Coglink networks reveal computational mechanisms of uncertainty management and its perturbation in schizophrenia.

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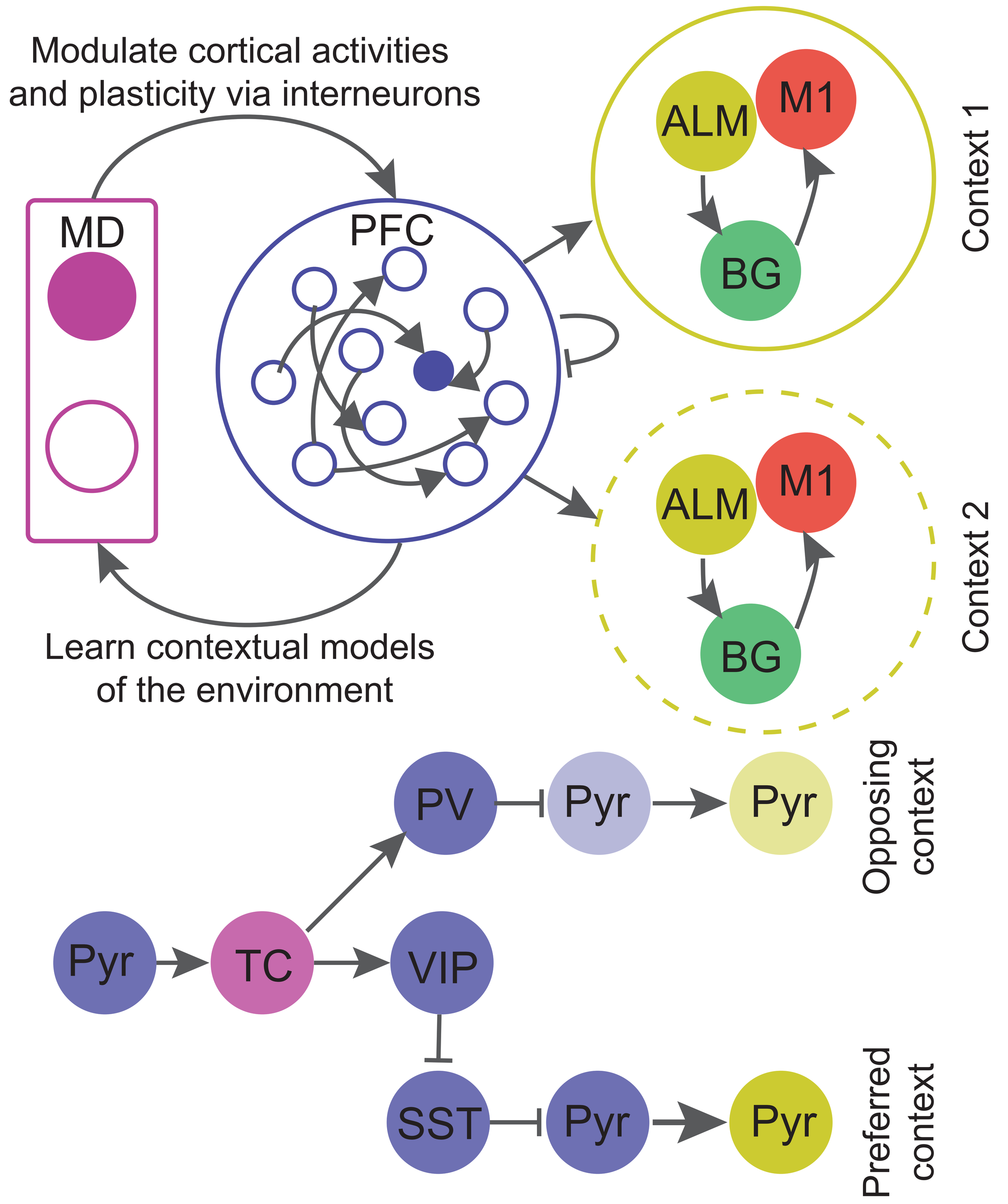
Introduction

- Genetic constitutes a significant risk in Schizophrenia (SZ) [1] and computational modeling has shown deficits in belief-updating processes as a key aspect of the disorder [2].
- However, the intricate mechanisms bridging these genetic risk factors and belief updating deficits remain poorly understood.
- Our model, CogLinks, capable of linking mechanisms with normative behaviors, offers an avenue to study such connections.
- CogLinks model prefrontal cortex (PFC) and mediodorsal thalamus (MD) which not only involve in belief-updating processes but also show altered functional couplings in patients [3].
- We consider a probability reversal task in which patients show slow switching upon reversal and elevated win-switch rate (choosing an alternative action after receiving rewards) [4].

A mechanistic neural model



PFC-MD connections **learn the contextual environmental model** through Hebbian plasticity and **infer the context in MD** via recurrent dynamics. MD then **contextually modulates cortical activity [5] and plasticity [6]** through interneurons, in which VIP neurons amplify context-relevant cortical connectivity while PV neurons suppress context-irrelevant information.

KEY REFERENCES

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[2] Baker, S. C.. Brain. 2019.
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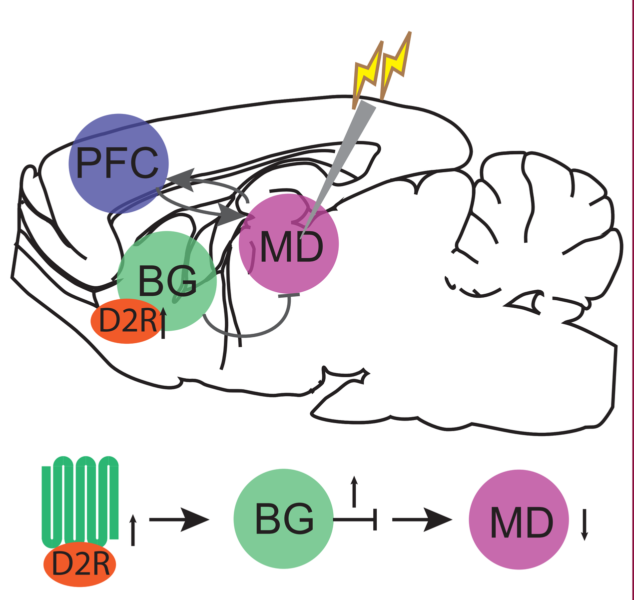
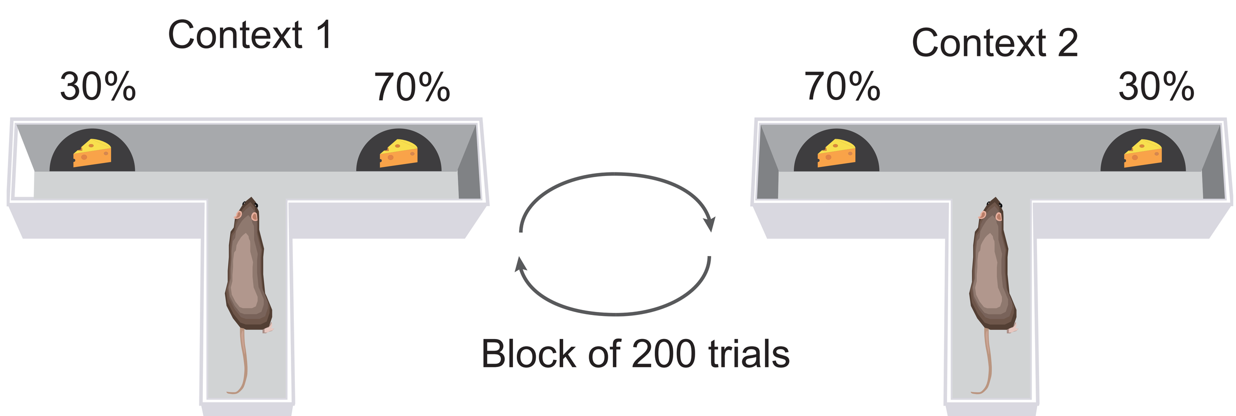
[5] Rikhye, R. V. et al. Nat Neurosci. 2018.
[6] Canto-Bustos, M. et al.. J Neurosci. 2022.
[7] Abi-Dargham, A. et al.. PNAS. 2000.
[8] Zhou, T. et al.. bioRxiv. 2024.

Schizophrenia model and rescue model



We consider a model with **hyperactivation of striatal D2 receptors** (D2Rs) because most SZ patients show elevated striatal D2Rs expression [7]. Since the abundance of D2Rs increases the inhibition from BG to thalamus, we model SZ by **reducing the excitability of MD** to mimic strong BG inhibition. To rescue the model, we **inject a small current in MD**.

Task

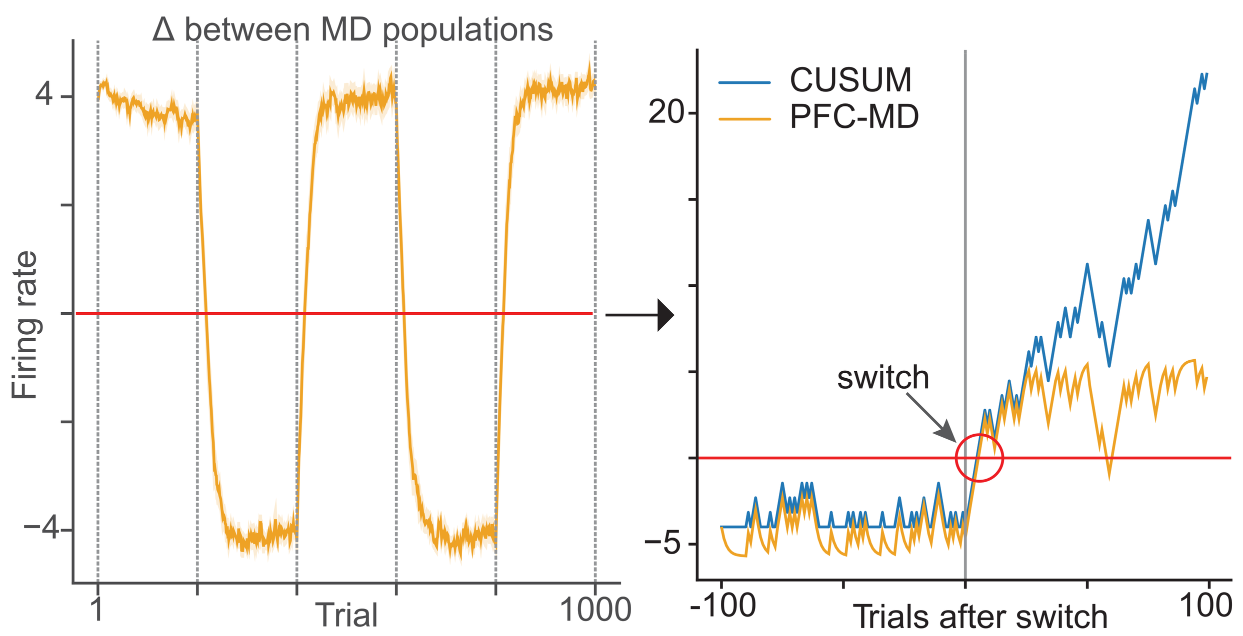


Approximation to normative model

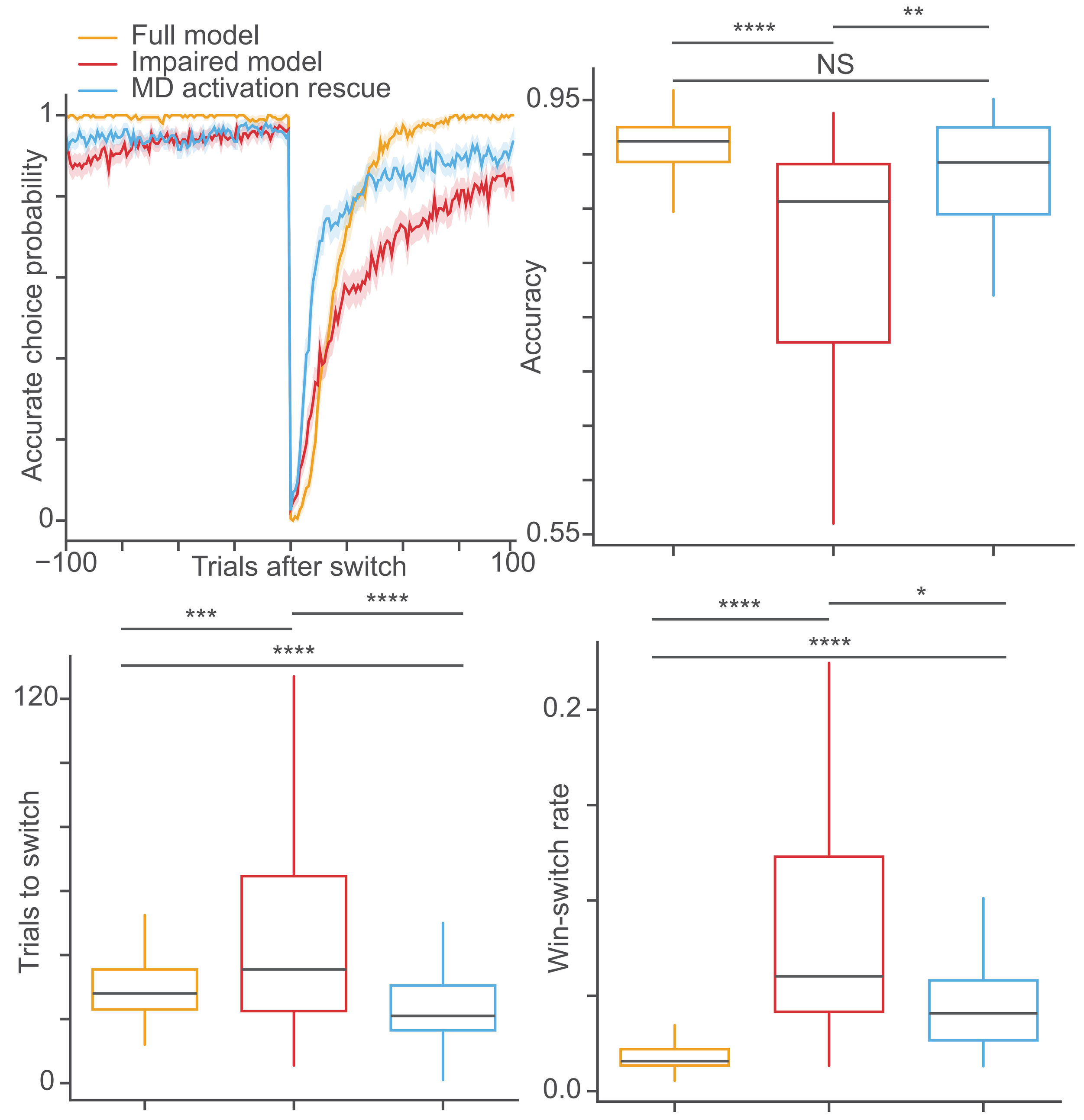
- It is usually difficult to understand a mechanistic model on a computational level due to its complexity.
- To overcome this, we mathematically approximate our mechanistic model to a novel normative model and analyze its functions and performance.

Theorem 1. *After PFC-MD synapses learn the contextual generative model $P(a_t, r_t|c)$, our PFC-MD circuit approximates to a multiple change points generalization of CUSUM algorithm, an algorithm that is known to detect single environmental changes optimally [10].*

Our PFC-MD circuit approximates a normative model that **detects sequential environmental changes optimally**.

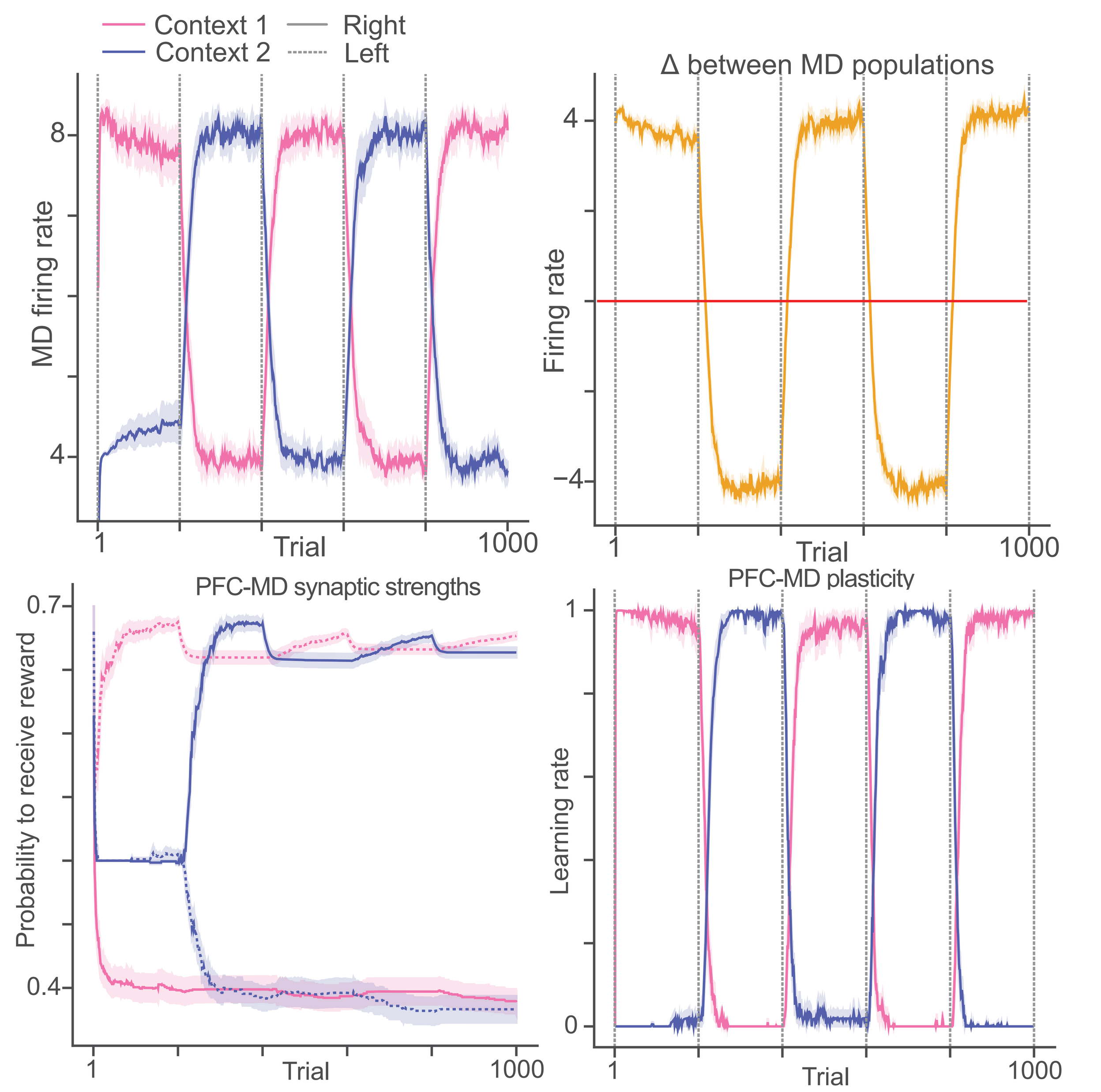


Behaviors

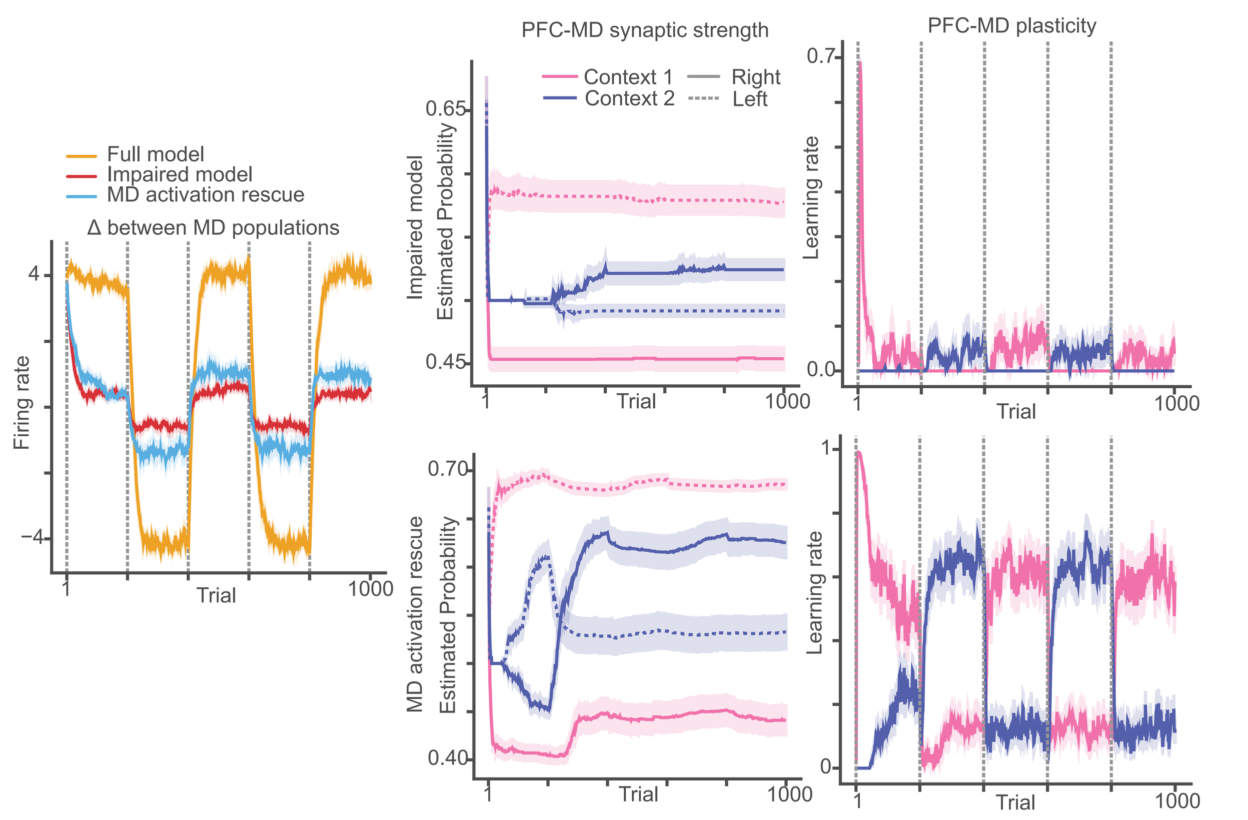


- Our SZ model has much lower accuracy with high variance compared to the normal model.
- It also shows slow switching upon reversal and elevated win-switch rates, consistent with the behavioral findings in patients.
- Our rescue model rescues the behaviors, consistent with the MD activation experiment on SZ-related mouse model [8].

MD activity tunes to contexts and contextually modulates PFC-MD plasticity



Neural signatures of SZ/rescue models



We first investigate the MD activity and the normative model:

- The normative model of SZ model has a much lower threshold.
- This shows that SZ model has a strong prior on environmental volatility and therefore much higher win-switch rates.

Theorem 2. *The threshold of the normative theory of the SZ model is* $T_{SZ} = \frac{2\beta_{d2}}{1-\beta_{d2}}|\langle I_1^{pfc/md} - I_2^{pfc/md}\rangle| \approx 0.64 \ll 4 = T_{normal}$, *much smaller than the threshold of the normal model. Furthermore, the corresponding normative model is a leaky integrator, further strengthening the prior on environmental volatility.*

Both MD activity and the corresponding normative model show SZ model has **a strong prior on environmental volatility**, potentially contributing to **paranoia**.

We then examine PFC-MD connectivity and plasticity:

- Indeed, compared to the normal model, SZ model struggles to learn the correct contextual model of the environments.
- The improper learning happens because of the abnormally low learning rate, potentially due to low MD excitability.
- By injecting the current into MD, the rescue model reinstates the proper learning of the environmental model.

The PFC-MD connections in SZ model are unable to learn proper environmental model, potentially contributing to **delusion**. By injecting current in MD, the rescue model recovers the proper learning of contextual model.

Conclusion

- Our work links neural mechanisms, normative models and cognitive (dys)functions together in a single framework.
- Our CogLink network approximates a normative model that detects environmental changes optimally.
- Our SZ model shows idiosyncratic behaviors observed in patients, including slow switching and elevated win-switch rates.
- Both MD activity and the normative model shows SZ model has a strong prior on environmental volatility (potentially paranoia).
- PFC-MD connectivity in SZ model cannot learn the proper environmental model, potentially contributing to delusion.
- By injecting the current in MD, the rescue model not only rescues the behaviors but also reinstates proper PFC-MD learning in environmental models.