Modeling Addiction in terms of fluctuating neurotransmitters within the reward system

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Relapse is the chief problem of drug addiction where a successfully abstinent patient returns to seemingly extinct manners of drug consumption. While various parameters were identified as affecting relapse, the general dynamics of drug consumption is yet to be understood. We introduce a model that describes addiction focusing on a single state-value factor, mediated in the Nucleus Accumbence (NAC) that subsequently affects the likelihood of drug consumption. Various parameters influence and change the state-value factor. These parameters represent afferent extracellular neurotransmitter levels affecting the cortico-striatal loops that determine behavior. This provides an interesting combination where the dynamics described by the model can describe the dynamic of drug consumption, including consumption, abstinence and relapse, and the model's details are based on extracellular neurotransmitter levels. Thus, our model can provide not only a more complete description of addiction as a dynamical decision biased process but may also turn useful for studying and evaluating possible treatments on individual basis.

Introduction

We propose to view addiction as a malfunction of the decision-making process, where addiction patients make choices although their negative consequences on their personal life [REF]. Most current computational models focus on one component, usually acquisition of drug addiction or craving, or on the monotonicity during the transition

from light to heavy addiction (Redish, 2004; Gutkin and al., 2006), although some new efforts were put on describing the fluctuating behavior of this condition (Levy and al., 2009). A main point which makes it so hard to model addiction is that the condition is affected by numerous parameters, from genetic predisposition, psychological conditions, environmental affects, and more. We here propose a new way to combine the different parameters affecting the cyclic dynamic of addiction by providing a unifying platform: the extracellular levels of neurotransmitters in the reward system, during different drug-addiction related states and behaviors.

These neurotransmitter levels are combined into a hidden parameter $n(t)$ ($0<n<1$) which describes globally the ongoing change in neuronal activity within the ventral striatum (nucleus accumbence - NAC in rats). This parameter $n(t)$ models the influence of the thalamo-cortical loops on the decision making processes in the prefrontal cortex (PFC) (Mogenson et al., 1980; Koob and Le Moal, 2001; Carelli and Wightman, 2004; Deadwyler et al., 2004; Day and Carelli, 2007). It represents the total effects of the main brain areas projecting to the NAC, which are known to be important for reward-related behaviors and drug addiction. For simplicity of the model, we focus only on several brain areas projecting to the NAC and only on dopamine (DA) and glutamate extracellular levels measured by microdyalisys techniques in rats and analogously on the activity in reward-related brain areas in humans based on imaging studies. We take into account the glutamate innervations towards the NAC from the PFC, amygdala and hippocampus and the DA transmission from the VTA (Voorn et al., 1986; Groenewegen et al., 1999; Kalivas and Nakamura, 1999; Zahm, 1999, 2000). For simplicity, we ignore neuronal firing and membrane potentials although it is recognized that they are important. In principle, they can be included in our model in future work as the model is defined in a way that enables the addition of mean neuronal firing in combination with extracellular transmitter levels. We suggest that this simple version model as it is now can already deepen our understanding regarding drug addiction (Fig. 1).

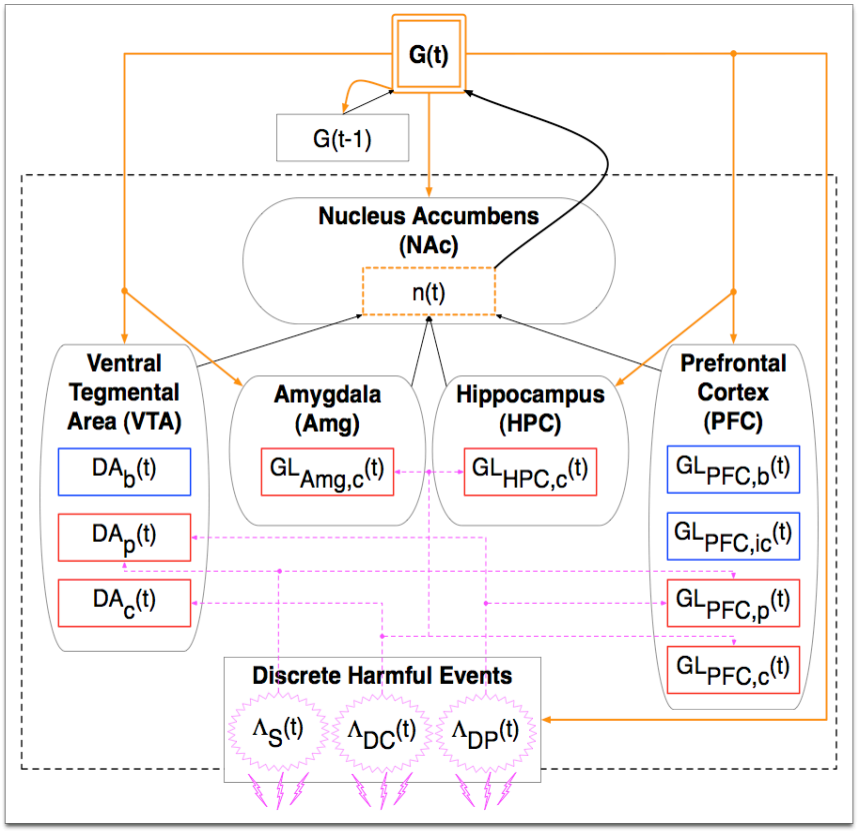


Figure1

The Model. A diagram describing the anatomical connections used in the model and the different signals representing extracellular levels of neurotransmitters in the nucleus accumbence. *G(t)* is the global variable representing the inverse-likelihood for a drug consumption. Red and blue rectangles represent a positive and negative influences on n(t), respectively. Discrete harmful events represent acute events that causes relapse. GL – glutamate; DA – dopamine; b – basal; p – phasic; c – cue; ic – inhibitory control; S – stress; DC – discrete cue; DP – discrete priming; Amg – amygdala; HPC – hippocampus;

The parameters influencing *n(t)*, which will be described in the next section, are not static themselves and they have their own physiological dynamics. The internal variables are affected by the different states the agent might be experiencing, for example, intoxication, chronic drug consumption, early withdrawal and long-term cessation. The external variables are pertaining to environmental influences. All these will be described by the extracellular neurotransmitters levels, which are represented to gain uniformity in describing the drug addiction process.

In this paper we do not describe new data but rather use existing data from both rat models of addiction and humans addicts with cocaine or amphetamine. We argue that the similarities in the consumption dynamics are larger than the differences between various classes of drugs of abuse and that within the levels of abstractions taken here the mechanisms are sufficient similar to create a common model.

Methods

On the highest level, the main two parameters are *G(t)* and *n(t)*, the latter as described in the introduction. *G(t)* (*G(t)* $\in [0,1]$), is the inverse-likelihood for a drug consumption (an action-taking parameter): The lower *G(t)* is the higher is the likelihood for drug consumption, and vise versa. The affect of *n(t)* on *G(t)* is described by the formula:

$$G(t) = \tanh\left(\alpha \cdot G(t-1) + \beta \cdot n(t) - \gamma\right) \quad (1)$$

Where α, β, γ are fixed values in $\alpha, \beta, \gamma \in [0,1]$. This formula means that the behavior is affected by both behaviors in previous time steps and by the parameter *n(t)* of the NAC. The other parts are added for bounding the functions and achieving correct values.

Parameters influencing the value-state factor *n(t)*

We next describe the parameters we included in the function *n(t)*, see Table 1 for a brief mathematical description and supplementary materials for the full description.

	effect on $G(t)$	when $G(t)=0$	when $G(t)<0$	when $G(t)>0$ and $d \le \Pi_X$	when $G(t)>0$ and $d > \Pi_X$	$\Lambda_{DP}(t)$ $G(t-1) \ge 0$ and $P_{DP} \le \theta_{DP}$	$\Lambda_{DC}(t)$ $G(t-1) \ge 0$ and $P_{DC} \le \theta_{DC}$	$\Lambda_S(t)$ $G(t-1) \ge 0$ and $P_S \le \theta_S$
$DA_b(t)$	$(+)$	$\rightarrow$	$\searrow$	$\nearrow$	$\nearrow$	$-$	$-$	$-$
$GL_{PFC,b}(t)$	$(+)$	$\rightarrow$	$\searrow$	$\searrow$	$\nearrow$	$-$	$-$	$-$
$DA_p(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$GL_{PFC,p}(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$GL_{PFC,c}(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$GL_{Amg,c}(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$GL_{HPC,c}(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$DA_c(t)$	$(-)$	$\rightarrow$	$\nearrow$	$\nearrow$	$\searrow$	$\nearrow$	$\nearrow$	$\nearrow$
$GL_{PFC,ic}(t)$	$(+)$	$\rightarrow$	$\nearrow$	$\searrow$	$\searrow$	$-$	$-$	$-$

Table 1

Effects on $G(t)$ and $n(t)$. A simplified mathematical description of the effect of each of the signals in the model on $n(t)$ and subsequently on $G(T)$.

Basal extracellular DA from the VTA: DA_b

There is ample evidence demonstrating that acute administration of drugs of abuse cause elevated levels of DA transmission in the NAC, for reviews see (Wise, 2002, 2004). However, repeated administration of drugs induces different effects on basal and phasic DA. The basal (tonic activity) DA level is defined here as the intrinsic extracellular DA activity not related to any external stimuli such as drug administration, encountering drug-associated cues etc. (Grace, 2000). In humans, repeated drug administration resulted in decreased basal activity in the PFC (Volkow et al., 1988) and striatal DA response (Volkow et al., 1993) as measured by PET. Upon repeated drug administration the basal level decreases (Gerrits et al., 2002), which corresponds to the gradual increase in depressed feelings while the addict is not presently intoxicated. If the addict is not taking drugs for some time then the basal levels recovers and gradually increases (Rossetti et al., 1992; Weiss et al., 1992; Chefer and Shippenberg, 2002; Mateo et al., 2005). Therefore, we've modeled the basal DA transmission from the VTA to the NAC, denoted DA_b. The function of DA_b is decreasing while $G(t)<0$ and it is increasing while $G(t)>0$. DA_b positively affects the level of $n(t)$ because depressed feelings (low DA_b) increases the probability for a subsequent drug administration (low $G(t)$) serving as a negative reinforcer.

Basal extracellular glutamate from the PFC: $GL_{PFC,b}$

Upon repeated drug administration in rats the basal glutamate level in the NAC decreases (Pierce et al., 1996; Bell et al., 2000; Hotsenpiller et al., 2001; Smith et al., 2003), while it continues to decrease during early withdrawal (Pierce et al., 1996; Hotsenpiller et al., 2001; McFarland et al., 2003). Due to lack of data, we assumed that it subsequently recovers after a long period of abstinence. Therefore, we've modeled the basal glutamate transmission from the PFC to the NAC, denoted $GL_{PFC,b}$. The function of $GL_{PFC,b}$ is decreasing while $G(t)<0$ and at the early stages of $G(t)>0$ while during late stages of $G(t)>0$ the function starts to increase. $GL_{PFC,b}$ positively affects the level of $n(t)$.

Drug-induced DA from the VTA: DA_p

The literature is not in agreement about the detail of this parameter. There is a discrepancy between the rat data and the primate and human data. We chose to model the human and primate data because we wanted the model to be as closest to human behavior as possible, however it is fair to model it according to the rat data as well. In primates (Bradberry and Rubino, 2006) and in humans (Volkow et al., 1997) it has been shown that DA transmission in the NAC is not sensitized following repeated cocaine self-administration. On the other hand, it has been shown in rodents that after repeated drug administration there is an increase in extracellular DA in the NAC as a response to a subsequent drug administration (Pettit and Justice, 1989, 1991; Kiyatkin and Stein, 1995; Ranaldi et al., 1999; Bradberry, 2000). This heightened response continues even during withdrawal (Hooks et al., 1994; Ito et al., 2000; Chefer and Shippenberg, 2002; Zapata et al., 2003). This discrepancy between rodents and primate data could be attributed to the greater cortical development in primates, and strong evidence of a cortical role in addiction (Porrino and Lyons, 2000; Goldstein and Volkow, 2002). This suggests that in the primate, other components of incentive motivational circuitry, such as glutamate in the NAC could mediate the ability of drugs to control behaviour (Wolf, 1998; Vanderschuren and Kalivas, 2000). Therefore, it is possible to simulate the agent in two possibilities. First, that the phasic DA system is sensitized and second, that it is not. Here we describe the rodent data because it is more complete. Taking into account the incubation of craving during withdrawal found in rats (Lu et al., 2004a), we assumed that the function of drug-induced extracellular DA from the VTA to the NAC, termed DA_p, increases while $G(t)<0$ and continues to increase during $G(t)>0$ including long-term abstinence. The effect of the drug-induced DA on $n(t)$ is negative. Whether this effect eventually decreases is not known. In the model we can decide if eventually after a significant amount of time the function starts to decline or stays in a high value.

Drug-induced glutamate from the PFC: $GL_{PFC,p}$

Similar data has been demonstrated regarding the levels of drug-induced extracellular glutamate in the NAC originating from the PFC. It has been shown that after repeated

drug administration in rats there is an increase in extracellular glutamate in the NAC as a response to a subsequent drug administration (Pierce et al., 1996; Baker et al., 2003), which continues to increase during withdrawal (Reid and Berger, 1996). Again, this is consistent with the incubation effect. Therefore, the function of drug-induced glutamate, termed $GL_{PFC,p}$, increases while $G(t)<0$ and continues to increase during $G(t)>0$ including long-term withdrawal. The effect of $GL_{PFC,p}$ on $n(t)$ is negative. As mentioned for DA, whether this effect eventually decreases is not known. In the model we can decide if eventually after a significant amount of time the function starts to decline or stays in a high value.

Saliency of drug-associated cues: $GL_{PFC,c}$, $GL_{Amg,c}$, $GL_{HPC,c}$ DA_c

Addiction is hypothesized to represent the pathological usurpation of neural processes that normally serve reward-related learning and that the persistence nature of it involves long-term associative memories in reward related brain areas such as the NAC and PFC (Hyman et al., 2006). Repeated learning results in a stronger association between the stimuli and the rewards, causing enhanced saliency for drug associated cues, which increases with repeated drug consumption (Robinson and Berridge, 2003). It was suggested that the amygdala is subserving the information about discrete drug associated cues while the hippocampus subserves the contextual cues and the PFC is involved in both types of information (Everitt and Wolf, 2002). It has been demonstrated that presentation of drug associated cues increased extracellular glutamate levels in the NAC, which led to the conclusion that the glutamate signal probably reflects inputs from limbic structures (Hotsenpiller et al., 2001). We modeled these learning related neural processes as the dynamics in extracellular levels of glutamate originating from the PFC, amygdala and hippocampus termed $GL_{PFC,c}$, $GL_{Amg,c}$, $GL_{HPC,c}$, respectively and DA originating from the VTA termed DA_c on the activity in the NAC. Therefore, while $G(t)<0$ the signals $GL_{PFC,c}$, $GL_{Amg,c}$, $GL_{HPC,c}$ increase over time and continue to do so during $G(t)>0$. When the signals increase they reduce $n(t)$, resulting in a higher probability to consume drugs.

We hypothesize that the value of these signals while $G(t)>0$ stays high for a relatively long time because cue-induced craving and relapse may occur even after long

abstinence (See, 2002). However, Shaham and colleagues showed in rats that the incubation effect on cue-induced relapse reduces after 6 months (Lu et al., 2004b). Therefore, these signals eventually decrease after the agent is in $G(t)>0$ for a relatively long time. The DA signal towards the NAC related to drug associated cues is relatively steady during drug intake (Bradberry, 2000; Ito et al., 2000). During early withdrawal, extracellular DA in the NAC increases in response to drug-associated cues exposure and gradually decreases over time (Ito et al., 2000). Therefore, while $G(t)<0$ the signal, termed DA_c, is steady over time and when $G(t)>0$ the signal increases and then decreases. An increase in the signal results in a decrease in $n(t)$ and a higher probability for drug consumption.

Harmful consequences caused by repeated drug consumption

Most drug addiction models do not address the issue of why some addicts succeed to abstain from taking the drug and even manage to totally quit after long-term consumption. It is known that long-term drug consumption has strong harmful health consequences, disrupts normal social relations, increases unemployment and may lead to economical problems and in some cases induce crime (De Alba et al., 2004; Saitz, 2005). However, as drug addiction persists for a long time there are addicts who are gradually becoming aware of these harmful consequences of their behavior. In some cases this knowledge drives the addicts and motivates them to seek help or to quit voluntarily (Melnick et al., 1997; Lancaster and Stead, 2005). A common aspect in many people who succeed to stop using drugs seems to be long-term increased rationality that enables the control of inhibition over compulsion. Some of these factors are family or social support in the form of economic help, rehabilitation programs, and anonymous meetings such as Alcoholics Anonymous (Ferri et al., 2006), psychological support and even religion (Galanter, 2006). In addition, there are some pharmacological substances that in some cases prevent addicts from relapsing such as methadone (Amato et al., 2004) or nicotine replacement therapy (Silagy et al., 2004).

As far as we know there is no microdialysis experimental data regarding this notion or any human imaging data. Therefore, in our model we assumed that these harmful events are mediated or manifested by extracellular glutamate signals associated

with cognitive inhibitory control pathways such as the cognitive corticostiratal loop, which involves the PFC, anterior cingulate cortex (aCC) and the NAC (Haber, 2003). The harmful consequences the agent faces initiate a signal that acts to reduce the high state-value drugs posses. The function of this signal termed, $GL_{PFC,ic}$, increases while $G(t)<0$ and the effect on $n(t)$ is positive, leading to a reduced probability to take drugs. While $G(t)>0$ the function decreases over time as the agent's condition gradually becomes better. Usually, in addicts this signal is always very low and does not affect behavior. As some people do manage to quit, our model assumes that in some agents or in specific circumstances this signal could increase enough in order to have control over behavior. The longer the agent is addicted (longer in $G(t)<0$) the value of $GL_{PFC,ic}$ is bigger. This means that as the agent becomes more addicted, he "accumulates" more harmful consequences, like an ongoing deteriorating health condition, etc. This accumulation increases the possibility that the agent will stop taking drugs; it is the signal that drives quitting.

Acute external events that cause relapse via changes to some of the above neurotransmitters

Up till here addictive behavior was described as continuous: gradually accumulating and escalating levels. However, there are occasions in which a sudden discrete acute event may influence the patient's behavior at once. Acute events influence the parameters for a definite amount of time. We propose that they also have a "memory" component in the sense that if a consecutive event occurred before the previous one ended then their joint influence on $n(t)$ is temporarily lengthened. This "memory" of the events represents the notion that repeated harmful acute events are more powerful than events occurring in a sporadic manner. While one can think of acute events that can affect $G(t)$ in either direction, we follow the literature and focus in this paper on these events that lead to relapse to drug during abstinence periods (Shaham et al., 2003). Three such major acute events are drug priming such as social drinking (Schmidt et al., 2005), a stressful event such as divorce (Ahmed and Koob, 1997; Shaham et al., 2000; Fox et al., 2007) and exposure to drug-associated cues, such as visiting a particular friend (See, 2002). In our model the signals modeling these events occur during withdrawal when $G(t)>0$ and

increase strongly and instantly, causing *n(t)* to decrease, shifting *G(t)* to become immediately negative and the agent undergoes a relapse episode.

Drug priming

Drug priming in humans resulted in increased cerebral blood flow (CBF) measured by PET in the PFC, aCC, and orbitofrontal cortex (OFC) (Volkow et al., 1999; Volkow et al., 2005) and in the BOLD signal measured by fMRI in the PFC, aCC, NAC, hippocampus, and VTA (Breiter et al., 1997). Importantly, these elevated activities where correlated with the feeling of high and craving. A drug priming event in rats during withdrawal from repeated drug intake resulted in an increase in extracellular DA in the NAC originating from the VTA (Kalivas and Duffy, 1993; De Vries et al., 1999) and in the extracellular glutamate in the NAC originating from the PFC (Cornish and Kalivas, 2000; McFarland and Kalivas, 2001; Park et al., 2002; Baker et al., 2003; McFarland et al., 2003). As described above, the signal, termed DA_p, will model the effect of a drug priming on the extracellular DA levels in the NAC from the VTA and the signal termed, $GL_{PFC,p}$, will model the effect of a drug priming on the extracellular glutamate levels in the NAC from the PFC. Upon exposure to a drug priming there will be a strong and rapid elevation in these signals resulting in a strong decrease in *n(t)* causing *G(t)* to instantly shift toward negative values and the agent undergoes a relapse episode.

Drug-associated cues

There is ample evidence using fMRI and PET demonstrating that upon presentation of drug associated cues there is increased activity in reward-related brain areas such as the PFC, aCC, amygdala and dorsal striatum, which is correlated with the sense of craving (Grant et al., 1996; Maas et al., 1998; Childress et al., 1999; Garavan et al., 2000; Wexler et al., 2001). In rats, exposure to drug-associated cues during withdrawal from repeated drug intake results in an increase in extracellular glutamate in the NAC originating from the PFC (Weissenborn et al., 1997; Neisewander et al., 2000; Ciccocioppo et al., 2001; Hotsenpiller et al., 2001), hippocampus (Neisewander et al., 2000), and amygdala (Meil and See, 1997; Neisewander et al., 2000; McLaughlin and See, 2003). As described above, the signals $GL_{PFC,c}$, $GL_{Amg,c}$, $GL_{HPC,c}$ model the effect of exposure to drug-

associated cues on extracellular glutamate in the NAC from the PFC, amygdala and hippocampus, respectively. Upon exposure to drug-associated cues there will be a strong and rapid elevation in these signals resulting in a decrease in *n(t)* causing *G(t)* to instantly shift toward negative values and the agent undergoes a relapse episode.

The data regarding the effect of drug-associated cues on extracellular DA in the NAC is inconsistent. There are reports demonstrating an increase (Gratton and Wise, 1994; Di Ciano et al., 1998; Weiss et al., 2000; Phillips et al., 2003), decrease (Meil et al., 1995; Neisewander et al., 1996) and no change (Bradberry et al., 2000) of extracellular DA in the NAC following exposure to drug-associated cues. Because most of the data supports an increase in the signal, we modeled therefore, an increase in the signal, termed DA_c, which is described above resulting in a decrease in *n(t)* causing *G(t)* to instantly shift toward negative values and the agent undergoes a relapse episode. However, in principle, this effect could be ignored in the model.

Stress

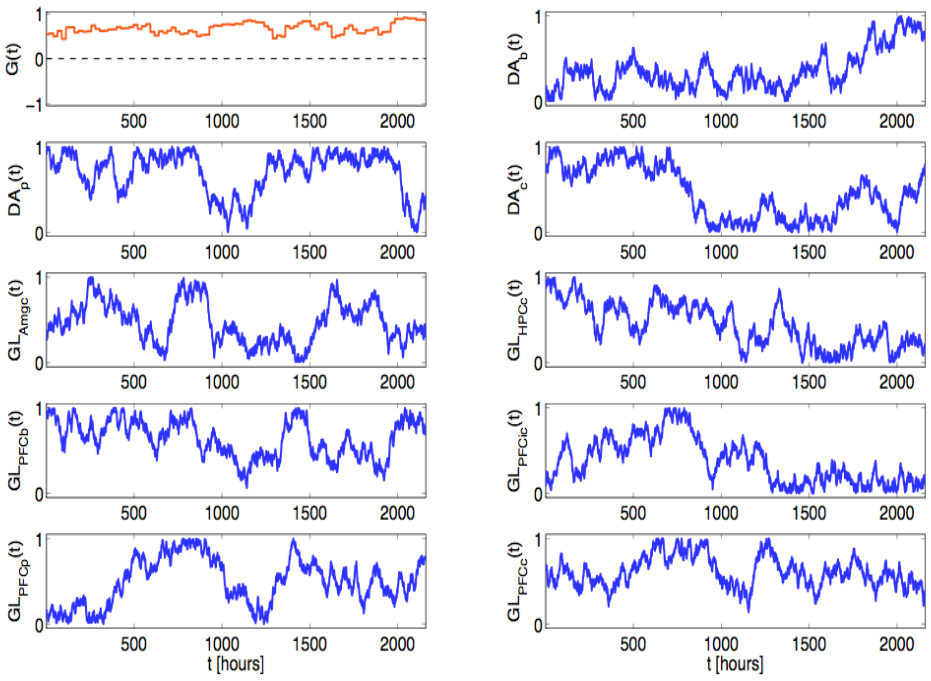
Exposure to a stressful event during withdrawal from repeated drug intake results in an increase in extracellular glutamate in the NAC originating from the PFC (Capriles et al., 2003; McFarland et al., 2004) and it is dependent on DA transmission in the NAC (Xi et al., 2004). As described above, the signal DA_p and $GL_{PFC,p}$, will model the effect of stress on extracellular DA and glutamate in the NAC from the VTA and PFC, respectively. Upon exposure to stress there will be a strong and rapid elevation in these signals resulting in a decrease in *n(t)* causing *G(t)* to instantly shift toward negative values and the agent undergoes a relapse episode. In the present model we have ignored the effect of stress hormones on relapse.

Results

Simulation with the Model

Each simulation we've made modeled behavioral attributes relevant to drug addiction. Each actual simulation was a 2000 time-step window that approximately is equivalent to

2000 hours (83 days) in real life. Thereafter, we have made 50 repetition runs for the same behavioral scenario to obtain a long-term expected behavior. The first scenario simulated a simple behavior in which an agent was never addicted before the time of the beginning of the simulation (t=0) and stays that way all the time (Fig. 2). That is, an agent that never uses drugs. The second scenario simulates the acquisition of drug addiction; an agent that was never addicted before t=0 but gradually becomes addicted due to occasional consumptions, which gradually affects extracellular levels and lowers G(t), increasing the likelihood to consume drugs. The agent stays addicted the whole time without recovering (Fig. 3). Note how the parameters dynamically change as a function of *G(t)* and how they recurrently influence *G(t)* via their influence on *n(t)*.



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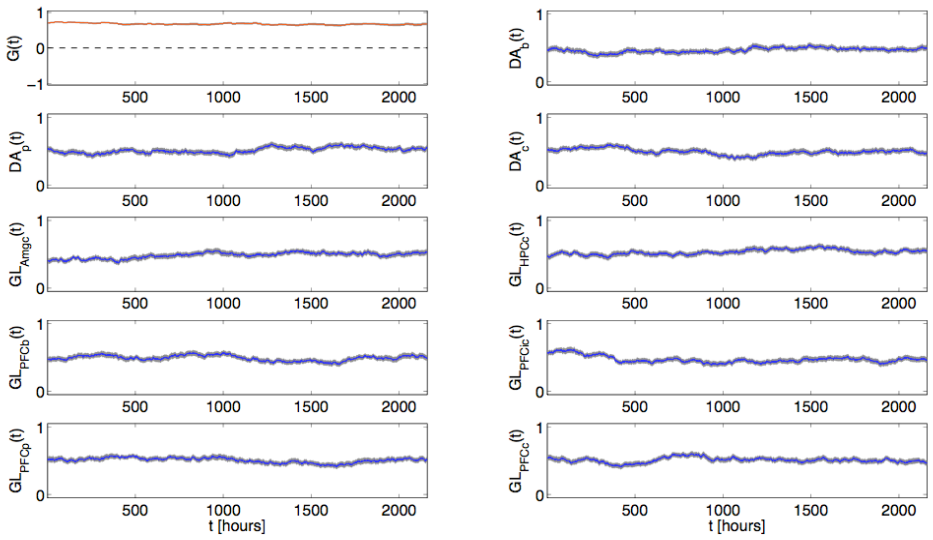

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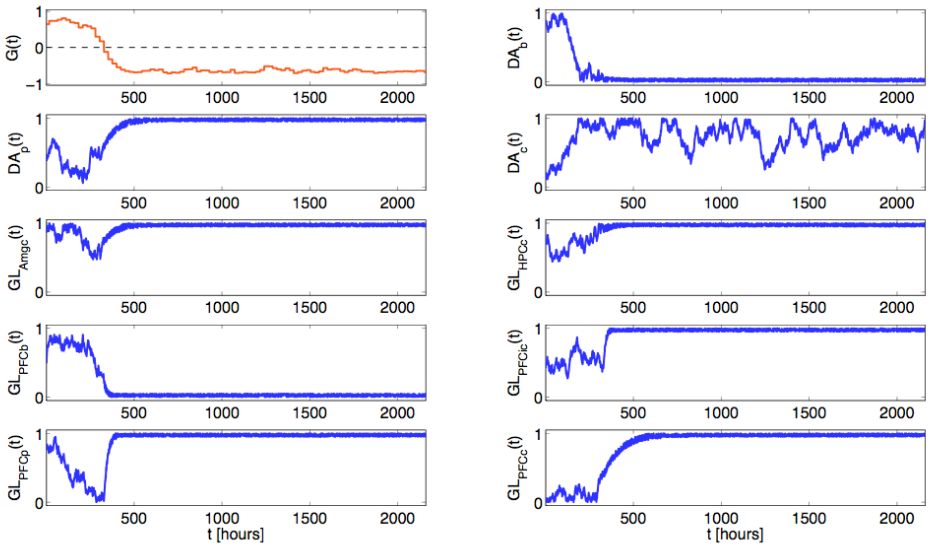
Figure 2

Agent not addicted. The agent was never addicted before the time in the model (before t=0) and is never taking drugs during the entire time window. **a**) One run of the simulation. **b**) Excepted behavior of the agent in the long term following fifty runs of the simulation. The graphs represent means ± S.E.M.



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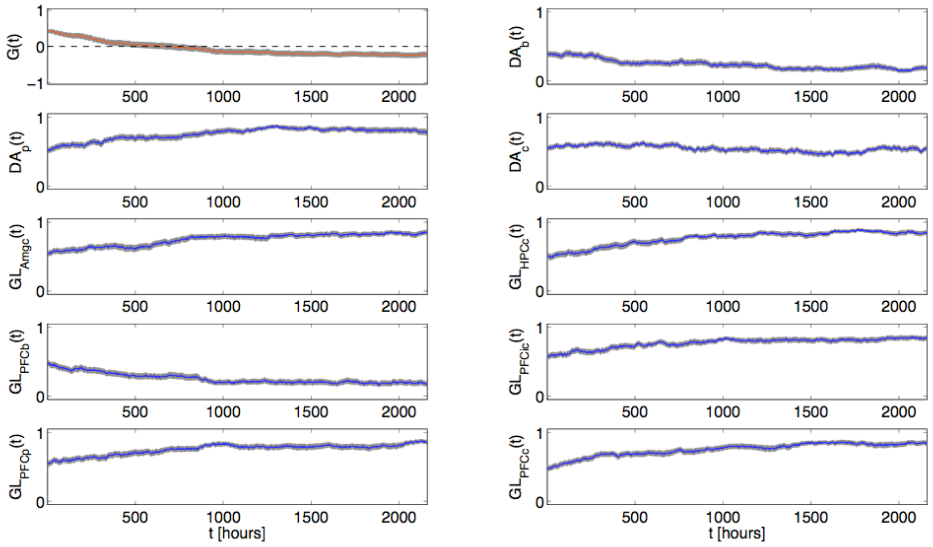
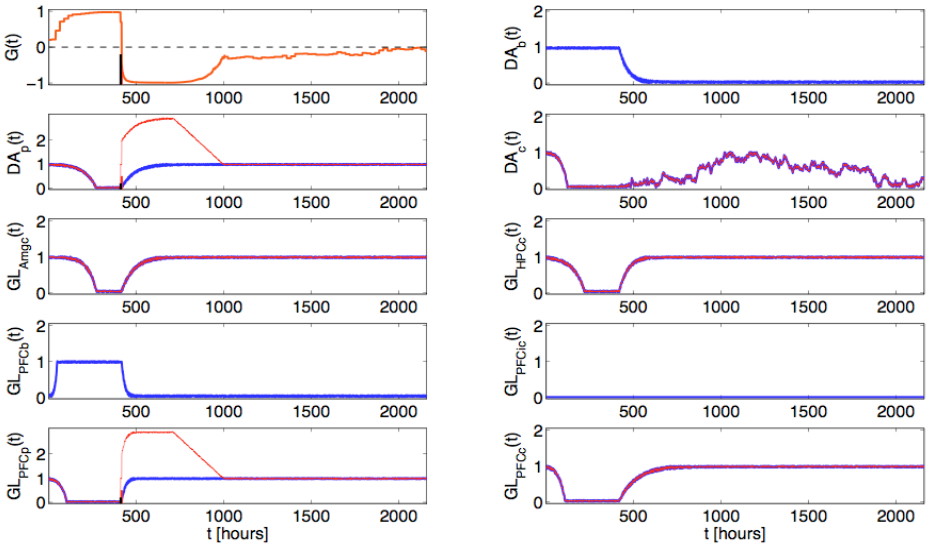


b

Figure 3

Agent becomes addicted. The agent was never addicted before the time in the model (before t=0) but starts to consume drugs and gradually becomes addicted when $G(t)<0$. **a**) One run of the simulation. Note that there is a recurrent influence of the various signals on $G(t)$ and that there is a change in the various signals as a function of the change in $G(t)$. **b**) Excepted behavior of the agent in the long term following fifty runs of the simulation. The graphs represent means ± S.E.M.

The third scenario describes an agent that was addicted before t=0, but has temporarily recovered and is abstain at t=0. However, at some point (black line at t=~400) he encounters an acute stressful event that causes him to relapse and the likelihood of drug consumption is very high once again. In this case we have assumed that the level of inhibitory control is very small and do not affect behavior at all (Fig. 4).



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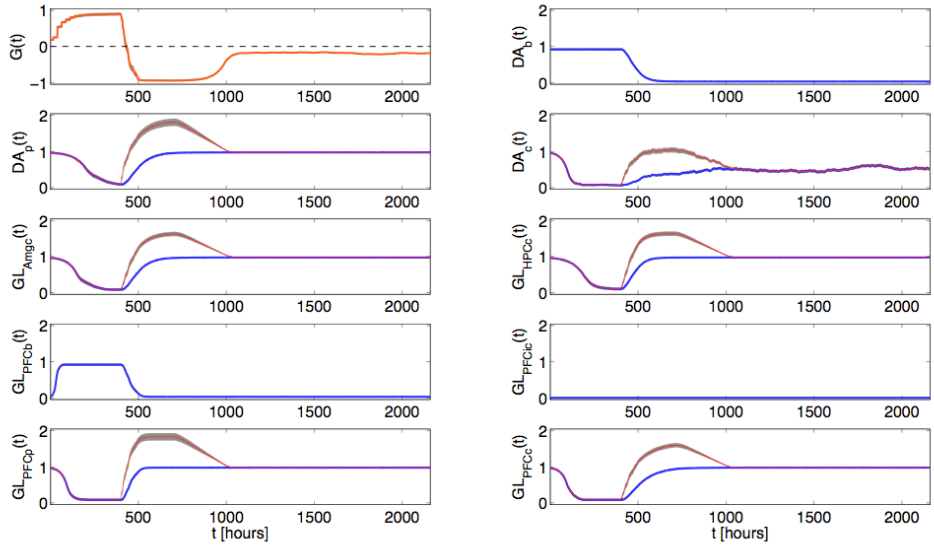
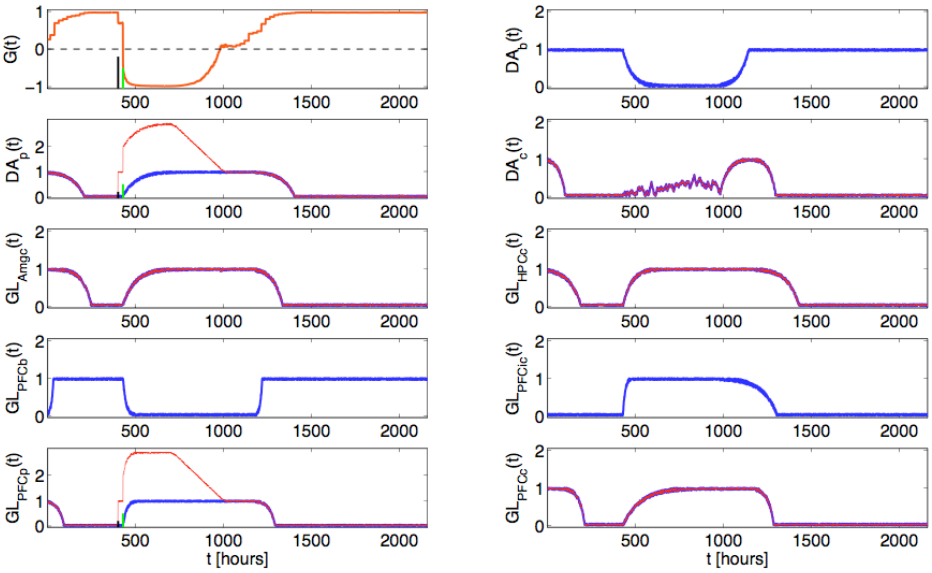


b

Figure 4

Relapse. The agent was addicted in the past but is not taking drugs at the beginning of the time in the model (t=0). At some point (~t=400) the agents encounters an acute event that causes relapse (black line that represents a stressful event). Due to very low inhibitory control signal the agent stays addicted through the time in the model. **a**) One run of the simulation. **b**) Excepted behavior of the agent in the long term following fifty runs of the simulation. The graphs represent means ± S.E.M.

This scenario is similar to the previous one but we have assumed that the inhibitory control signal is influencing *n(t)*. Therefore, after relapse, due to a priming event in this case, the agent is addicted for some time but eventually the inhibitory control signal is strong enough to override the positive addiction signals and the agent stop taking drugs (Fig. 5). This scenario rarely occurs in real life, but sometimes do occur. There are cases that addicts do manage to overcome their addiction. We emphasize the fact that a good model has to account for all behavioral possibilities in order to model life more accurately.



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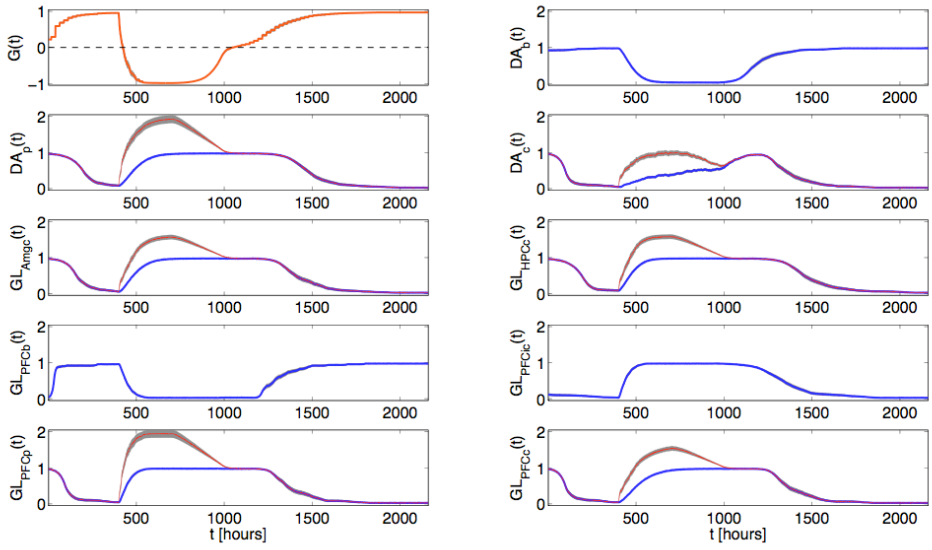
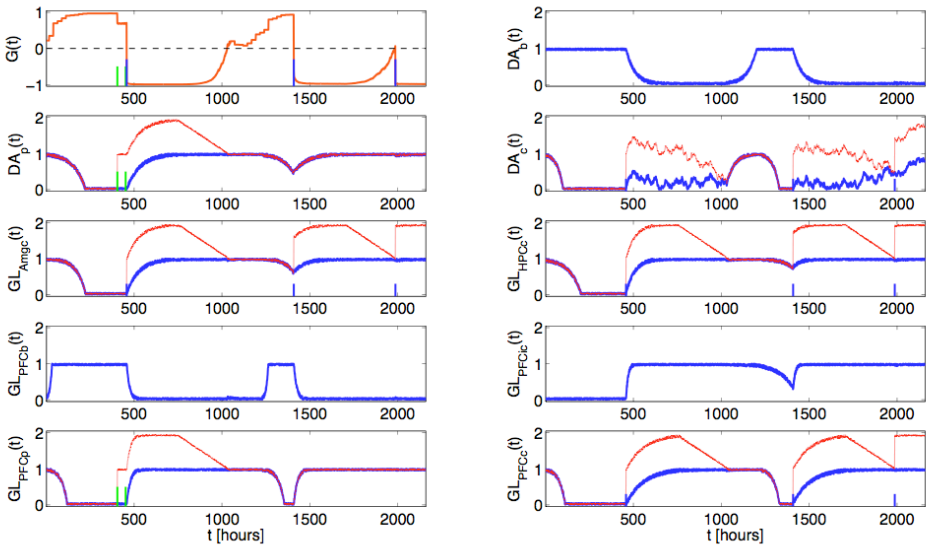


b

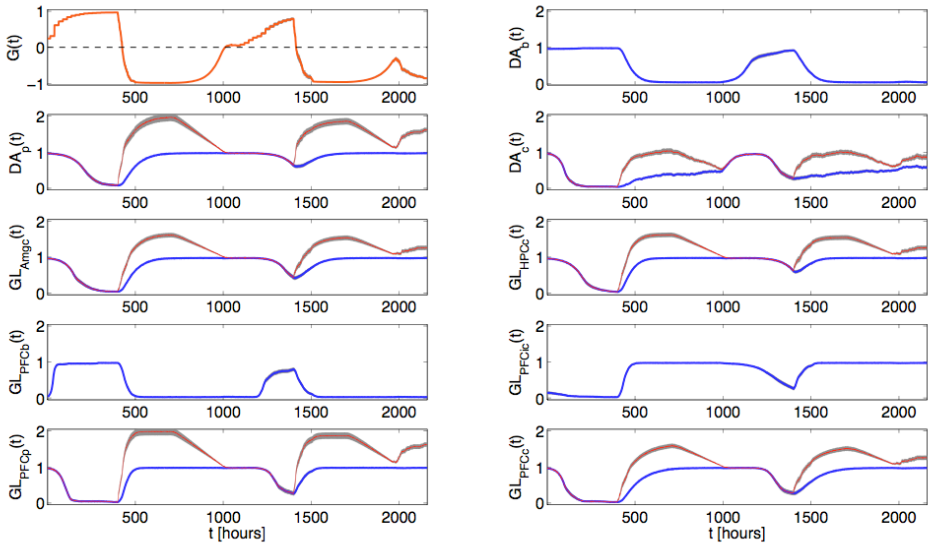
Figure 5

Relapse and recovery. The agent was addicted in the past but is not taking drugs at the beginning of the time in the model (t=0). At some point (~t=400) the agents encounters an acute event that causes relapse (green line that represents a drug priming event). Due to a high inhibitory control signal the agent gradually recovers and eventually stops taking drugs through the time in the model. **a**) One run of the simulation. **b**) Excepted behavior of the agent in the long term following fifty runs of the simulation. The graphs represent means ± S.E.M.

The last scenario models the sad reality of most addicts; a vicious cycle between active states of drug consumptions, abstinence and relapse. When the agent is abstinent, acute events cause him to relapse and to consume drugs again, while thereafter, the inhibitory control drives him back to an abstinent period and vise versa. This is the full cycle of addicted behavior (Fig. 6).



a



b

Figure 6

The vicious cycle of addiction. The agent was addicted in the past but is not taking drugs at the beginning of the time in the model (t=0). At some point (~t=400) the agents encounters an acute event that causes relapse (green and blue lines that represent a drug priming and encountering a drug associated cue events, respectfully). Due to a high inhibitory control signal the agent gradually recovers and eventually stops taking drugs for some time. However, additional acute events causes relapse once again represnting the cyclic nature of addiction. **a**) One run of the simulation. **b**) Excepted behavior of the agent in the long term following fifty runs of the simulation. The graphs represent means ± S.E.M.

Discussion

The model computationally demonstrates why addiction is so persistent, as well as its cyclical dynamics of activity. Previous models do not explain the maintenance phase of addiction, the ability to quit, abstinence periods and the propensity to relapse after drug cessation, which are the most important factors in addictive behavior and rehabilitation. The prediction of most current computational models {Redish, 2004 #4;Gutkin, 2006 #79}is that addiction can be modeled by a monotonic function, deterministic in nature and unidirectional. Our alternative computational theory of drug addiction described here takes into account that the main problem of addiction is the tendency to relapse and the hardship to remain abstain. Yet, our model does not doom addicts to a bad end but rather

includes the possibility that addicts can cease using drugs depending on their neuronal state.

In our model we introduced the value-state factor *n(t)* that determines the balance between drug taking and abstinence. The value-state factor *n(t)* is a general principle, which serves for describing the pattern of neuronal activity in the striato-cortical loops that assigns values to states and eventually determines behavior. To our knowledge this is the first time that there is an attempt to model drug addiction in a framework of a well defined anatomical circuit combined with a comprehensive description of the dynamics of extracellular neurotransmitter levels in specific synapses between well defined brain areas, as identified in the literature. This is an attempt to recurrently connect dynamics in the neurotransmitter level through anatomy up to the behavioral level and back to model a complicated behavior such as drug addiction.

The model provides some testable hypotheses regarding addictive behavior. We predict that the value-state factor *n(t)* is elastic and could be influenced by various factors, such as deep brain stimulation, transcranial magnetic stimulation, pharmacology, and behavioral and cognitive treatments. Various available treatments target and affect one or more of the parameters described in the model that influence *n(t)*. This model, and more elaborative models of its kind as planned for future work, may turn to help us simulate the effects that potential treatments have on the different parameters and brain areas in the reward system and on behavior. We can introduce an external input, simulating a treatment, to the model and examine how *n(t)* changes and how it affects the agent's behavior. Moreover, it will help us iterate and modify a specific treatment by allowing us to examine its effect on each of the different parameters, saving time and money on real experiments by first redirecting efforts to specific promising paths. Finally, using fMRI to measure the level of activity in brain areas related and influencing the value-state factor may serve as a tool for evaluating the severity of the addiction. This knowledge may serve as a method to identify people who have a predisposition for addictive behaviors and provide clues for treatment strategies.

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