Modeling the Effects of Dopamine on the Antisaccade Reaction Times (aSRT) of Schizophrenia Patients

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Abstract. In the antisaccade task, subjects are instructed to look in the opposite direction of a visually presented stimulus. Controls can perform this task successfully with very few errors, whereas schizophrenia patients make more errors and their responses are slower and more variable. It has been proposed the fundamental cognitive dysfunction in schizophrenia involves prefrontal dopaminergic hypoactivity. We examine via computer simulations the effects of dopamine on the variability of aSRTs in a neural cortico-collicular accumulator model with stochastic climbing activity. We report the simulated aSRTs for the hypo-DA level have higher standard deviation and mean values than in the normal and hyper DA level. The simulated higher mean and standard deviation for the hypo-DA group resemble the performance differences in the antisaccade task observed in patients with schizophrenia and are in accordance with the theory of a hypo-DA state in the frontal cortical areas of patients with schizophrenia.

Keywords: Accumulator model, schizophrenia, antisaccade task, reaction times, dopamine, cortex, superior colliculus, pyramidal cells, inhibitory interneurons

1 Introduction

It has been hypothesized that patients with schizophrenia are hypo-dopaminergic in their prefrontal cortex and this state has been related to their poor performance in decision making and working memory tasks [10]. In this study, we

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V. Kůrková et al. (Eds.): ICANN 2008, Part II, LNCS 5164, pp. 290–299, 2008.

examine the effects of dopaminergic state of a cortical input to a collicular neural model by simulating its performance in the antisaccade task. In particular, we extend a biophysical cortico-collicular neural model [3], [4], [5], [6] and model the DA-D_1 effects on the generation of slowly varying climbing activity of the reactive and planned input decision signals of a SC model in the antisaccade task [1], [2]. Psychophysical parameters such as the decrease of mean and standard deviation, as well as the independence of the mean of error prosaccades observed among two groups of individuals are explained qualitatively through the variation of D_1 component of dopamine (DA) in the modeled prefrontal cortex (PFC). The groups that are compared to the simulations are: (1) a group 2006 normal subjects and (2) a group of 30 patients suffering from DSM-VI schizophrenia. This work combines and extends previous biophysical models [3], [4], [5], [6]. A much larger set of modeled empirical findings have been presented in [30].

2 Materials and Methods

2.1 Basis of the Model

In a modeling attempt of the antisaccade task [1],[2], Cutsuridis and colleagues [3], [8], [9] hypothesized that the preparation of an antisaccadic eye movement consisted of two cortically independent and spatially separated decision signals representing the reactive and planned saccade signals, whose linearly rising phases were derived from two normal distributions with different means and standard deviations. These two cortical decision signals were then integrated at opposite colliculi locations, where they competed against each other via lateral excitation and remote inhibition. A saccade was initiated when these decision processes, represented by the neuronal activity of SC buildup neurons with nonlinear growth rates varying randomly from a normal distribution, gradually build up their activity until reaching a preset criterion level. The crossing of the preset criterion level in turn released the "brake" from the SC burst neurons and allowed them to discharge resulting in the initiation of an eye movement. One of the model's predictions was that there is no need of a top-down inhibitory signal that prevents the error prosaccade from being expressed, thus allowing the correct antisaccade to be released. Moreover, the model offered a functional rationale at the SC neuronal population level of why the antisaccadic reaction times are so long and variable and simulated accurately the correct and error antisaccade latencies, the shape distributions and the error probabilities.

In a follow up of this study Cutsuridis and colleagues [4], [5], [6] modeled the decision signals with adjustable slopes with the population activities of two cortical networks of pyramidal neurons and inhibitory interneurons and predicted that only the currents NaP, AMPA and NMDA can produce the range of slope values of these decision signals in the collicular model.

In this study, we extend the latter model to incorporate and study the effects of dopamine on the conductances of the predicted NaP, AMPA and NMDA currents and simulate qualitatively a number of psychophysical parameters in the antisaccade task. Preliminary results of this study have been published in [7], [31].

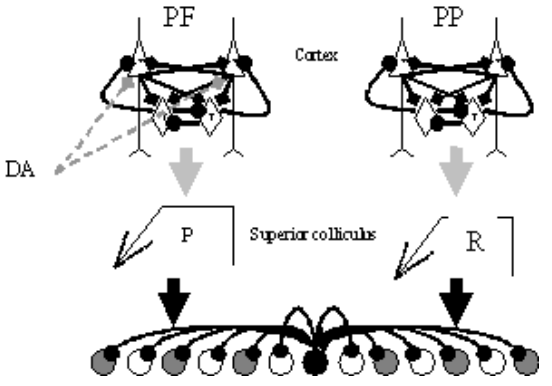

Fig. 1. Composite model architecture of cortical modules and superior colliculus module with reactive and planned inputs. Cortex: triangular neurons symbolize pyramidal cells and diamond shaped neurons symbolize GABAergic inhibitory inteneurons. Superior colliculus: black nodes are fixation cells, gray nodes are buildup cells, and white nodes are burst cells. The inputs to this layer are classified as reactive (R) and planned (P). DA: mesocortical dopamine innervation of prefrontal cortex (PFC). Their respective time course is shown schematically corresponding to an onset and offset.

2.2 Cortical Network Architecture

Standard Hodgkin-Huxley modeling techniques were used to simulate networks of single compartmental models of cortical pyramidal neurons and cortical inhibitory interneurons (IN). Pyramidal neuron membrane potential obeyed

$$CdV/dt = -(I_{leak}+I_{Na}+I_k+I_{NaP}+I_{k(Ca^{2+})}+I_{AMPA}+I_{NMDA}+I_{GABAA}+I_{inj})$$

with Cm = 1.2 μF/cm^2. GABAergic inhibitory interneuron membrane potential obeyed

$$CdV/dt = -(I_{leak} + I_{Na} + I_k + I_{AMPA} + I_{NMDA} + I_{GABAA} + I_{inj})$$

with Cm = 1.2 μF/cm^2. The synaptic currents I_{AMPA}, I_{NMDA}, I_{GABA-A} are represented by the equation $I_X = g_X$ (V - E_X), where the conductances are measured in mS/cm^2 and the reversal potentials in mV (see fig. 2 for numerical values). In addition I_{NMDA} contained a voltage dependent Mg^+ gate s(V)=1.08(1+0.19exp(-0.064V))$^{-1}$. The persistent sodium current (NaP) was modeled as in [14]. The calcium activated potassium current is given by

$$I_{k(Ca^{2+})} = g_{k(Ca^{2+})}Cai(V - E_{k(Ca^{2+})})$$

where the conductance $g_k(Ca^{2+})$=0.07 mS/cm^2 and the reversal potential $E_k(Ca^{2+})$=-95 mV. The variable Cai was the intracellular calcium concentration measured in μM [24]. Because very little is known about the detailed

connectivity of neurons and the associated synaptic strengths in the frontal and posterior parietal cortices, we intentionally kept the network model as general as possible. Two networks of 20 pyramidal cells and 4 GABAergic interneuron each were simulated. In each network, we assumed that all pyramidal cells and GABAergic interneurons were fully connected [5]. The output of each network was the average population activity of a homogenous population of neurons with identical connections. These outputs were then used as the input drives of the superior colliculus (SC) model [3].

2.3 Superior Colliculus Model

The superior colliculus model is a one-dimensional on-center off-surround leaky competitive integrator of the intermediate layer of the superior colliculus developed by [13] and extended by our group [3]. The neural architecture of the model is described in figure 1. Self-excitation and lateral inhibition is assumed between all neurons in both superior colliculi.

2.4 Dopamine Modification

The effects of DA-D_1 on the ion conductances were the following:

1. Enhancement of I_{NMDA} (replacing g_{NMDA} with $r_{NMDA}g_{NMDA}$) [15],[16]
2. Enhancement of I_{NMDA} for the inhibitory inteneurons (replacing g_{NMDA} with $r_{NMDA}g_{NMDA}$) [17]
3. Suppression of I_{AMPA} (replacing g_{AMPA} with $r_{AMPA}g_{AMPA}$) [15]
4. Enhancement of I_{NaP} (replacing V_{NaP} and E_{NaP} with $V_{NaP+\delta v}$ and $E_{NaP+\delta v}$) [18]
5. Reduction of $I_K(Ca^{2+})$ (replacing $g_K(Ca^{2+})$ with $r_K(Ca^{2+})g_K(Ca^{2+})$) [28]
6. No effect on the GABA current [16]

Symbol	Value
$C_p(\mu F/cm^2)$	1.2
$C_{inh}(\mu F/cm^2)$	1.2
$g_L(mS/cm^2)$	0.02
$g_{nmda}(mS/cm^2)$	0.17-0.25
$g_{ampa}(mS/cm^2)$	4
$g_{gaba}(mS/cm^2)$	1.45
$g_{NaP}(mS/cm^2)$	4
$g_{K(Ca)}(mS/cm^2)$	0.07
$E_L(mV)$	-65
$E_{nmda}(mV)$	0
$E_{ampa}(mV)$	0
$E_{gaba}(mV)$	-70
$E_{Nap}(mV)$	-55
$E_{K(Ca)}(mV)$	-95

Fig. 2. Synaptic and ionic model parameters. All the other values of the parameters used in the model were obtained from [5], [6].

	low	optimum	high
r_{NMDA}(pyramidal cell)	0.300-0.400	1.000-1.010	1.180-1.200
r_{NMDA}(interneuron)	0.001-0.080	1.000-1.300	2.500-3.000
r_{AMPA}	1.110-1.100	1.000-0.950	0.930-0.900
$r_{I(Ca)}$	1.110-1.100	1.000-0.950	0.930-0.900
δv(mV)	2.0-1.5	0-(-0.5)	-2.0-(-2.5)

Fig. 3. The effects of D_1 receptor activation on the ion channels

The detailed values of the above parameters for the three levels of dopamine (D_1) for which the network was simulated are given in fig. 3. The factor r represents the amount of available receptors for a given level of dopamine and it is incorporated in the simplified kinetic model theory [19]. All of the r-values given in fig. 3 are experimentally measured values of the given currents, in patch clamp experiments, under the action of D_1 agonists-antagonists [20],[14]. In the case of the persistent sodium current no effect on the amplitude of the current was observed but rather a shift of the potential at which the maximum amplitude occurred. The GABA current remained unchanged under the action of D_1 agonists-antagonists [20].

3 Experimental Setup

The control data used in this study were collected in an antisaccade task [1],[2]. Details of the experimental procedure used for the collection of these data are described therein [1],[2]. The same experimental setup as in [1],[2] was used for collecting the reaction times of the group with schizophrenia. The mean and standard deviation of the aSRT's for each group was calculated using Ratcliff

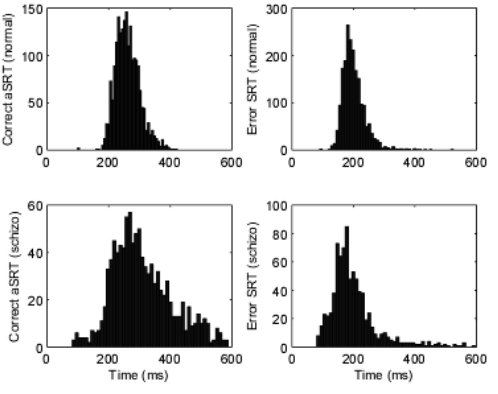

Fig. 4. (Top-left)Histogram of correct antisaccade reaction times (aSRT) of normal subjects. (Top-right) Histogram of error prosaccade reaction times (SRT) of normal subjects. (Bottom-left) Histogram of correct antisaccade reaction times (aSRT) of schizoophrenia subjects. (Bottom-right) Histogram of error prosaccade reaction times (SRT) of schizophrenia subjects.

analysis [12]. The aSRT's for each subject were sorted and then divided into four quantiles, the mean for each quantile was calculated among each group. This procedure produced a distribution of aSRT's, which was considered to be the average distribution of the group under question. From these distributions all the features of the group reaction times could be calculated, mean and standard deviation of the whole set of answers as well as mean and standard deviation of the correct antisaccades and error prosaccades separately. Figure 4 depicts the correct and error SRT histograms of the normal and schizophrenia populations.

4 Results

In a network of 20 pyramidal neurons and 4 inhibitory interneuron and for each of the three dopamine levels, for each simulation, 480 reaction times were obtained from the collicular model. The values of the rising phase of the signals were obtained from the cortical model described above. A variation for the conductance of the NMDA current in the pyramidal neurons gave rise to a bell-shaped rising phase (slope) in the spiking of the cortical network. The spiking of the cortical network was linearly fit with a line from the beginning of the spiking to its maximum value. Then this bell-shaped distribution of gradients was fed into the superior colliculus model to produce the antisaccade reaction times for each dopamine level. In these simulations we assumed that the signal of the error prosaccades was not affected by dopamine, since it is not being produced by the prefrontal cortex, whereas the signal of the correct antisaccades is modified by dopamine (D_1).

4.1 Effects on the Mean of the Antisaccade Reaction Times

The effects of (D_1) dopamine modification of the cortical signal was to decrease the mean of the aSRT's as indicated by Fig. 5 (Left) of the simulated results for

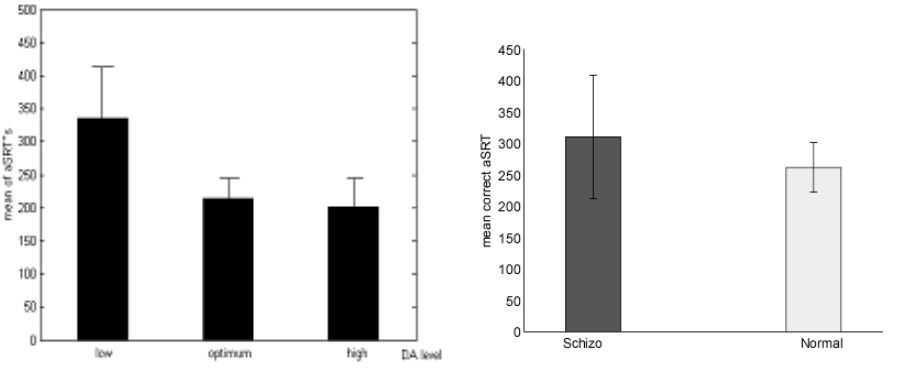

Fig. 5. (Left) Qualitative simulation results indicating a decrease of mean of the aSRT's as D_1 level increased. (Right) The experimental data of the mean of the aSRT's for the two groups (normal and patients) show a similar decrease.

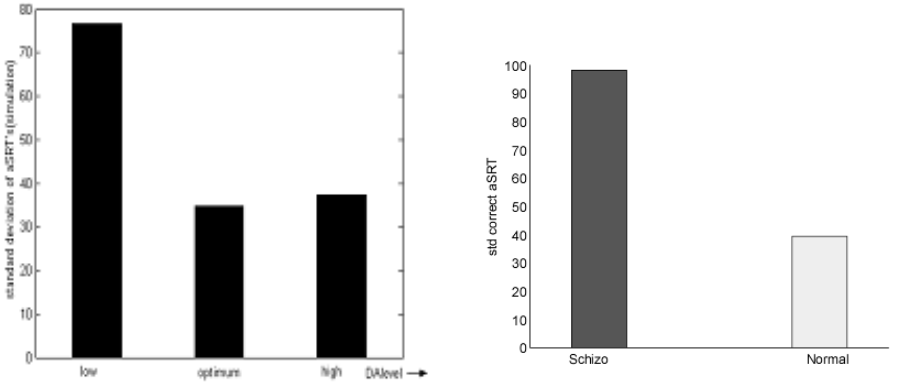

Fig. 6. (Left) Qualitative simulation results showing a decrease of the standard deviation of the aSRT distribution as dopamine level is increased. (Right) The experimental data for the groups under study show a similar decrease.

the three levels of dopamine. In Fig. 5 (Right) the experimental data of the two groups show a similar decrease in mean aSRT [21],[22].

4.2 Effects on the Standard Deviation of the Antisaccade Reaction Times

The effect of (D_1) modification of the cotical signal was an increase in the standard deviation of the aSRT's as the dopamine level was decreased (Fig. 6 Left). This observation was resembled qualitatively the observed increase of the standard deviation in the patient group (Fig 6 Right) [21].

5 Conclusion

The psychophysical data and results of the simulations presented in this study provide evidence that there is a modification of the cortical signal (prefrontal cortex) due to dopamine component D_1, and that this modification can explain the increase in the mean and variance in the antisaccade reaction times produced by patients.

Other models concerning the modification of cortical signals by a D_1 action of dopamine can be found in the literature concerning working memory tasks, the inverted U-shape of firing of the PFC neurons as well as the operation of the PFC under the action of psychostimulants [24],[14],[25],[26]. In all of the above studies the action of D_1 on the cortical currents was modeled and in all of the studies the qualitative action of dopamine on ionic currents was the same.

The effect of dopamine on D_2 receptors was not investigated in this study. This effect could be significant at high dopamine levels [28] and may interpret other sets of data regarding the function of the prefrontal cortex when high levels

of dopamine are observed. Hence we could conclude that the lack of a principal neurotransmitter in the prefrontal cortex can have very significant effects in decision making, generating poorer performance in such tasks.

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