

# Drug induced Synaptic Plasticity in the Mesolimbic Reward Pathway

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## Introduction

In the last decade or so, cellular mechanisms of learning and synaptic plasticity have been central in neuroscience, informing research across diverse fields of study. Synaptic changes similar to those described by the prevalent model of cellular memory, NMDAR regulated Long Term Potentiation (LTP) and Long Term Depression (LTD), have been isolated in many brain areas. What is more, advances in experimental techniques have allowed researchers to identify the cell and molecular changes that facilitate synaptic plasticity *in vivo* so that plasticity has become a viable element in research. This paradigm has especially informed the study of drug addiction. Historically, models explaining drug addiction have looked at the motivations driving continued drug use in terms

of withdrawal, tolerance, psychological reward, and behavioral sensitization. But in a broad sense, both the symptoms and the physiological changes associated with drug addiction can be understood in terms of memory: in response to an initial exposure to a drug, physiological changes take place that potentate behavior in a way that makes future exposure more likely.

More specifically, the defining characteristics of drug addiction can be separated in terms of a distinction between two forms of memory. The first, “homeostatic learning” refers to cellular changes that minimize external changes over time, in effect pushing a neural system back towards equilibrium. Homeostatic plasticity seems plausible as a physiological basis for drug tolerance, withdrawal and physical dependence. Many of the actual physiological mechanisms behind these kinds of symptoms have been isolated and well understood. On the other hand, “Hebbian learning” refers to cellular changes that increase or exaggerate external changes over time, in effect changing a neural system away

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from its original state. Hebbian plasticity is a plausible substrate that might account for the physiological basis of sensitization, cue related association, and the long-term threat of relapse. These more complex elements of drug addiction are often the most frustrating clinically, and are the least understood physiologically (Hymen et al., 2006).

Although the distinction between homeostatic and Hebbian elements of drug addiction is somewhat heuristic, it provides a good perspective from which to evaluate models of drug addiction. In this review, recent research into Hebbian synaptic plasticity of the

### **LTP and LTD**

Before analyzing NMDAR mediated synaptic plasticity in drug addiction, it is valuable to review the LTP-LTD model and its limitations. NMDAR mediated LTP and LTD represent an experimental model of Hebbian synaptic plasticity of glutaminergic synapses, which was first identified in the CA1 area of the hippocampus. LTP takes place in response to

mesolimbic dopamine reward circuit, including the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC), is examined in the context of the latest models of dopamine reward. The literature shows that NMDAR mediated synaptic plasticity takes place in response to exposure to many drugs of addiction. In fact, this drug induced synaptic plasticity is emerging as an important component of addiction. What is more, a learning model of addiction provides an interesting case in which physiology explains behavioral memory.

high frequency stimulation of an excitatory synapse. In such conditions, NMDAR receptors open and allow the influx of  $Ca^{2+}$ . Although the mechanisms past this point are not entirely understood,  $Ca^{2+}$  influx triggers a synaptic cascade involving calcium/calmodulin dependent protein kinase 2 (CaMKII), protein kinase C (PKC) and other down stream messengers. Whatever the exact biochemical pathway, the  $Ca^{2+}$  cascade leads an up

regulation of the number of AMPA receptors at a synapse and an increase in the phosphorylation of AMPA receptors. In addition to the short term up regulation of AMPA receptors, LTP is thought to cause an up regulation in the genetic production of the receptors. As a result, the activation of a synapse causes the opening of more ion channels, each of which is more conductive. Both of these factors scale up the depolarization produced by the presence of glutamate in the synaptic cleft, leading to a stronger synapse. (Malenka and Bear, 2004)

On the other hand, LTD takes place in response to a low frequency (0.5-5 Hz) stimulation of an excitatory synapse. In such conditions, NMDAR receptors are activated, but the size of the Ca<sup>2+</sup> influx is far smaller than that elicited by a tetanus that might lead to LTP. The mechanism of LTD is not fully understood, but it involves a comparable second messenger cascade which leads to the down regulation of AMPA receptors and a decrease in their phosphorylation. These changes scale down the depolarization produced by glutamate in the

synaptic cleft, leading to a weaker synapse. (Malenka and Bear, 2004) LTP and LTD are exciting because they represent a cellular mechanism that provides a possible substrate for many forms of associative memory.

However, two considerations about the LTP-LTD model of synaptic plasticity are important to keep in mind for this study. First, as Malenka and Bear point out, "LTP and LTD are experimental phenomena, which can be used to demonstrate the repertoire of long-lasting modifications of which individual synapses are capable." (Malenka and Bear, 2004) Since their initial discovery in the hippocampus, the study of LTP and LTD has been expanded to many other brain areas. Although the mechanisms and mechanics of LTP and LTD are documented in experimental conditions, the model might not apply to all forms of synaptic plasticity. While the classical model is valuable, its extension to new brain areas must be performed with care.

Second, the dynamics of LTP and LTD allow it to be measured in terms of a ratio of currents mediated by the two glutaminergic

receptors. While the activation of a synapse at various frequencies leads to a change in the expression of AMPA receptors, the number of NMDA receptors in a synapse is thought to remain fairly constant. As a result, the ratio of a depolarizing current mediated by AMPAR's to that mediated by NMDAR's changes in response to LTP or LTD. Simply stated, an increase in the AMPAR/NMDAR current ratio indicates LTP while a decrease indicates LDP. (Hymen et al., 2005) While this assay is a good indicator of synaptic plasticity, it is important to keep in mind the limitations of describing the synaptic changes in terms of the LTP-LTD model. Nonetheless, the AMPAR/NMDAR ratio provides a fairly robust measure of changes in synaptic strength that is applicable to a wide range of experimental stimuli. (Hymen et al, 2005) In fact, this assay has been essential to the observation of plasticity in drug addiction.

### **Drug induced LTP in the Dopamine Reward Circuit**

There is a large body of evidence suggesting a close relationship between drug addiction and the dopamine pathway from the ventral tegmental area (VTA) to the nucleus accumbans (NAc). When performed in the VTA, self administration experiments show a much lower threshold for addictive drugs in the VTA and the NAc than most other areas of the brain. Many addictive drugs are known to cause the release of dopamine from neurons in the VTA. What is more, there is a close connection between the VTA and behavioral sensitization, which is a prominent model for addiction in animal studies. Finally, the VTA and the NAc also show correlations to associations between drugs and related contextual cues. (Kauer, 2007) Qualitatively, many of these mesolimbic related symptoms of drug addiction seem to be similar to Hebbian synaptic plasticity. In an important study, Ungless et al. put this informal notion to the test by looking for NMDAR mediated synaptic plasticity of excitatory synapses of dopamine neurons in the VTA.

In the Ungless experiment, brain slices from the VTA of rats given a single peripheral exposure to cocaine were analyzed by measuring the AMPAR/NMDAR ratio as discussed above. Cocaine treated rats showed a significant increase in overall synaptic strength, and a significant increase in the ratio of AMPAR to NMDAR currents. (Ungless et al., 2001) On its own, this result is not particularly revealing: cocaine is known to cause many changes to dopamine releasing neurons in the VTA and it is plausible that this change has little to do with LTP. However, using the same experimental methods, a 2003 study by Saal et al. showed that exposure to other addictive drugs, including morphine, nicotine, amphetamine and ethanol, induce similar changes. What is more, while this effect results from many addictive drugs, it is not produced by other non-addictive psychoactive agents such as the SSRI fluoxetine. (Saal et al., 2003)

Two aspects of this experiment make it a truly amazing finding. First, even though addictive drugs act through a diverse set of

immediate mechanisms, they all converge to produce an identical change in the VTA. Consider, for example, the action of opiates compared to that of cocaine. Although both drugs act directly on dopaminergic neurons in the VTA, opiates take effect by stimulating  $\mu$ -opioid receptors, while cocaine works by blocking the reuptake of catecholamines. That the actions of both drugs converge to raise the AMPAR/NMDAR current ratio suggests the results of this assay are unlikely to be the coincidental effect of an either drug. Second, the fact that many different addictive drugs produce this shared physiological change indicates that it is likely to play an important role in addiction. Psychoactive drugs produce a wide range of physiological changes in many different regions of the brain. Addictive drugs often cause a wide range of changes to many brain areas. Since LTP in the VTA is common to all addictive drugs it is a promising substrate that could be at the root of addiction.

Another telling characteristic of drug induced LTP in the VTA is the time course during

which the change takes place. Both studies found that drug induced LTP in the VTA only lasted for about five days. (Ungless et al., 2001, Saal et al 2003.) This fact is important because it shows that synaptic plasticity in the VTA itself cannot account for the long lasting effects of drug addiction. In fact, the temporal relationship between drug exposure and LTP in the VTA suggests that it is likely important in the creation, rather than the maintenance of addiction. (Hymen et al., 2005) To identify longer lasting changes produced by drugs of addiction, it is necessary to look down stream from the VTA.

Many of the dopanamergic neurons in the VTA release dopamine in the Nucleus Accumbans (NAc). A 2001 study by Thomas et al. found that exposure to cocaine produces Long Term Depression of excitatory synapses onto neurons in the NAc. Unlike the potentiation identified in the VTA, this synaptic depression requires a long term of exposure and it persists for a long period after exposure. Interestingly, the study found that the LTD in the NAc is

correlated to behavioral sensitization, a long-standing model of drug addiction. (Thomas et al, 2001) Based on the temporal differences between synaptic depression in the NAc and potentiation in the VTA, these two forms of synaptic memory seem to result from different mechanisms of induction, and likely have very different roles in drug addiction. While the short timeframe of LTP in the VTA suggests that it might be involved in the formation of addiction, the long timeframe of LTD in the NAc indicates that it might have a role in the maintenance of addiction.

While both of these Hebbian synaptic mechanisms seem to be important in the physiology of drug addiction, they clearly they cannot be sufficient to explain addiction and learning in the reward circuit. Rather, it is difficult to understand the impact of these synaptic changes without a better knowledge of their functional context. In order to understand how drug induced synaptic plasticity takes effect, is necessary to develop a more rigorous understanding of the functioning of the

mesolimbic dopamine pathway in reward and behavior.

### **Dopamine and The Encoding of Reward**

Dopamine release from VTA neurons into the NAc has long been associated with the signal of a reward, but the precise meaning of dopamine release has been elusive. The most compelling model of release dopamine comes from an experiment performed by Shultz et al. first in 1997. Based on temporal recording of dopaminergic neurons in the VTA in response to rewards, Shultz demonstrated that dopamine release is related to learned associations between rewards and reward associated cues.

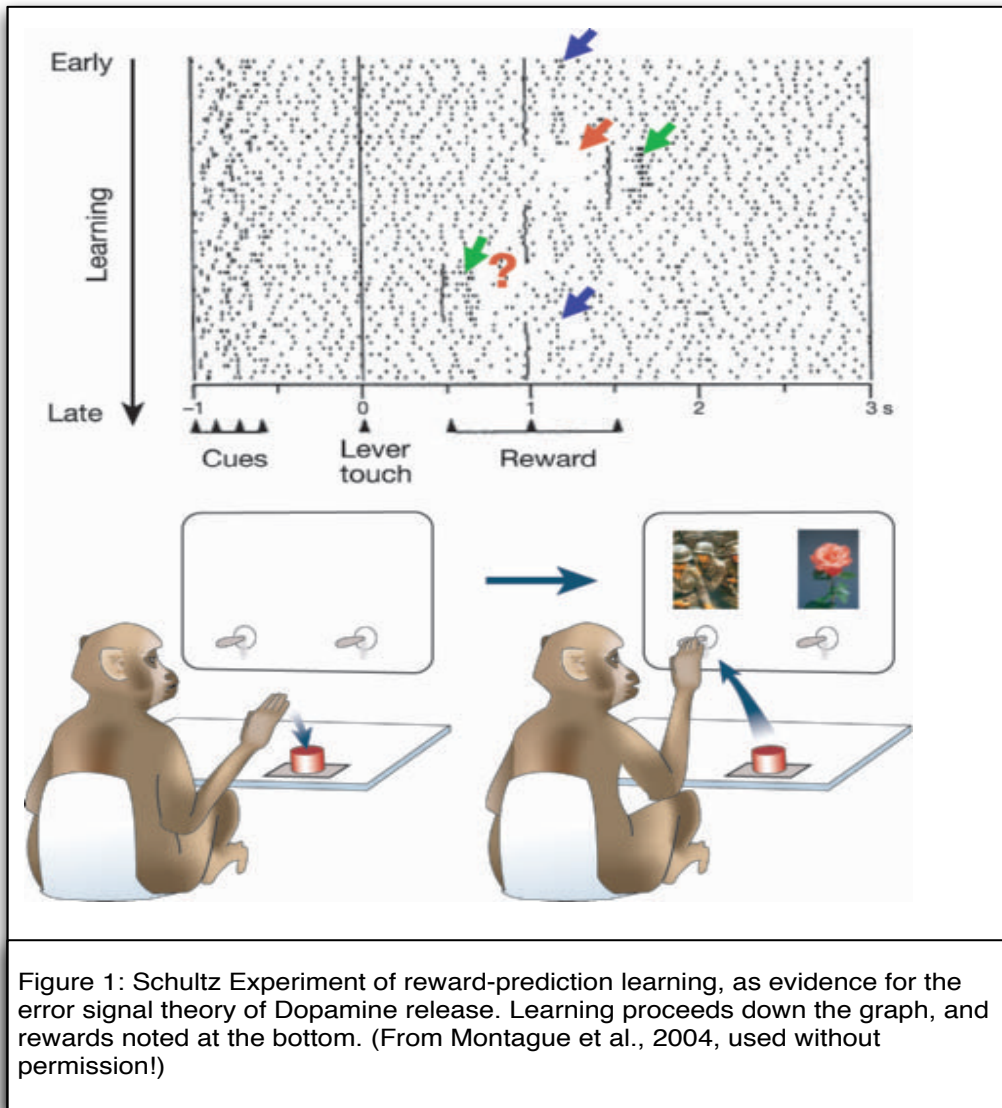
In the experiment, monkeys were trained to associate the administration of a sugar water “reward”, with a preceding visual or auditory stimulus “predictor”. Shultz observed the behavior of dopamine cells throughout this learning process. At the beginning of the experiment, dopamine cells fired in response to the reward. But as the animal learned to associate the predictor and the reward, the

dopamine cells fired in response to the predictor rather than the reward. (Shultz, 2002, Montague et al., 2004)

Based on these findings, Shultz suggested that the firing rate of dopamine neurons in the VTA serves as an error signal between the reward that an animal expects, and that it actually receives. A reward greater than that expected produces a burst of firing, a reward as expected produces a baseline level of firing, and the absence of an expected reward produces a deficit in firing (Figure 1), (Shultz, 2002). This model of dopamine as an error signal can be summarized in the following relationship:

$$\text{Dopamine firing rate} = \text{Actual Reward} - \text{Expected Reward} \text{ (Shultz, 2007)}$$

As Shultz notes, this kind of a relationship fulfills a necessary task predicted by computational models of associative learning. In this sense, the dopamine error signal might serve as a substrate for the development of associations between rewards and cues. (Shultz, 2007)



Two aspects of Shultz's model are especially relevant to the analysis of drug induced LTP in the VTA. First, the timing of stimulus events and their response is very precise and relevant. According to the model, the timing of the reward and predictor directly affect the activity of dopamine neurons. In addition, the resulting cellular changes occur over a very

short time frame. Second, while the dopamine error signal encodes prediction error and contributes to memory, it is only part of a larger neural system. Although the firing rate of dopamine neurons is involved it, serves as an element in the larger substrate for memory. In light of Shultz's model, it is clear that modifications of the synaptic strength of dopamine neurons could have a significant effect on

the brain's reward circuit. However, understanding the actual effects of synaptic plasticity, and that produced by drugs of addiction, requires more data.

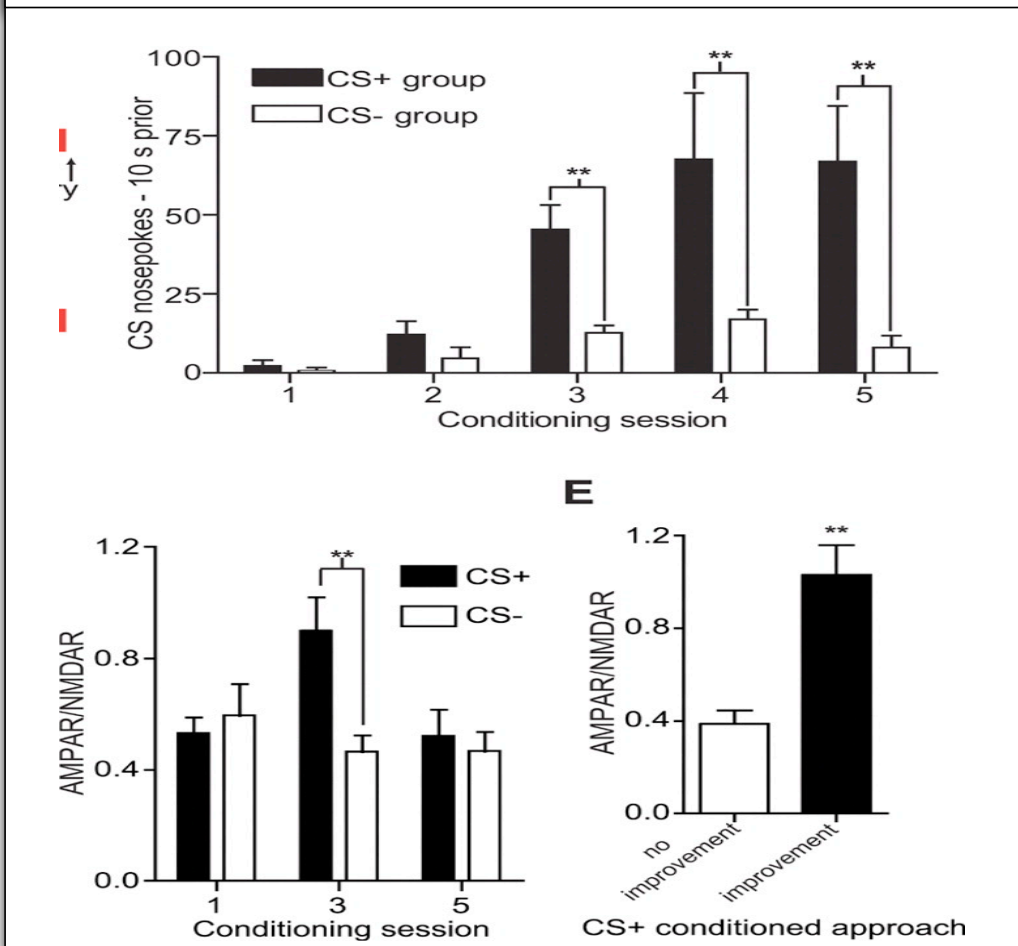
### Recent Studies on Synaptic Plasticity in Dopamine Neurons

Two lines of evidence are particularly helpful in understanding exactly how synaptic plasticity change the dopamine circuit. First, it is interesting to ask whether plasticity has a role in the normal functioning of the dopamine reward circuit. In a crucial study released only a few months ago, Stuber et al. looked for signs that synaptic plasticity in the VTA is directly involved in a learning task similar to that of the Shultz experiment. In the Stuber study, two groups of rats were trained in an analogous system to that of the Shultz experiment. In the first group, CS+, a reward stimuli was preceded with a time locked light cue stimulus, while in the second group, CS-, the cue did not accurately predict the reward. As expected by the Shultz model, VTA dopamine neurons in rats in the CS- group, and untrained rats in the CS+ group, were time locked with the reward stimulus. After rats in the CS+ group were trained to associate the predictor with the reward, their VTA dopamine cell firing became time locked with the predictor. (Stuber et al., 2008)

After cataloging learning process for rats in the CS+ group, Stuber compared the ratio of AMPAR/NMDAR currents in VTA neurons of the two groups before, during and after the learning had taken place. Initially, the current ratio in groups was comparable. However, during training, CS+ rats had a significant increase in the AMPAR/NMDAR ratio, suggesting that LTP was involved in associating predictor with reward. After the training, the ratio returned back to normal. (Figure 2) What is more, the administration of an NMDAR antagonist blocked this observed plasticity and the cue-reward learning. (Stuber, 2008) This is a remarkable experiment because it shows NMDAR mediated synaptic potentiation was essential to the development of a cue-reward association. In the context of the Shultz model, the Stuber finding suggests that NMDAR mediated synaptic potentiation is an integral part of the normal dopamine reward circuit: it is necessary for the production and maintenance of cue related associations. But in order extend this evidence to drug addiction, it is also necessary to examine

have been unable to isolate the effect of NMDA receptors in dopamine neurons from that in other surrounding neurons. In the Zweifel study on the other hand, the genes for NMDAR were selectively knocked out in dopaminergic neurons using the gene for the DA-Transporter protein as a genetic control. Therefore, the results from the Zweifel study are likely to reflect

**Figure 2:** Learning Predictor-Reward Associations involves NMDAR Mediated LTP. Top shows assay of learning on the y-axis, and conditioning sessions of the X-axis. Bottom: AMPAR is elevated for the CS+ group in the middle of the learning process but normal before and after. (From Stuber et al 2008, used without permission!)



the precise effects when plasticity is mediated by drugs.

In a second line of evidence, Zweifel et al. analyzed the role of NMDAR mediated synaptic plasticity in drug addiction by interfering with the action of the NMDA receptor. As Zweifel and colleagues point out, past studies have attempted similar methods using NMDAR antagonists, but

an absence of synaptic plasticity in dopamine neurons in the VTA, without changing other elements of the system. Zweifel then measured the response of knock out (KO) mice compared to that of controls when administered various drugs of addiction.

Zweifel tested the KO mice for two common models of addiction: conditioned place

preference (CPP) and behavioral sensitization to cocaine. For the purposes of this study, CPP can be considered analogous to the formation of cue-reward associations. As might be expected from the Stuber findings, blocking NMDAR mediated LTP blocked the formation CPP, which is normally a robust result of exposure to addictive drugs. Similarly, behavioral sensitization to cocaine, normally a good assay for the development of drug addiction, was reduced in the KO mice. (Zweifel et al, 2008) Thus, drug induced plasticity in the VTA can be implicated as necessary in producing associative memories between drugs and cues, as well as behavioral sensitization.

### **Conclusions: A Model for Drug Induced LTP in the VTA**

As an analysis of the literature shows, there is a strong relationship between synaptic plasticity in the mesolimbic dopamine pathway and the addictive qualities of drugs. Drugs of addiction, which act through a variety of mechanisms, all seem to converge in the

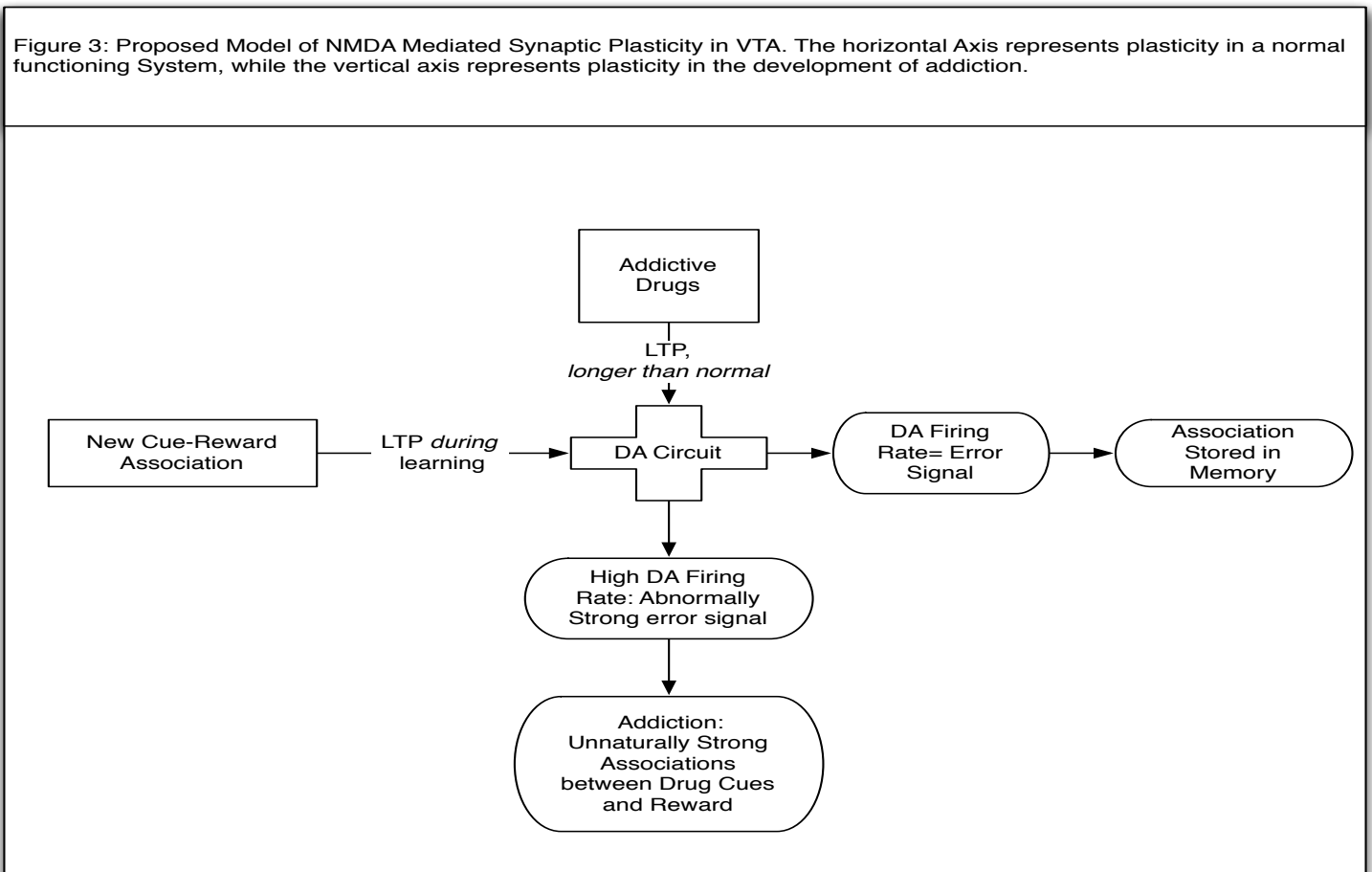
induction of NMDAR mediated synaptic plasticity of excitatory synapses onto dopaminergic neurons in the VTA. This is certainly not the only area in which drugs induce synaptic plasticity. In fact, as demonstrated by the short life of cellular changes in the VTA, long term maintenance of drug addiction must require longer lasting substrates of memory. But as emerging evidence shows, NMDAR mediated synaptic potentiation in the VTA appears to be important in normal functioning of reward and memory as well as the formation of addiction.

Drawing from the insights of the Shultz model of error prediction in dopamine neurons and the emerging research, the following model seems to explain both of these roles of synaptic plasticity in the VTA. As the Stuber study shows, LTP takes place in the VTA during the course of associative learning between cues and rewards, and their initial experiments suggest that it is necessary for the development of associations. Similarly, exposure to drugs of addiction produces LTP in the VTA. According to the Zweifel study, NMDAR mediated synaptic

plasticity is necessary to produce signs of addiction as measured by animal models. The crucial difference between the normal functioning of LTP in the dopamine error signal and that induced by exposure to drugs seems to be that of time. While the normal expression of LTP is limited to the process of learning, LTP produced by drugs of addiction lasts between 5 and 10 days. As a result, drugs of addiction consistently produce a stronger than normal error signal.

A normal dopamine error signal is likely to lead to many changes down stream from the VTA, in areas such as the prefrontal cortex (PFC). Synaptic plasticity in these regions is probably responsible for longer term memories of reward-predictor association. When drugs cause LTP in the VTA, these same mechanisms might be overwhelmed by an abnormally strong error signal. This could lead to an abnormally strong association between drug related cues and the perception of a rewarding stimulus. A strong

Figure 3: Proposed Model of NMDA Mediated Synaptic Plasticity in VTA. The horizontal Axis represents plasticity in a normal functioning System, while the vertical axis represents plasticity in the development of addiction.



error signal in the presence of drugs might also explain synaptic changes like LTD in the NAc, which do not take place in the normal functioning of the reward circuit. As the Thomas et al. study shows, these types of changes are correlated to symptoms like behavioral sensitization. (Figure 3)

Although this model of LTP in the VTA during drug addiction is promising, a lot more research is required to identify the mechanisms behind longer term memories, and longer term symptoms of drug addiction. In the future, the same methods used by the Stuber and Zweifel studies in the VTA might be useful in identifying synaptic plasticity in other brain areas induced by drugs as well as normal rewards. For example, Thompson et al. used this kind of approach to show that cocaine can modulate LTP in the Hippocampus. (Thompson et al, 2004) Synaptic changes to be isolated in many of the areas innervated by dopaminergic cells in from the VTA, and interconnected with the NAc. Because the reward circuit is so easily manipulated by experiment, these efforts might

be more successful than other attempts to isolate the substrate of more general long-term memory. In this sense, the dopamine reward circuit is an interesting area of study because it represents a relatively simple example of the physiology of behavioral memory. Interestingly, the methods and models developed in examining memories in this reward circuit could go on to inform the search for more complex forms of long term memory.

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