parameter determines the number of neurons performing the function assigned. The more neurons in an *ensemble*, the more accurate the *ensemble* is at computing the function while scarifying the efficiency of computing. The fewer the neurons, the faster the *ensemble* computes the function but with worse accuracy. Fewer neurons also produce more noise in the visualization of the decoded value of neuron spikes. After the initial testing of the model, we set all *ensembles* in our four models to have N=1000 neurons, to achieve satisfying computational accuracy. The detailed Nengo codes of the four models can be retrieved from https://github.com/Freda-Peiying-Jian/computational-Incentive-Sensitization.

The primary purpose of exploring the above options in these models is to identify the core mechanism responsible for an abnormal level of sensitized wanting. To examine each model, we fed in repetitions of drug intake or drug cue presence as inputs. We evaluated either the level of wanting or mesolimbic DA sensitivity as the output. For Models I and II, we fed in 0.6 seconds of *drug_intake = 1* following 0.4 seconds of drug absence. This relatively long duration of drug administration (0.6 s out of every 1s) provides a clear visual demonstration of its effect on mesolimbic DA sensitivity. Because Models III and IV contain an associative learning process, we designed the pattern of input so that drug and drug cue are presented separately, then simultaneously, and then separately again. We compared the results of the model qualitatively to the claims of the Incentive-Sensitization theory as well as to the addiction literature.

3.2 Model I -- Salience Value of Drug Intake

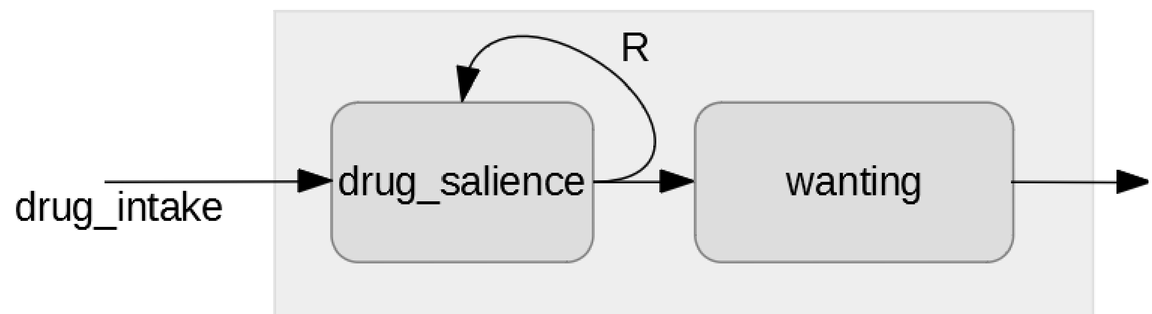

Figure 4: Nengo Structure of Model I. Rounded boxes are groups of neurons; arrows are all-to-all connections approximating functions. R refers to the recurrent strength of drug_salience. The computational features of these connections are described in section 2.2

3.1.1 Structural Design:

Building on previous evaluations, our first model is a direct representation of the top section of the schematic flow: from drug intake to drug salience to wanting (Figure 4). The *drug_intake* component is an external stimulus, with a value of 0 or 1. *Drug_intake* = 1 indicates the presence of drug intake (i.e., drug administration), while *drug_intake* = 0 reflects drug absence. The value of *drug_salience* and *wanting* were set to 0 initially. *Drug_salience* is the incentive salience attributed to drug intake, which contributes to the baseline *wanting* for drugs. Both *drug_salience* and *wanting* are implemented as groups of neurons in Nengo, responsible for a given function. We created a recurrence value of *drug_salience*, storing and manipulating the value of *drug_salience* stored at the previous time point. The recurrence strength reflects how fast the learned association decays in a group of neurons. Therefore, the value of the recurrent strength can represent how sensitive an individual's mesolimbic DA system is to the exposure of a substance.

3.1.2 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 DA system, while the decay of the sensitization during drug absence should be slow. To create simple representations of this mechanism, we computationally manipulated Model I to perform the following 3 functions (Table 1):

Table 1: Model I Computational Options

Simulation	Recurrence	S(t): the function for *drug_salience*(t)
Simulation1	1	S(t-1) + 0.04 if *drug_intake* = 1
		S(t-1) - 0.02 if *drug_intake* = 0
Simulation2	0.9	S(t-1) + 0.04 if *drug_intake* = 1
		S(t-1) - 0.02 if *drug_intake* = 0
Simulation3	0.9	S(t-1) + 0.1 if *drug_intake* = 1
		S(t-1) - 0.01 if *drug_intake* = 0
Simulation4	0.85	S(t-1) + 0.1 if *drug_intake* = 1
		S(t-1) - 0.01 if *drug_intake* = 0

Note: S(t) is short for drug_salience(t). S(t) is used to reduce space.

Neurons implemented using Nengo Neural Network Simulator are most effective at approximating values between 0 and 1. For the model components such as drug_salience (represented as a rounded box in Figure 4), 0 represents minimal activation, while 1 represents the maximum capacity of normal activation. We can then manipulate the function implemented by these Nengo elements to represent the degree to which neural activities increase or decrease during drug intake and drug absence. As introduced in section 2.2, the recurrence value represents the amount of information that is retained by the neural structure. We then set up simulations by adjusting both the recurrence value and the function for *drug_salience* in order to evaluate their effects on the overall level of *wanting*.

Simulation1 has a *drug_salience* recurrence strength of 1, indicating that there is almost no decay of information over time. The other two simulations have a recurrent strength of 0.9, indicating that approximately 90% of the neurological changes are retained. Simulation1 and Simulation2 have an increase of 0.04 in *drug_salience* with drug intake and a decrease of 0.02 with no drug intake. Simulation3 has a more aggressive increase in *drug_salience* due to drug intake and a smaller decrease when there is no drug intake. Simulation4 has the same *drug_salience* function as Simulation3 but adjusts the recurrence value to 0.85, meaning that the neuron group of *drug_salience* reserves 85% of the activation that occurred at the previous time point.

To examine the model, we feed 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. With ten repetitions of *drug_intake*, the three simulations are shown in Figure 5.

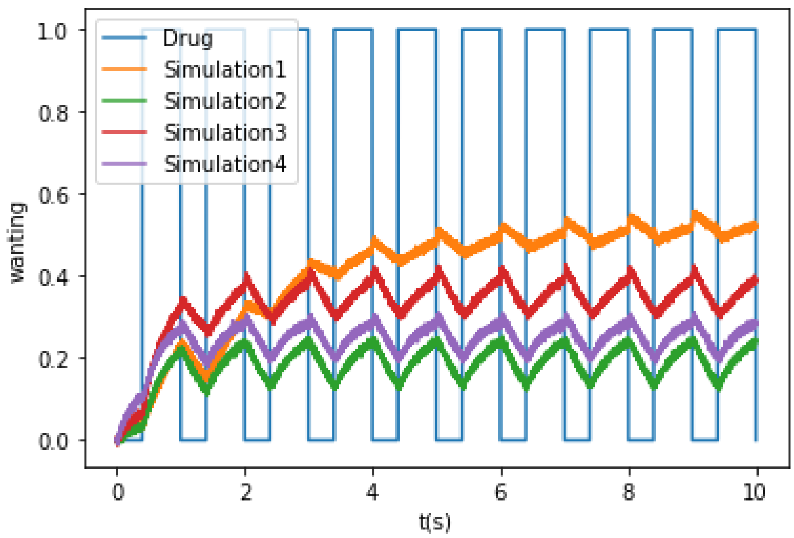

Figure 5: *wanting* output of four variants of Model I in response to *drug_intake.* X-axis is the time variant with the unit of seconds. Y-axis is the activation level of the Nengo neuron groups of *wanting* in the four simulations. The blue line represents the on-and-off of drug intake (i.e., presence and absence of drug intake).

3.1.3 Model Evaluation:

In this model, the long-lasting effect of incentive sensitization is implemented by adjusting 2 vectors: the recurrence value of *drug_salience* and the nonlinear change *of drug_salience* as a function of drug intake. Simulation1 showed a noticeable increase of *wanting* by the end of the drug intake repetitions compared to the baseline at t=0. However, the recurrence value in Simulation1 was set to be 1, indicating no decay of learned information over time. This setup does not coincide with the Incentive-Sensitization theory in which the salience value attributed to drug intake slowly decays during abstinence. Compared to Simulation1, Simulation2 reduced the recurrence value to 0.9, while keeping the nonlinear function of *drug_salience* the same. The result showed that overall *wanting* in Simulation2 did not increase much from baseline. In other words, the sensitization power, represented by the increase in *drug_salience* during drug intake, failed to counterbalance the decay of information (i.e., 1 - recurrence value).

Therefore, to implement addiction, the level of sensitization needs to be more aggressive. In Simulation3, the sensitization of *drug_salience* was 10 times the decay of *drug_salience* in between drug intakes. The result showed that *wanting* after repeated drug intake increased to a more significant level, matching Simulation1. Therefore, one way to implement the neurobiological effect of drug sensitization is to have neurons responsible for attributing salience to drug intake at least 10 times more prone to develop sensitization with drug intake than to decay during non-drug intervals. In Simulation4, we adjusted the recurrence value from 0.9 in Simulation3 to 0.85 while keeping the function of *drug_salience* consistent. The plateau of wanting during drug presence dropped from 0.4 to 0.3. Overall, Adjusting the recurrence value and non-linear function of *drug_salience* both affected *wanting*. Although there was a general trend of increase in *wanting* across the four simulations, the maximum *wanting* did not exceed 0.6, which is still within the normal range of activation of 0 to 1.

A closer examination revealed some ambiguity in Model I. For example, the model does not specify how drug salience is represented in the brain. Model I had a group of neurons specializing in representing the salience value of *drug_intake*. However, according to the Incentive-Sensitization theory, the salience value of drugs reflects the hyper-reactivity of the mesolimbic DA 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 & Berridge's 1998). Therefore, at least two components should replace *drug_salience*: DA activation and mesolimbic sensitivity.

3.2 Model II – Dopamine Activation and Mesolimbic Sensitivity

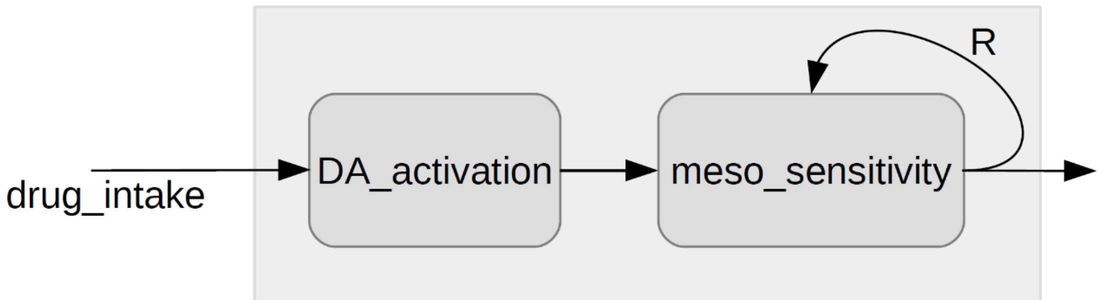

Figure 6: Structure of Model II. DA_activation fluctuates with drug_intake. The baseline of meso_sensitivity increases in response to higher DA_activation

3.2.1 Structural Design:

In this model, *DA_activation* approximates the value of *drug_intake*, increasing when *drug_intake* = 1 and decreasing when *drug_intake* = 0 (Figure 6). 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 DA system hypersensitive to drug intake, as described in Statement(3). To store the sensitization of the mesolimbic DA system, the recurrent *meso_sensitivity* component reflects both increased baseline synaptic dopamine transmission reacting to drug intake and the structural changes that increase the capacity of mesolimbic DA activity (Robinson & Berridge, 2001). The output of the salience attributor integrates with other mechanisms (such as incentive salience for drug cue) to form an overall wanting for drugs.

3.2.2 Model Behaviour:

Similar to Model I, to represent the long-lasting effect of mesolimbic sensitization, we implemented four functions with Model II. 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 positive dopamine activation and is decreased when *DA_activation* is minimal (Table 2). Given the results in Model I, when recurrence was set as low as 0.85, wanting in Model I simluation4 reached a plateau at approximately 0.3. Therefore, for the following simulations, we set the recurrence at 0.9 to have an observable baseline increase in the tested model component. Under this setup, our manipulation of the *meso_sensitivity* function can produce noticeable fluctuations.

Table 2: Model II Computational Options

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

Note: S(t) is short for drug_salience(t). S(t) is used to reduce space.

To examine Model II, we feed in 0.6 seconds of *drug_intake = 1* following 0.4 seconds of drug absence. With ten repetitions of *drug_intake*, the four simulations are compared as shown in Figure 7.

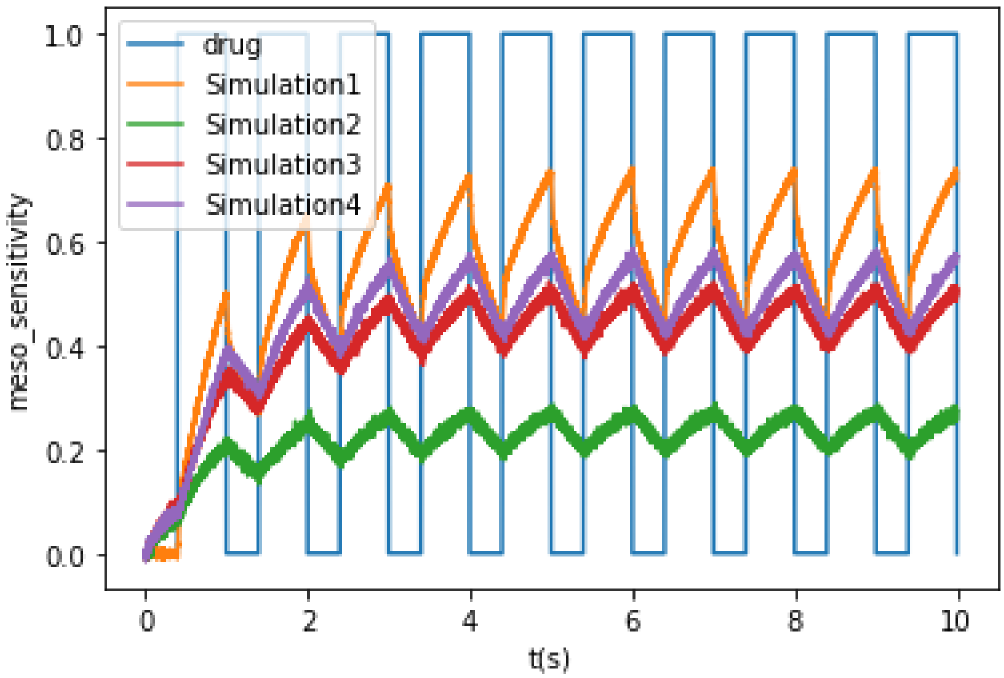

Figure 7: *meso_sensitivity* output of 4 variants of Model II. X-axis is the time variant with the unit of seconds. Y-axis is the activation level of the Nengo neuron groups of *meso_sensitivity* in the four simulations. The blue line represents the on-and-off of drug intake (i.e., presence and absence of drug intake).

3.2.3 Model Evaluation:

Simluation1 showed a significant overall growth in mesolimbic DA sensitivity with drug intake repetitions. 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 DA sensitivity compared to the other two simulations. In Simulation4, the amount of increase in *meso_sensitivity* with drug intake was 20 times its decrease in between drug intakes. Therefore, if the mesolimbic DA system achieves sensitization by implementing the nonlinear function in Model II, it must be 20 times easier to develop sensitization than to decay the sensitized information. Comparing Simulation1 to Simulation4, although they reached similar levels of mesolimbic DA sensitivity with repeated drug intake, Simulation1 had a greater spike in mesolimbic DA sensitivity in response to each drug intake. This characteristic of Simulation1 correlates with the hyperactivity feature of a sensitized mesolimbic DA system described in the Incentive-Sensitization theory. However, it can also be argued that Simulation4 reached a higher baseline wanting during drug absence, which also coincides with the Incentive-Sensitization theory. Also, Simulation4 contains a nonlinear function, making it harder for neurons to implement compared to the linear function in Simulation1. Therefore, we chose the function in Simulation1 going forward with our modelling.

All three simulations in Model I and the four simulations in Model II reached a maximum level of wanting within 5 representations of drug intake. In contrast, pathological drug use is often characterized by a ramping up of craving (i.e., wanting) with repeated drug use. Thus, with the current structural design, Model II 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.

3.3 Model III – Drug Cue Salience

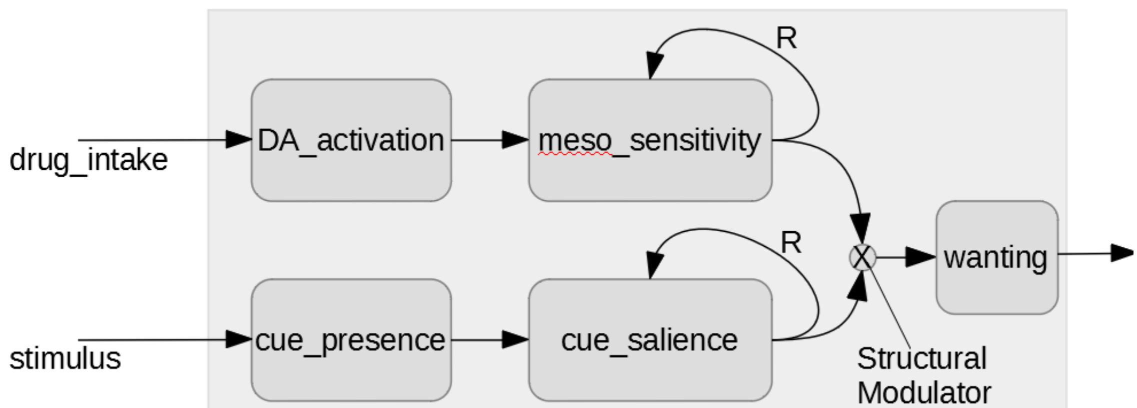

Figure 8: Structure of Model III. Circled X is a multiplicative modulation of connection strengths.

3.3.1 Structural Design:

The sensitization track, from *drug_intake* to *DA_activation* to *meso_sensitivity* is the same as Model II (Figure 8). On top of that, to implement statement(3) of the Incentive-Sensitization theory, we added drug-associated cue processing. Drug-associated stimuli are conditioned stimuli, so their presentation leads to neurological representation of drug 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 process of associative learning is complex, and the available computational models of associative do not provide a unified account of associative learning. Therefore, in model III, we kept the rate of associative learning stable, with *cue_salience* implementing the same function as *meso_sensitivity*. This way, we can achieve an increase in *cue_salience* with repeated drug and drug cue presentations, and explore its interaction with *meso_sensitivity* without dealing with the computational process of associative learning. Model IV will further manipulate the associative learning process and its role in Incentive-Sensitization.

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

Fsm(x, y) is the function performed by the structural modulator.

x = meso_sensitivity

y = cue_salience

$$G(x) = 1+(x-0)*(10-1)/(1-0) = 1+x*9.$$

This step of G(x) scales up the value of y to achieve the amplifying effect.

Simulation1:

$$Fsm (x, y) = x*G(y)$$

Simulation2:

$$Fsm (x, y) = y*G(x)$$

3.3.2 Model Behaviour:

To examine the model, we fed in *drug_intake*=1 every 0.65 seconds with a drug presence of 0.1 second, and *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 presence at t=3 and t=6. This design of drug and drug cue presence is crucial to the examination of Model IV. To compare the behaviours of models III and IV, we kept the input pattern consistent. With 13 repetitions of drug_intake and 10 repetitions of *stimulus*, the two simulations are compared in Figure 9.

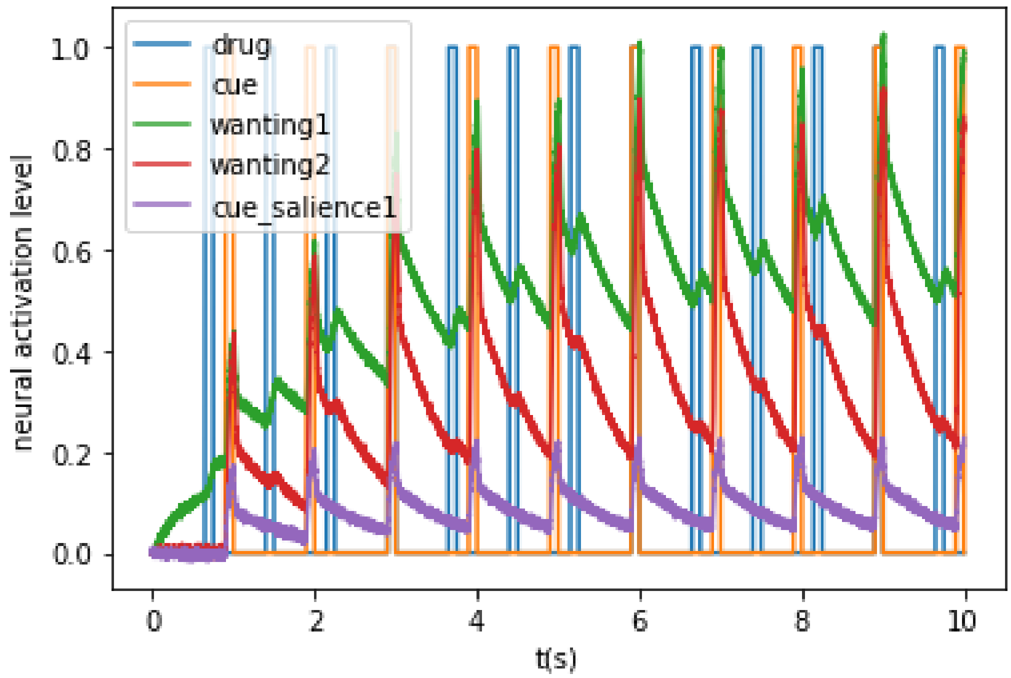

Figure 9: X-axis is the time variant with the unit of seconds. Y-axis is the activation level of the Nengo neuron groups in the two simulations. *wanting* in Simluation1 and 2 are presented in green and red respectively. Cue_s is the value of *cue_salience* in Simluation1 presented in purple. The blue line represents the on-and-off of drug intake (i.e., presence and absence of drug intake).

3.3.3 Model Evaluation:

Both simulations had an accumulated increase of *wanting* at t=6 compared to baseline at t=0. Compared to Model I and Model II, the two simulations in Model III also had a continual increase, extending beyond the plateau in Model II. However, Simulation1 had an overall steeper increase in *wanting* than Simulation2.

The two simulations also showed different behaviours in their response to drug intake and drug cue presentation. 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 in Simulation2, *wanting* failed to respond to the first presentation of *drug_intake.* Thus, Simulation1 is a more realistic representation of addiction formation, according to the Incentive-Sensitization Theory.

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 II.

So far, we have adjusted the degree of change in mesolimbic DA sensitivity and cue salience, while leaving the two processes independent of each other. The primary purpose of exploring the above options in these models is to identify the core mechanism responsible for an abnormal level of sensitized wanting. Another way to create an extraordinary level of wanting is to have the sensitization process and the associative learning process 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 a sensitized mesolimbic DA system can intensify the learning of drug-drug cue associations, triggering more craving for drugs.

3.4 Model IV – Intensified Associative Learning

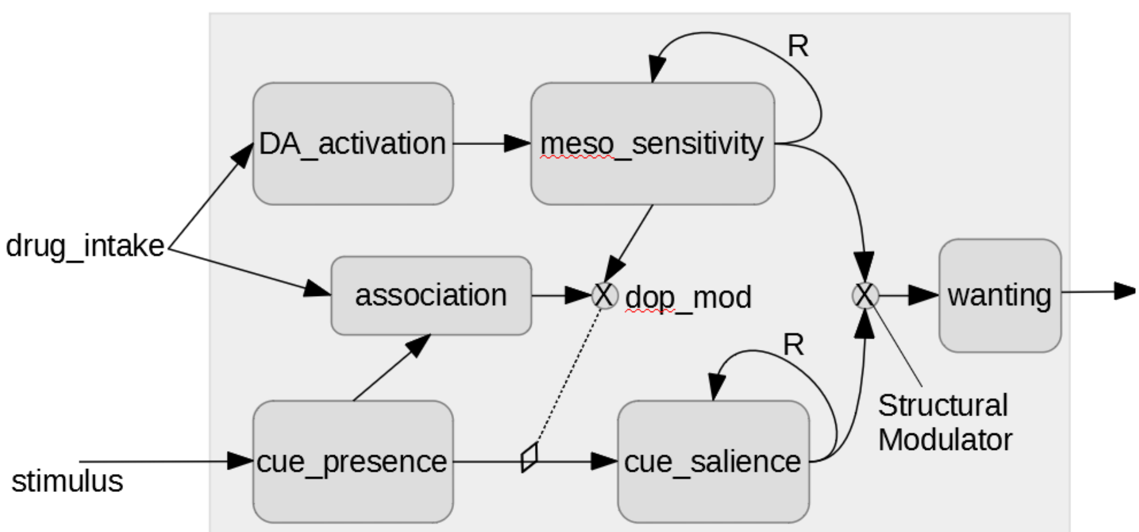

Figure 10: Structure of Model IV. Dotted line is a learning signal, adjusting the strengths of the connection weights to which it is connected

3.4.1 Structural Design:

The main feature of this model is that mesolimbic DA 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 (Figure 10). The stronger the drug-cue association, the more *cue_salience* should increase. The dopamine modulator (*dop_mod)* component takes in the value of *association* and *meso_sensitivity*. Then, *dop_mod* scales up *association* based on *meso_sensitivity.* The integrationof *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 DA system should intensify the power of drug-cue association, leading to a faster increase in cue salience.

3.4.2 Model Behaviour:

Our primary goal in this simulation is to test the new *association* and *dop_mod* components. To reduce uncertainties in the other processes in the model, we used the linear option for *meso_sensitivity*, with a recurrence value of 0.95. To simplify the process, we designed the model so that it only registers an association when drug and drug cue are presented simultaneously. We fed the model with *drug_intake*=1 every 0.65 seconds with a drug presence duration of 0.1 seconds, and *stimulus* every 0.9 seconds, for 0.1 seconds. As described in Model III, this set up allows the independent presence of drug and cue, as well as a combined presence of both at t=3 and t=6. With 13 repetitions of drug_intake and 10 repetitions of *stimulus*, results are shown below:

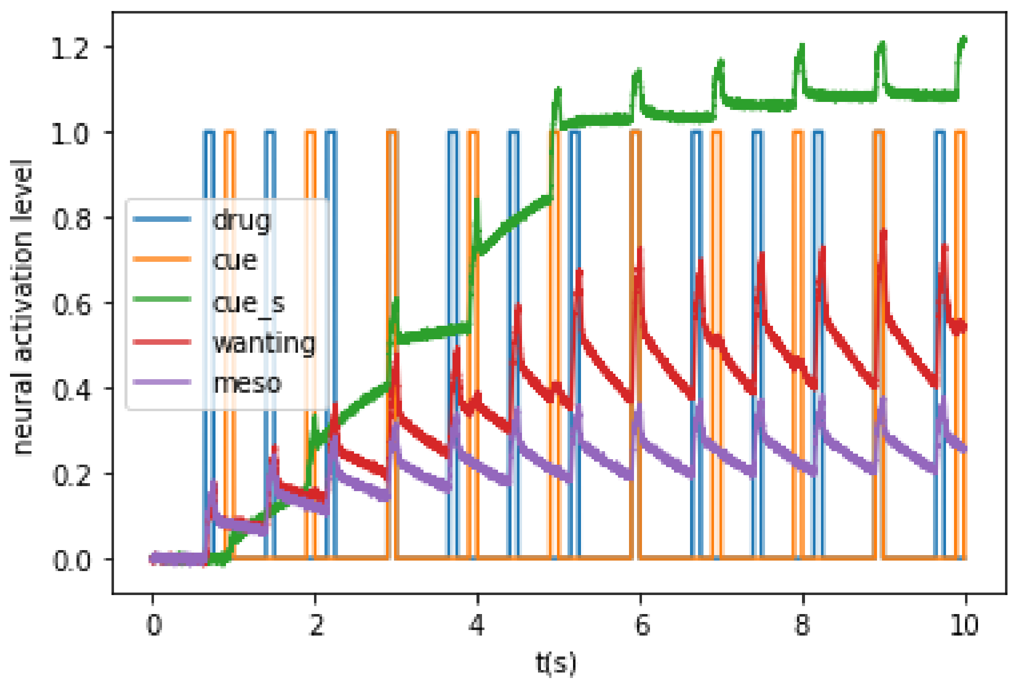

Figure 11: X-axis is the time variant with the unit of seconds. Y-axis is the activation level of the Nengo neuron groups in the simulations. The value of *cue_salience* is presented as *cue_s* in green. The value of *wanting* is in red, and *meso_sensitivity* is *meso* in purple. The blue line represents the on-and-off of drug intake (i.e., presence and absence of drug intake).

3.4.3 Model Evaluation:

Model IV simulation generated overall increases in mesolimbic sensitivity, wanting and cue salience. Cue salience in Model IV increased with a significantly steeper slope than the *cue_salience* curve in Model III Simluation1 (Figure 11). 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 IV 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 presentations, *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 noticeable increase in *wanting*. In other words, in accordance with the Incentive-Sensitization theory, Model IV simulation demonstrated sensitization in mesolimbic reactivity, drug cue related response, and overall wanting for drugs.

Chapter 4

Discussion

Overall, our study took a structuralist computational approach, rebuilding the neurological process of addiction according to a blueprint provided by the Incentive-Sensitization theory of addiction. We reviewed the core statements in the Incentive-Sensitization theory of addiction and explored different ways of computationally implementing the mechanisms. Our innovative methodology allowed us to examine the hypothesized mechanisms of drug addiction and to identify assumptions of this theory. 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 computational studies on drug addiction.

4.1 Computational Implementation of the Incentive-Sensitization Theory

Here, we discuss the processes of Incentive-Sensitization theory that were successfully implemented, and areas of ambiguity in the theory that were identified by the models. The three statements are ‘potentially addictive drugs share the ability to produce long-lasting adaptations in neural systems.’ (Statement(1)). ‘The brain systems that are changed with chronic drug use include those normally involved in the process of incentive motivation and reward’ (Statement(2)). ‘The critical neuroadaptations associated with addiction render brain reward systems hypersensitive (“sensitized”) to drugs and drug-associated stimuli’ (Statement(3)).

4.1.1 Computational Implementation of Statement(1):

In this thesis, we explored both linear and non-linear options of implementing the long-lasting effect of sensitization on neural adaptations related to drug addiction. Simulations in Model I and II demonstrated that both linear and non-linear functions are computationally plausible to describe the sensitization of mesolimbic DA system. However, differences in the resulting level of sensitization were evident. For example, in Model I, the linear Simulation1 had the same recurrence rate as the non-linear Simulation2. Simulation1 had a greater spike in mesolimbic sensitivity in response to drug intake, which correlates with hyperactivity of a sensitized mesolimbic system described in the Incentive-Sensitization theory. Therefore, although the trend of increased sensitization is evident with repeated drug use, the Incentive-Sensitization theory does not specify the qualitative mathematical characteristic of such increase or the quantitative strength of its long-lasting effect.

The computational characteristic of sensitization is crucial because it helps identify the critical points where substance intake develops into addiction. According to the learning perspective adopted in this thesis, neural adaption occurs with each instance of substance intake. Natural incentives can also affect the mesolimbic system (based on Statement(2)) and potentially result in sensitization. Determining the computational critical values in sensitization can help clarify qualitative and quantitative features that separate substance addiction from normal incentive learning. To determine the exact value of recurrence strength in the linear function, or the variables in the non-linear function, future work should be undertaken with real data with human subjects. Ideally, this would include the speed of sensitization 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 could perform data fitting and select the model with the best fit.

4.1.2 Computational Implementation of Statement(2):

The mesolimbic DA system is the neural centre for reward processing (T. E. Robinson & Berridge, 1993), but it is difficult to determine the brain area responsible for cue salience attribution. All organisms have an adaptive bias towards natural rewards, such as food or sexual partners. According to the Incentive-Sensitization theory, chronic drug use will produce an abnormal attentional bias towards drug-associated cues (Robinson & Berridge, 2003). Therefore, other than sensitization in the mesolimbic DA pathway, there must be a neural activation pattern that specializes in directing the sensitization towards drug-associated cues. In our current models, we did not specify the neurological areas corresponding to *cue_salience* and *structural_modulator.* Therefore, to successfully map the models to neural circuits, we need to identify the brain areas responsible for attributing salience to drug-associated cues.

Although not specified in the Incentive-Sensitization theory, past research has proposed the amygdala and its projection to the orbitofrontal cortex (OFC) as the brain area responsible for cue-triggered reward processing (Cardinal et al., 2002). More specifically, the basolateral amygdala (BLA) codes the expectation value of rewards predicted by cues (Lichtenberg et al., 2017), while the central nucleus of the amygdala is responsible for generating arousal responses related to motivation (Corbit & Balleine, 2005). The signal processing required for the motivational function of the amygdala is still debated. On a neuromodulator level, glutamate release in the amygdala promotes reward-seeking behaviours (Malvaez et al., 2015). Different types of opioid receptors located in BLA seem to have specialized roles in reward expectation (Lichtenberg & Wassum, 2017), but this topic is not fully explored in the literature. Different cues and drugs likely activate different neural circuits that code cue salience presentation, making it challenging to represent the process in models like Nengo that are built on neural circuits, not molecular mechanisms.

4.1.3 Computational Implementation of Statement(3):

By including the cue association process, Model IV generated more realistic simulations than Model III, in that it extended the system's capacity of wanting growth, allowing for the continual increase in wanting beyond the plateaus in Model III. Furthermore, Model III simulated two possible mechanisms of combining mesolimbic DA sensitization and drug cue associative learning. The results supported the hypothesis of the Incentive-Sensitization theory that intensified drug cue salience affects the sensitization of the mesolimbic system, triggering spikes in wanting rather than the other way around.

Despite their strengths, neither Model III nor IV included a complete process of the development of drug-cue associative learning. For example, our simulations registered successful drug-cue pairings only when *drug_intake* and *stimulus* are presented simultaneously. In reality, strength is the strongest when the conditioned stimulus is presented slightly before the unconditioned stimulus (i.e., cue precedes drug intake). This thesis modelled the central process of mesolimbic DA system sensitization, and only the final effects (not detailed process) of associative learning. The associative learning process is more complicated than presented in the models. Future studies should utilize well-established computational models of associative learning to expand the utility of the model.

This thesis also explored the possible interaction between mesolimbic DA sensitization and an associative learning process. As discussed above, natural reinforcers can impact the mesolimbic DA system and lead to the development of cue-associated learning. A primary distinction between addiction and motivation for natural reinforcers is hyperreactivity towards drugs, and drug-associated cues resulting from brain changes during chronic drug use (Statement(3)). Therefore, one way of implementing Statement(3) is to have DA activation directly impact the learning curve of associative learning, making the drug-cue association easier to form under the influence of DA activation (Model IV). Results in Model IV showed a significantly steeper increase in *wanting* compared to Model III, where mesolimbic DA sensitization and associative learning do not interact with each other. Future studies can further determine whether this interaction between mesolimbic sensitization and cue association formations is necessary for addiction development.

4.2 Updating the Incentive-Sensitization Theory

Overall, this study revealed several ambiguities in this theory through computationally implementing the three core statements of the Incentive-Sensitization theory. First, the rate and type of increase in mesolimbic DA sensitization are unclear. As revealed in Model I and Model II, the mesolimbic system's memory strength and the function through which the mesolimbic DA system manipulates and implements sensitization can result in different model behaviour of ‘wanting’.

Second, as demonstrated in Model IV, the development of drug-cue salience is crucial to a hyperreactive mesolimbic DA system. As described in the Incentive-Sensitization theory, chronic drug users develop an abnormal attentional bias towards drug-associated cue. But the Incentive-Sensitization theory does not specify how such bias occurs. More specifically, it is unclear if/how mesolimbic DA sensitivity interacts with associative learning. In Model IV, mesolimbic DA sensitization enhanced the rate of learning of drug-associated cues. Still, the mechanism may work in the opposite direction, with acquired drug-cue salience facilitating sensitization of the mesolimbic DA system. The neurological mechanism behind cue salience formation is still debated. Particularly, the BLA to OFC pathway and its role in associative learning, as well as addiction formation, needs further exploration. A better formulated neurological account of associative learning can complement the current Incentive-Sensitization theory, providing a more complete description of addiction.

Third, other than increased *wanting*, cognitive capacities such as memory, attention, executive functions, and decision-making are usually impaired in addicts (Verdejo-Garcia et al., 2019). Deficits in higher-order executive functions and decision-making are significant predictors of relapse. The potential interaction between higher-order processes and the incentive sensitization process is not examined in the thesis. Correspondingly, neurological adaptations in addiction are not restricted to the processes described in the Incentive-Sensitization theory. Areas such as OFC, hippocampus, amygdala, and cingulate gyrus are also affected (Goldstein et al., 2009; Kutlu & Gould, 2016). It is unclear if any of the above changes, in addition to incentive sensitization, are determining factors in the development of addiction.

4.3 Limitations

Models in this thesis are shortened approximations of real-life neurological processes. One assumption of our work is that the qualitative brain changes we modeled would be similar if the models' time scale is increased to match actual drug-use experiences. However, this assumption requires validation with human data and more extended simulations that run for weeks, if not months. Extensive simulations may reveal a faster rate of Incentive-Sensitization formation and a slower rate of its recovery because the ratio of drug intake duration to drug absence duration in our current models is significantly higher than in reality. For instance, Model II Simluation4 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. At the same time, drug users with longer abstinence between episodes of drug use 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 (Roy A. Wise & Kiyatkin, 2011). This means that mesolimbic DA sensitization could form within minutes of drug use and remain robust beyond drug absence periods specified in the models. In Model II simulation 4, the recurrent strength of the mesolimbic DA system is set to 0.9. The increase in mesolimbic DA sensitization during drug intake is 20 times larger than its decrease during drug absence. Given the analysis above, the computational difference between mesolimbic DA sensitization increases and decreases 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.

This thesis focusses on examining the neurological changes in addiction proposed by the Incentive-Sensitization theory. Many researchers, however, have pointed out that brain changes alone cannot lead to addiction – social factors also play crucial roles (e.g. (Levy et al., 2013). Many previous drug users quit without professional intervention, and financial and familial issues were highly correlated with those remissions (e.g., Klingberg, 2010). Experimental findings also corroborate this social-based addiction model. For example, 'rats will forego cocaine for the opportunity for same-sex snuggling, and impaired social interaction is a significant characteristic of drug users (Zernig et al., 2013). There is a strong connection between neural changes associated with social exclusion, and other social stressors and addiction (Heilig et al., 2016). Other social factors that influence the development of addiction include: adverse early childhood experience (Harmer et al., 1999), dysfunctional interpersonal relationships (Mudry et al., 2019), and anhedonia, which influences perceived reward (Pizzagalli et al., 2005).

With the assumption that incentive sensitization may be a common mechanism across all substance use disorders, this thesis did not specify which drug was modelled. Incentive sensitization is likely to manifest differently for each pharmacological substance. For example, in animal studies, 'wanting' (measured as drug-seeking behaviour) is increased in the home cage when rats are responding for heroin, but is higher outside of the cage when they are responding for cocaine (Badiani et al., 2019). Human data support this conclusion in that participants with chronic misuse of both heroin and cocaine preferred using heroin at home, but cocaine outside of the home

(Badiani et al., 2019; Badiani & Spagnolo, 2013; Caprioli et al., 2009). Similarly, ‘liking’ for heroin was much greater at home than outside, whereas ‘liking’ for cocaine was more significant outside of the home (Badiani et al., 2019). These findings suggest that factors such as context can interact with drug class, leading to inconsistent incentive sensitization and drug-taking behaviour in different environments.

4.4 Future directions

4.4.1 Next Steps of the Current Study:

As presented in Chapter 3, the results of the models are mainly qualitative. That is, we were comparing whether each step of the model presented noticeably different behaviour compared to the other models. To verify the conclusions, we require quantitative measures that are 1) easy to record in the model, 2) meaningful to addiction, and 3) consistent with the literature. For example, a measure could be the number of drug repetitions required to reach a wanting of 0.9, time duration needed to restore wanting to close to 0 with drug absence, or the number of drug-cue pairings required to establish cue salience. Another approach is to use appropriate laboratory data and conduct model fitness experiments. This method may help us to clarify the ambiguities of the Incentive-Sensitization theory mentioned above. For example, with data on the rate of development of addiction, we might learn the rate of mesolimbic DA sensitization.

An advantage of this thesis's work is that it focused on a single theory, but a disadvantage is that the models only accounted for a process that linked drug intake to drug-wanting. The final output of drug addiction, however, is not wanting, but the probability of drug-taking behaviour. Therefore, to complete the process of addiction, the next step of the project should be to model the entire process described in the schematic flow chart (Figure 2), including liking, executive inhibition, and the behavioural probability of drug intake.

Understanding the fundamental mechanism of addiction is the basis for studying more complex processes in addiction. Particularly, understanding how addiction can manifest differently in different populations, with varying types of drug and social environments, is highly relevant to real-world clinical cases of addiction. Therefore, future projects should investigate the interaction between the incentive sensitization process and factors such as social factors, types of drugs, etc.

4.4.2 Future Directions for Computational Modelling of Addiction:

This project also promotes reflections on existing computational models of addiction. Many current computational models of addiction focus on the transfer from goal-directed drug intake to habitual drug intake. These two drug intake patterns are often computationally implemented as model-based versus model-free decision-making patterns. The assumption is that, as an addiction develops, addiction behaviours develop from purposeful goal-seeking to habitual behaviours that are less informed by the consequence of the decisions, leading to a more compulsive pattern. A review study by Heizn and colleagues (2009) revealed inconsistent evidence for the transfer from model-based to model-free decision-making in addiction. The authors proposed that contextual factors might lead to contradictory results of the studies. Importantly, it is still unclear if the transfer from goal-directed to habitual behaviour patterns is sufficient to lead to addiction. As Robinson and Berridge argued, the behaviour of tying shoes is a habitual behaviour that all individuals repeat multiple times. But it is unlikely that individuals will develop an addiction to shoe-typing even if the behaviour becomes habitual (Robinson & Berridge, 1993).

Computational models under the framework of model-based versus model-free decision making often do not examine the DA activation pattern during addiction. Because this is a cognitive-behavioural description, most models under this framework do not discuss the underlying neurological processes in detail. Researchers can implement model-based and model-free decisions based on either the Incentive-Sensitization theory (i.e., increased DA activation in addiction) or the Dopamine Suppression theory (e.g., decreased DA sensitization in addiction). Therefore, models of model-based versus model-free decision making do not directly assess theories of the fundamental neurological mechanism of addiction.

Current scientific practices follow the cycle of hypothesis development, data collection and analysis, conclusions, and revision of theories that lead to new hypotheses. In the field of cognitive neuroscience, it is difficult to test theories of neural networks since we cannot directly access human brain circuits. This project is a clear example of how a single theory, generated from numerous experiments and data, can be implemented neurologically in multiple ways. The value of computational modelling is to explore these options by simulating a neurological network without violating ethics. Another benefit of this project is its step by step approach. In this project, we started with the smallest processing component, adding more complex features with each model. This approach allowed us to assess the target theory's details, thereby identifying the defining features as well as unnecessary components. Programming packages such as Nengo can sufficiently design, implement and measure the proposed neural network models.

4.4.3 Treatment Implications:

Treatment plans for any mental health condition are dependent on contemporary perspectives of the disorder. In the case of addiction, 'treatment' was legal punishments under the moral model. With the emergence of the disease model, both cognitive-orientated therapeutic plans and pharmaceutical options were developed. With a learning perspective of addiction, the corresponding treatment plans should focus on how the acquired pattern of behaviour can be relearned. Computational modelling projects such as the present one can help to identify a route to help to retrain the brain out of the cycle of addiction.

First, it is important to identify the individuals most vulnerable to developing addiction. Substance use behaviours do not necessarily lead to chronic addiction. As discussed in the introduction section, almost 80% of substance users mature out of addiction spontaneously (Figure 1). A small proportion of substance users experience the downward spiral of addiction, including destructive effects on their mental and physical health, finances, social relationships, etc. Therefore, cognitive and neurological characteristics can help identify vulnerable individuals and provide early intervention. Taking into account contextual cues, Heinz and colleagues proposed future studies on ambulatory assessment tools that measure mood-states, recordings of geolocation and psychomotor activity in real life (Heinz et al., 2019).

Second, the structural design of the models provides a potential target of neurological intervention. One way to intervene in addiction is to reverse or reduce incentive sensitization. Past research has attempted to counteract incentive sensitization in three alcohol-dependent users (Heinze et al., 2009). The authors treated the participants with high-frequency deep brain stimulation of the NAcc bilaterally. All three participants reported less craving after the treatment. Although more robust research is needed to fully support the treatment's efficacy, it is a promising start. The prevalence and efficacy of high-frequency deep brain stimulation in treating refractory depression and Parkinson's disease can serve as guidance to develop clinical trials and procedures in addiction treatment. To verify the effect of the high frequency deep brain simulation in treating addiction, future computational studies can describe the neural activation patterns before and after the treatment with neuroimaging tools.

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 is indispensable to drug addiction formation, 3) identifying the neurological area responsible for storing associated salience to drug cues is key to completing the Incentive-Sensitization theory, and 4) our method of disentangling complex theories into simpler building blocks is useful for identifying limitations and ambiguities in neurological theories.

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