Computational Insights into Schizophrenia: Linking Hyperactive D2 Receptors with Belief Updating Impairments

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Genetics are recognized as a significant risk factor in schizophrenia [1], and computational modeling studies have highlighted deficits in belief updating as a key aspect of the disorder and an underlying cause of delusion [2]. In particular, the patients often show strong priors on environmental volatility. However, the intricate mechanisms bridging these genetic risk factors and belief updating deficits remain poorly understood. Our challenge here was to build a biologically plausible neural network that provides a link between genetic risk factors and impaired belief updating.

In constructing our schizophrenia model, we first focused on the prefrontal cortex (PFC)-mediodorsal thalamus (MD) circuit, given mounting evidence implicating alterations in these regions in schizophrenia pathology [3]. Drawing from experimental findings demonstrating the involvement of MD neurons expressing D2 receptors in cognitive flexibility [4], the known association of D2 receptor genes with heightened schizophrenia risk [5], and the predominant mode of action of antipsychotic treatments as dopamine antagonists at D2 receptors [6], we simulated schizophrenia by reducing the excitability of MD neurons to mimic the hyperactive D2 receptors in Schizophrenia.

To investigate the belief updating process, we consider a probability reversal task, in which the reward structure switches in blocks for every 200 trials. Our normal thalamocortical model is capable of flexibly switching across blocks and its PFC-MD connections learn the contextual model of the world, a neural signature for continual learning. We further mathematically analyze the model and deduce that under mild assumptions, the model approximates CUSUM algorithm, an algorithm known for its optimality in detecting environmental changes [7]. On the other hand, our schizophrenia model exhibited a stronger bias towards environmental volatility, prompting exploratory behaviors following contextual switches. By mathematical analysis, we deduce that the decreased excitability makes the evidence accumulation dynamics leaky and therefore the model can sporadically switch, consistent with the qualitative results in Schizophrenia patients [2]. Additionally, decreased excitability in MD compromised the ability of PFC-MD connections to accurately learn the environmental model. To address this impairment, we applied current injections to MD to restore activity levels to a range conducive to Hebbian plasticity. Remarkably, the rescue model demonstrated reduced exploratory behavior following switches and exhibited a higher threshold for MD activity switching, indicative of a diminished bias towards environmental volatility. Moreover, the rescue model exhibited improved learning of the environmental model within its PFC-MD connections. These findings suggest a potential mechanism for utilizing deep brain stimulation at a novel site to mitigate schizophrenia symptoms.

Model We consider the neural network of PFC and MD and its projection to downstream premotor cortex (ALM) with rate neurons of the form $\tau\frac{dx}{dt} = -x + f(Wx + I)$. We stipulate PFC to jointly represent action and outcome association while MD computes a conditional likelihood of a context given the ongoing history of action-outcome associations, $p(c|a_{\leq t}, r_{\leq t})$ based on the discovery of context representation in MD [4]. Specifically, the MD circuit can be written as:

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$$\tau \frac{dx_1^{md}}{dt} = -x_1^{md} + d * (f(wx_1^{md} - wx_2^{md}) + I_1^{pfc/md}) + I^{rescue} \tag{0.1}$$

$$\tau \frac{dx_2^{md}}{dt} = -x_2^{md} + d * (f(wx_2^{md} - wx_1^{md}) + I_2^{pfc/md}) + I^{rescue} \tag{0.2}$$

where $w = \frac{1}{2}$, x_c^{md} is the activity of MD neuron tuned to context c, $d = 0.85$ in Schizophrenia model and 1 in normal model, $I^{rescue} = 0.45$ in rescue model and 0 otherwise, and the nonlinearity $f(x) = x + 1$ if $-1 \leq x \leq 1$, 2 if $x > 1$ and 0 if $x < -1$.

We show that when the PFC-MD connections learn the contextual model of the environment, the above dynamics approximate CUMSUM algorithm (see next section). In order to learn the contextual model, we consider the following Hebbian learning rule, $\Delta V_{(c,A_t)}^{pfc/md} \propto g(x_c^{md}) x_{(A_t,-)}^{pfc}$, to allow the PFC-MD connections to learn the contextual generative model of the environment where $V_{(c,A_t)}^{pfc/md}$ are PFC-MD synapses that connects prefrontal neurons tuned to action A_t and MD neurons tuned to context c, $x_{(A_t,-)}^{pfc}$ are the activities of prefrontal neurons tuned to action A_t and g is a nonlinearity.

However, our thalamocortical projection does not merely serve as a simple contextual switch. When animals encounter high contextual uncertainty, their behaviors should be more exploratory since they are not sure which context they are currently in. In other words, thalamocortical projections must include a mechanism to modulate the downstream corticostriatal networks in a manner proportional to contextual uncertainty. It has been shown in past experimental works that the MD thalamus modulates cortical functions via two types of interneurons, VIP amplifying the context relevant connectivity and PV inhibiting context relevant activities[8]. Therefore, we included both thalamic projections into our model:

$$\tau \frac{dx_{(c,a)}^{bg}}{dt} = -x_{(c,a)}^{bg} + g(x_{(c)}^{vip} - x_{(c)}^{pv}) V_{c,a}^{pmct/bg} \circ x_{(c,a)}^{pmct}. \tag{0.3}$$

where $x_{(c,a)}^{bg}, x_{(c,a)}^{pmct}$ are activities of BG and premotor cortex tuned to context c and action a respectively, $V_{c,a}^{pmct/bg}$ is the strength of corticostriatal synapse, $x_{(c)}^{vip}$ is the VIP-mediated mechanism which receives MD inputs tuned to preferred context, $x_{(c)}^{pv}$ is the PV-mediated mechanism which receive MD inputs tuned to opposing context and g is the nonlinearity.

In addition to modulating the exploratory behaviors, contextual uncertainty should modulate learning as well. When the contextual uncertainty is high, naive dopamine dependent plasticity can easily attribute an association to the wrong context. To circumvent this issue, we allow interneuron-mediated inputs to gate the plasticity of corticostriatal models as well based on the discovery that interneuron mediated pathways modulate cortical plasticity [9, 10]. Specifically, we have

$$\delta_{(c)} = r - \Delta V_{c,A_t}^{pmct/bg}, \Delta V_{c,A_t}^{pmct/bg} \propto g(x_{(c)}^{vip} - x_{(c)}^{pv}) \delta_{(c)} \tag{0.4}$$

$V_{c,a}^{pmct-bg}$ is the strength of corticostriatal synapse, $x_{(c)}^{vip}$ is the VIP-mediated inputs which receive MD inputs tuned to preferred context, $x_{(c)}^{pv}$ is the PV-mediated inputs which receive MD inputs tuned to opposing context and $\delta_{(c)}$ is the dopamine activities tuned to context c.

Result We run the full model, the impaired model and the rescue model in the probability reversal task (Figure 1a, b). We see that the regret of the impaired model is significantly worse than that of the full model and the rescue model improves the impaired model's performance (Figure 1c). If we look at the behaviors right after a block switch, the impaired model shows longer

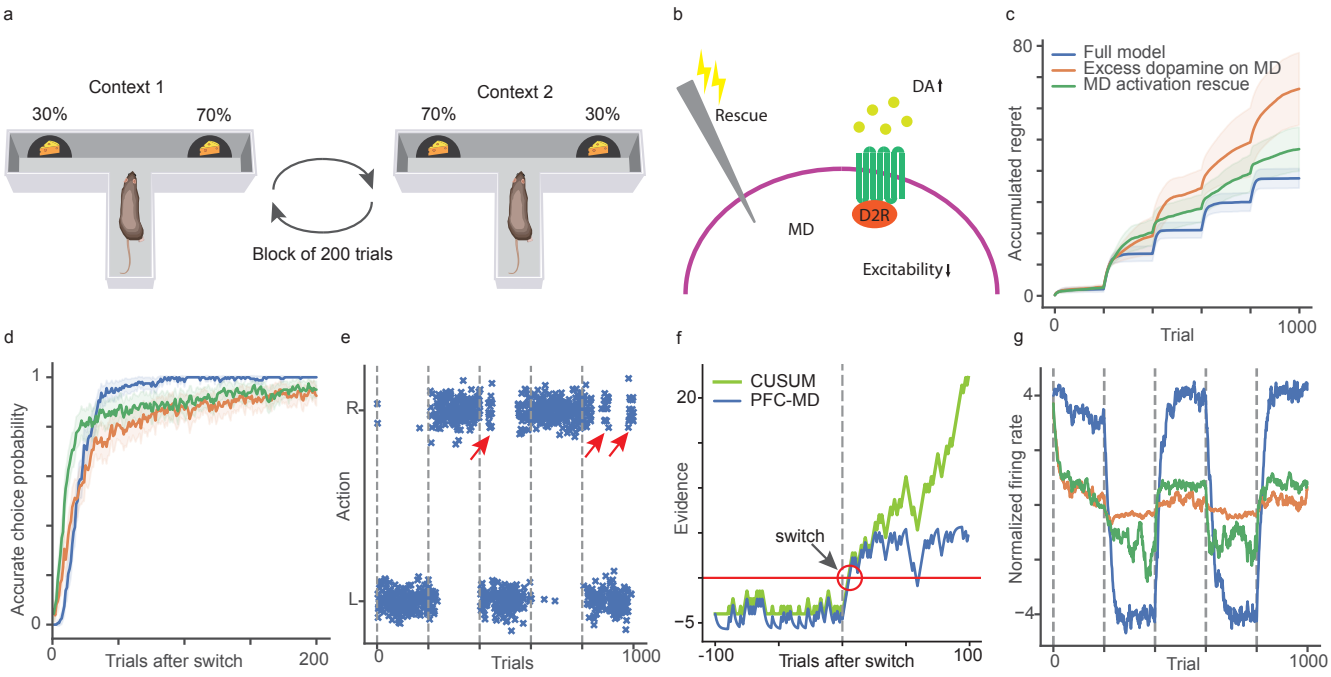

Figure 1: A D2R hyperactive model in MD replicates qualitative results in Schizophrenia patients and MD current injection rescues the symptoms. a. The probability reversal task we model. **b.** A schematic on the D2R hyperactive model and current injection rescue. **c.** The averaged regret of the full model, the impaired model and the rescue model. **d.** The averaged accurate choice probability after a block switch. **e.** A sample of actions taken by the impaired model. **f.** Comparison between PFC-MD circuits and CUSUM algorithm. **g.** Difference in firing rates between two MD populations tuned to different contexts.

exploratory behaviors. Furthermore, if we look at the sample actions, we discover that the impaired model frequently commits to the other actions for a small block instead of prolonged exploration (Figure 1e). This indicates that the impaired model contains strong prior on the environmental volatility, consistent with past Schizophrenia literature [11]. To understand mathematically how the full model and the impaired model compute the context, we prove the following theorem:

Theorem 5. *The full model can be approximated to a drift-diffusion process with thresholds at* $\pm 2\tau$. *The impaired model can be approximated as a leaky drift-diffusion process with thresholds* $|\langle \pm (I_1^{pfc/md} - I_2^{pfc/md}) \rangle| \ll 2\tau$. *Furthermore, let* $X = x_1^{md} - x_2^{md}$, $X_0 = -2a\tau$ *and* $S_0 = X_0 + 2\tau$. *If* $I_1^{pfc/md}(t) = \log P(A_t, r_t | c = 1), I_2(t)^{pfc/md} = \log P(A_t, r_t | c = 2)$, $I_1^{pfc/md} - I_2^{pfc/md} \ll a$, *then the evolution of* S_t *follows the classical CUMSUM algorithm* $S_n = \max(0, S_{n-1} + I_1^{pfc/md} - I_2^{pfc/md})$.

As we can also see from the simulation that our PFC-MD circuits approximate CUMSUM algorithms well (Figure 1f). From the drift-diffusion process perspective, we can give two reasons on why the impaired model has a strong prior on environmental volatility: first, the evidence accumulation threshold becomes much smaller and second, the leaky dynamics constantly forgets previous evidence toward the current context.

To further understand the impaired mechanisms and how to treat the symptoms, we examine its PFC-MD connections which encode environmental models and corticostriatal connections which encode action values. We observe that although all model learns the contextual action values (Figure 2c), the impaired model completely fails to learn the contextual model of the environment (Figure 2a). This inability to learn the environmental model might suggest why delusion arises in

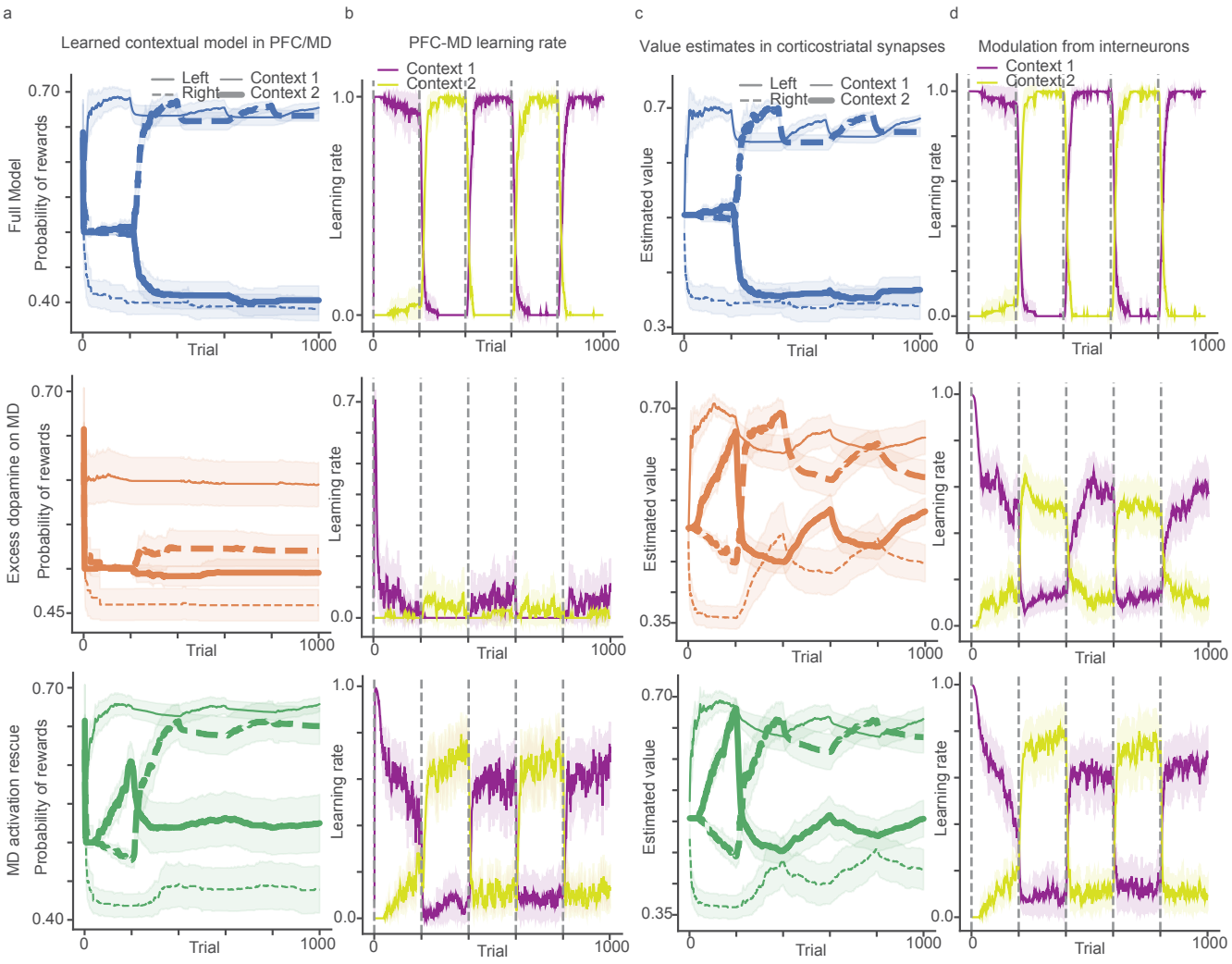

Figure 2: The impaired model is incapable of learning the proper model of the environment while the rescue model recovers the model learning by restoring plasticity between PFC and MD. First, second and third rows indicate the full model, the impaired model and the rescue model respectively. **a.** Learned contextual model of the environment decoded in PFC-MD connections. **b.** Normalized learning rates of PFC-MD connections. **c.** Learned contextual value estimates in corticostriatal connections. **d.** Corticostriatal learning rate modulation from cortical interneurons.

these patients. To investigate why the impaired model cannot learn the environmental model, we examine the learning rate in PFC-MD connections (Figure 2b). Indeed, because of the decreased MD excitability, the MD activities are not enough to drive Hebbian learning. By injecting current into MD to restore the plasticity, the rescue model successfully learns the model of the environment (Figure 2a, b). Furthermore, the within-context learning rates in corticostriatal synapses are also much slower in the impaired model (Figure 2d). This is consistent with the slow update within a context observed in Schizophrenia patients [2].

This work provides a link to connect hyperactive D2 receptors at MD with various cognitive symptoms in Schizophrenia and provides a computational ground for a novel deep brain stimulation site for treatment.

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