How bursting and tonic dopaminergic activity generates LTP and LTD

Adedoyin Maria Thompson, Bernd Porr*, Alice Egerton† and Florentin Wörgötter‡

1 Introduction

A popular interpretation of the dopamine activity is that of an error signal [1] where activation corresponds to a positive error and depression to a negative error. For example the activity of dopamine increases during learning and decreases during omission [1]. Such activation or depression causes long term potentiation (LTP) or long term depression (LTD) in their target areas, respectively.

Based on recent experimental evidence in the cortical and sub-cortical areas of the brain [2], [3], a different way of generating LTP or LTD by dopaminergic activity is proposed. We suggest that dopaminergic *bursting* causes LTP while *tonic* activity causes LTD. Thus LTP or LTD are controlled not by the dopaminergic activity itself, but by the rate of the dopaminergic activity. A simple reversal learning task will be used to demonstrate how this new theory can be used to learn and reverse a simple food seeking task. The experiment setup in [4] was used to test our paradigm. In this experiment, a rat learned to associate food reward with stimulus 1 of 2 presented in the arena. Once this discrimination had been learnt, the contingency was reversed, so that stimulus 2 of 2 was now associated with reward, and the rat had to inhibit the previous response pattern and learn the new association. We model reversal learning by introducing real and fake foods where only the real food excites a primary reward signal.

This paper focuses on the following nuclei of the limbic system: The nucleus accumbens (NAcc), which can be further divided into two distinct areas namely the shell and core [5], and the ventral tegmental area (VTA), which provides a Dopamine (DA) input to the NAcc. The ventral pallidum (VP) and the lateral hypothalamus (LH) are also integrated into the model. It will be shown that during learning, bursting will dominate and cause LTP, whereas during reversal learning, tonic activity will cause LTD.

2 Reversal learning performed by the limbic system

Fig. 1A,B shows the agent in the environment in which experiments were performed. There are real and fake food disks each of which appear in either a left or right color location. This is implemented as either Landmarks (S_b and s_g) for spatial navigation, or Place fields (P_l and P_r) for reversal learning. Before learning, the agent moves in a straight line and turns randomly when it bumps into the play area's boundaries. The LH is activated only when the agent comes in contact with the real food. Either food is replaced shortly after it has been consumed. Food retrieval is successful if the agent learns to eat the real food ten times in a row while ignoring the fake food. The positions of the foods in the colored landmarks are swapped and the agent has to unlearn this original behavior and learn to approach the real food in opposite colored landmark.

Central to our model Fig 1C, is the nucleus accumbens (NAcc) with its subunits NAcc shell and NAcc core. The NAcc core is implemented as a simple decision maker and performs the motor learning which guides the animal to the food. It is a simplified design of the [6] Basal ganglia model. The NAcc shell is essential for implementing reversal learning and stores the reward value of the conditioned stimuli i.e. a place or time which coincides with the presence of the reward [7]. In this case, it associates place field information from the hippocampus with food rewards.

Plasticity in the NAcc is controlled by three factor learning [8]. This is differential hebbian learning modulated by DA. The rate of DA activity functions as a switch during which a burst leads to the generation of LTP and tonic DA results in LTD. Learning and unlearning which occur locally in the NAcc core and shell are controlled respectively by the production of phasic or tonic DA from the VTA.

*Department of Electronics & Electrical Engineering, University of Glasgow, mariat,B.Porr@elec.gla.ac.uk
†Psychiatry Group, & Imperial College London, a.egerton@imperial.ac.uk
‡Bernstein Center of Computational Neuroscience, University Göttingen, Germany, worgott@chaos.gwdg.de

Bursting dopamine is generated when the LH is active. On the other hand, tonic activity is caused by the disinhibition of the VTA by the VP which in turn is inhibited by the NAcc shell. This means that increased activity in the NAcc shell will cause an increased release of tonic DA by disinhibiting the VTA.

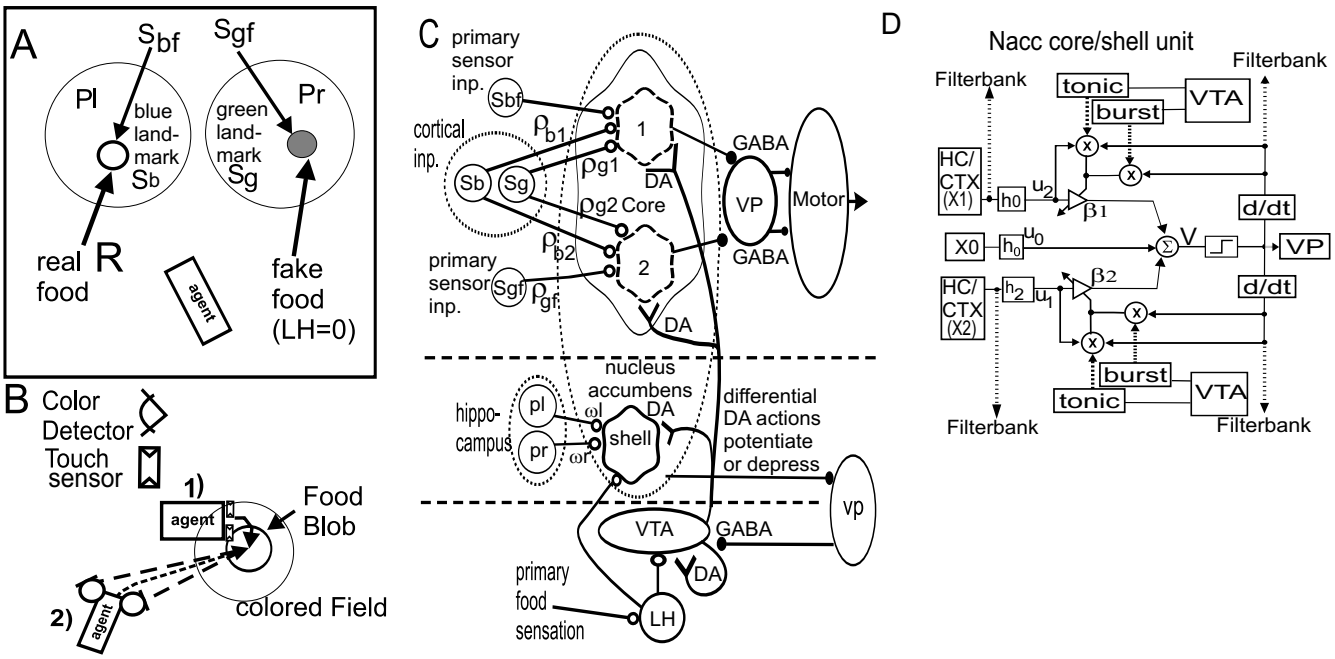

Figure 1: A) The agent in the playground which contains the real and fake food disks on the LHS and RHS respectively. B 1) The agent using its touch sensor when in direct contact with the food disk and 2) The color sensors at a distance. C) A model of the sub-cortical nuclei of the limbic system. D) The NAcc neural unit. The x_1 and x_2 inputs correspond to the cortical(CTX) or hippocampal inputs(HC).

The signals manipulated by the NAcc shell and core are obtained from the environment. The core receives low level primary sensor inputs (s_{bf}) and (s_{gf}) from the brain stem area and generates a curiosity reaction to the food in the blue or green landmarks. It also receives pre-processed sensor inputs from the cortical areas (s_b) and (s_g) which corresponds to the the euclidean distance from the coloured landmarks. The cortical inputs have plastic synapses (ρ_b) and (ρ_g) while the primary sensor inputs possess fixed synapses (ρ_{bf}) and (ρ_{gf}). The core comprises of two decision units which choose whether to go for the food disk in the blue or green area.

The shell receives place cell information from the hippocampus (p_l) and (p_r) which have plastic synapses (ω_l) and (ω_r) respectively. The LH projects an active input into the shell when reward has been obtained. All NAcc neurons are implemented as a neural unit.

The neural unit has a fixed input (x_0) and two plastic inputs (x_1) and (x_2) which develop to drive learning. The fixed (x_0) input can be substituted with (s_bf) or (s_gf) inputs when representing either of the core's decision units, or can be substituted by the LH input to the shell. Meanwhile, the plastic (x_1) inputs and (x_2) can be substituted with (s_b) and (s_g) signals to the core or the (p_1) and (p_2) signals to the shell.

The x_0 and x_1 or x_2 signals are filtered as follows: $u_0 = h_0 * x_0$ for the primary sensor or the limbic input and $u_k = h_k * x_k$ for the either of the cortical or hippocampal inputs, where $k > 0$.

These filtered signals converge as a neural sum:

$$V = \sum_{k=0}^{N} \beta_k u_k \tag{1}$$

and the NAcc is defined as follows:

$$NAcc_{shell/core_n} = \begin{cases} V, & \text{if } V \leq L \\ L & \text{otherwise} \end{cases} \tag{2}$$

The rate by which the VTA releases DA is given by:

$$VTA = \frac{LH + VTA_{baseline}}{1 + netInhibition} \tag{3}$$

where;

$$netInhibition = D2_{vta} + VP + NAcc_{shell/core_n}. \tag{4}$$

This is the overall inhibitory influence on the VTA i.e. the inhibition from the VP (Lisman,2005,groenewegen1993), the NAcc shell and D2 receptors located on the VTA ($D2_{vta}$).

The LH maintains a value of 1 during the consumption of a reward and 0 if otherwise. The phasic release of DA is represented as follows:

$$DA_{burst} = \theta\left(\frac{dVTA * h_{burst}}{dt}\right) \tag{5}$$

θ is the heaviside step function. The tonic release of DA can be expressed as:

$$DA_{tonic} = \begin{cases} VTA * h_{tonic}, & \text{if } DA_{burst} = 0 \\ 0, & \text{otherwise} \end{cases} \tag{6}$$

The weight change can thus be represented as:

$$\frac{d\beta_k}{dt} = \mu(DA_{burst} * NAcc'_{shell/core_n} * u_k - *DA_{tonic} * \beta_k * \mid NAcc_{shell/core_n} \mid' * \mid u_k \mid) \tag{7}$$

The weight β can be substituted with ρ or ω which correspond respectively to the core or shell weights.

3 Simulation and results

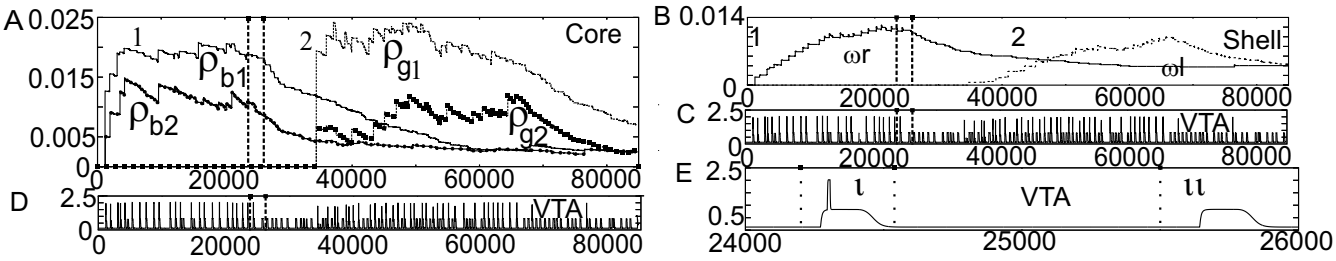

Figure 2: A) Simulation results which lasted 85000 time steps. A) The weight development in the core. B,D) An overview of the VTA. C) The weight development in the shell. E) A section of the VTA at the time steps between 24000...26000 showing (i) The moment a reward is received. A dominating DA_{burst} which is occurs over the DA_{tonic}. The timing of burst is irrelevant. (ii) after the foods are swapped a fake food produces only DA_{tonic}.

At the beginning of the experiment, the real food was placed in the blue landmark on the LHS of the play ground. The agent found the real food and the LH was triggered. This caused bursting in the VTA (Fig 2E(i)). The $\rho_{b1,2}$ and ω_l weights in the core and shell respectively began to grow (Fig 2 A and C (1)). The real and fake food positions were swapped after 10 consistent real food retrievals. The agent continued to approach the food disk in the blue landmark which now contained the fake food disk. This time a burst was not generated and the disinhibition of the VTA by the NAcc shell caused a rise in tonic DA (Fig 2E(ii)). The $\rho_{b1,2}$ and ω_l weights began to decrease and the agent slowly began to explore the play ground. The real food in the green landmark was found and $\rho_{g1,2}$ and ω_r began to grow . The agent kept interchanging between going for the real and fake food until the $\rho_{b1,2}$ and ω_l weights decreased further and the $\rho_{g1,2}$ and ω_r weights grew stronger (Fig 2 A and C (2)). The agent eventually approached for the real food and ignored the fake food and the whole process was repeated. Fig 2E (i) shows the VTA DA_{burst} (LTP) and (ii) DA_{tonic} (LTD) at the time step 24000 to 26000, when the agent has successfully learned and reversal learning begins respectively.

4 Discussion

In this paper we have introduced a new coding of dopaminergic activity in which bursting causes LTP in the target areas and tonic firing causes LTD. The limbic system circuitry has be shown to implement a process in which learning and reverse learning of reward stimulus associations can be achieved. However, the common interpretation to date has been that the dopamine activity is an error signal [1] where an increase in activity codes a positive error

(LTP) whereas a decrease in DA concentration codes a negative error (LTD). [9] has recently challenged this view and argued that this "dip" in dopaminergic activity cannot be recognised by dopaminergic receptors because it is too small. Thus another coding scheme has to be considered.

It is interesting to note that both a "dip" and a tonic elevation is supported by anatomy. The dip would be generated by the direct pathway from the NAcc shell to the VTA, whereas the tonic elevation would be implemented by the disinhibition of the VP. The latter pathway is considered to be stronger so that the resultant effect of the NAcc shell on the VTA is disinhibition. This also explains why in some single neuron recordings, a "dip" has been found [1] but not in population responses recorded in particular by voltammetry [10].

LTP via neuromodulators has recently been attributed to three factor learning where either just the D1 or both D1 and D2 receptor activation enables LTP [8], [11]. However, very little is known about how LTD is controlled by neuromodulators. There is evidence that tonic activity is the key to LTD in this case. [2] has argued that LTD is caused by the activation of D2 receptors while the D1 receptor is not activated. It is obvious that more research should be conducted on LTD modulated by dopamine.

Acknowledgement

The authors are grateful to Dorothea Hämmerle for constructive feedback.

References

[1] W. Schultz, P. Dayan, and P. Read Montague. A neural substrate of prediction and reward. *Science*, 275:1593–1599, 1997.

[2] S. Otani, H. Daniel, M. Roisin, and F. Crepel. Dopaminergic Modulation of Long-term Synaptic Plasticity in Rat Prefrontal Neurons. *Cerebral Cortex*, 13(11):1251–1256, November 2003.

[3] SB. Floresco, CD. Blaha, CR. Yang, and AG. Phillips. Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. *J Neurosci*, 21(8):2851–2860, Apr 2001.

[4] A. Egerton, RR. Brett, and JA. Pratt. Acute Δ^9-Tetrahydrocannabinol-Induced Deficits in Reversal Learning: Neural Correlates of Affective Inflexibility. *Neuropsychopharmacology*, 30:1895–1905, Febuary 2005.

[5] GF. Alheid and L. Heimer. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience*, 27(1):1–39, Oct 1988.

[6] KN. Gurney, TJ. Prescott, and P. Redgrave. The basal ganglia viewed as an action selection device. *In the Proceedings of the Eighth International Conference on Artificial Neural Networks*, 2-4:1033–1038, September 1998.

[7] SI. Wiener, R. Shibata, O. Tabuchi, E.and Trullier, SV. Albertin, and AB. Mulder. Spatial and behavioral correlates in nucleus accumbens neurons in zones receiving hippocampal or prefrontal cortical inputs. *International Congress Series*, 1250:274–292, 2003.

[8] John N.J. Reynolds and Jeffery R. Wickens. Dopamine-dependent plasticity of corticostriatal synapses. *Neural Networks 15 (2002) 507521*, 15:507–521, 2002.

[9] S. Cragg. Meaningful silences: How dopamine listens to the ACh pause. *Trends in Neuroscience*, 29(3):125–131, March 2006.

[10] RM. Wightman. Dopamine concentration transients: an unrecognized form of chemical communication. *FENS Forum Abstracts*, 3(A102.4), 2006.

[11] M. Lindskog, M. Kim, MA. Wikström, KT. Blackwell, and JH. Kotaleski. Transient Calcium and Dopamine Increase PKA Activity and DARPP-32 Phosphorylation. *PLOS Computational Biology*, 2:1045–1060, September 2006.