SIMULATION OF GLUTAMATE DYSFUNCTION ON CINGULO-FRONTAL NETWORK

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- Numerical results
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MOTIVATION

THE CINGULO FRONTAL CORTEX

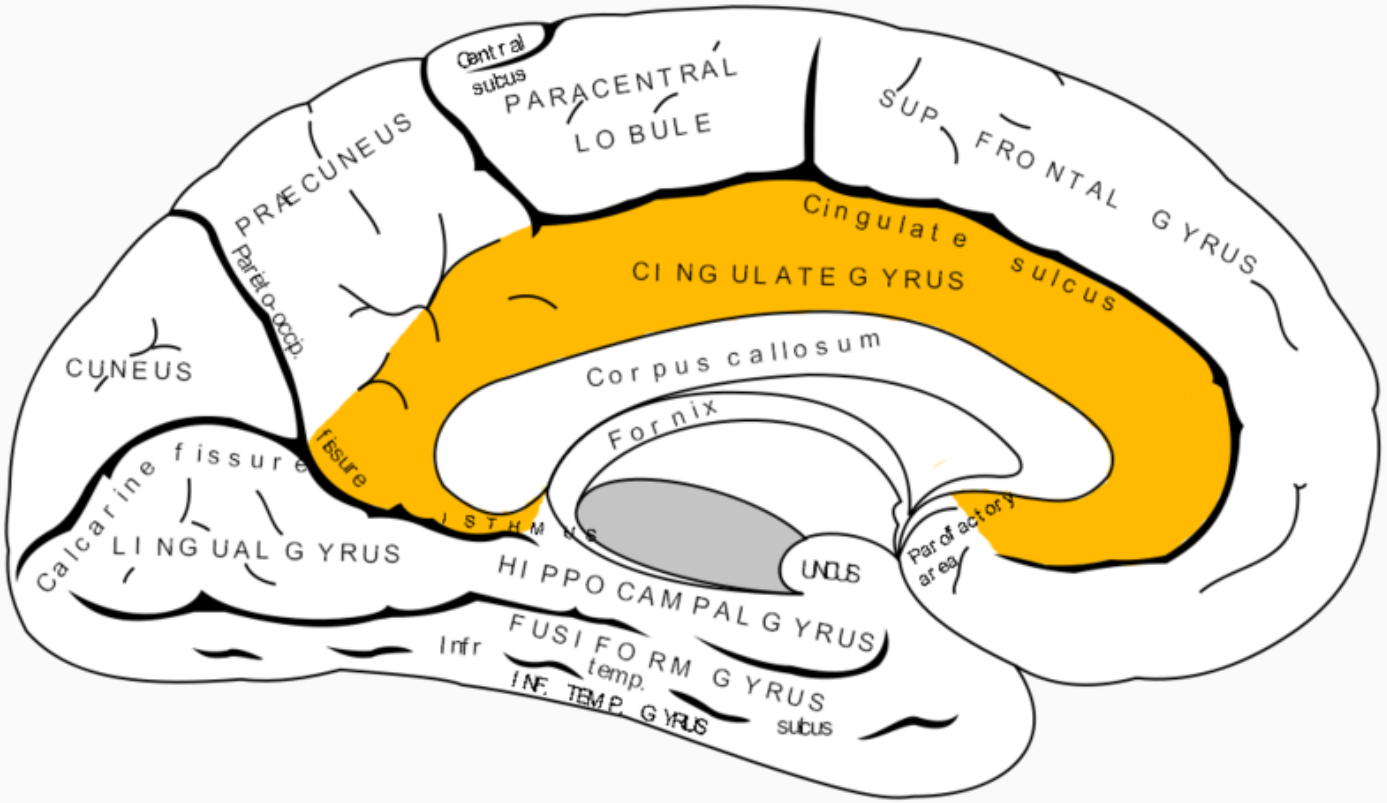

Figure 1 - The cingulato frontal cortex.

Cingulate cortex includes specific processing modules for sensory, motor, cognitive and emotional information.

DORSOLATERAL PREFRONTAL CORTEX

Studies suggests that the dlPFC involved in cognitive processes such as working memory , but dlPFC is also involved in action selection tasks without a strict working-memory component.

But the role of the dlPFC in the control of behavior remains a topic of ongoing controversy, and some theories advocates that the dlPFC works with the ventrolateral prefrontal region to perform the maintenance of the working memory tasks.

ANTERIOR CINGULATE CORTEX

Studies attribute specific functions such as error detection, anticipation of tasks, attention, motivation, and modulation of emotional responses to the ACC.

Furthermore, multiple studies point at the ventral anterior cingulate cortex (vACC) as the critical hub within this distributed network of regions that drives alterations in system dynamics in major depression disorder (MDD).

Major depression disorder (MDD)

MDD is the most common of all psychiatric disorders affecting millions of people worldwide. It is characterized by persistent negative mood and selective deficits in cognitive, circadian, and motor functions.

Neuroimaging studies reveal hyperactivity of vACC in MDD patients, but this hyperactivity sometimes is reduced after clinical treatments, such as Selective serotonin reuptake inhibitor (SSRI) medication.

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Original Article

ORIGINAL ARTICLE

A Computational Model of Major Depression: the Role of Glutamate Dysfunction on Cingulo-Frontal Network Dynamics

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Abstract

Major depression disease (MDD) is associated with the dysfunction of multinode brain networks. However, converging evidence implicates the reciprocal interaction between midline limbic regions (typified by the ventral anterior cingulate cortex, vACC) and the dorso-lateral prefrontal cortex (dlPFC), reflecting interactions between emotions and cognition. Furthermore, growing evidence suggests a role for abnormal glutamate metabolism in the vACC, while serotonergic treatments (selective serotonin reuptake inhibitor, SSRI) effective for many patients implicate the serotonin system. Currently, no mechanistic framework describes how network dynamics, glutamate, and serotonin interact to explain MDD symptoms and treatments. Here, we built a

Cingulo-frontal network model

CINGULO-FRONTAL NETWORK MODEL

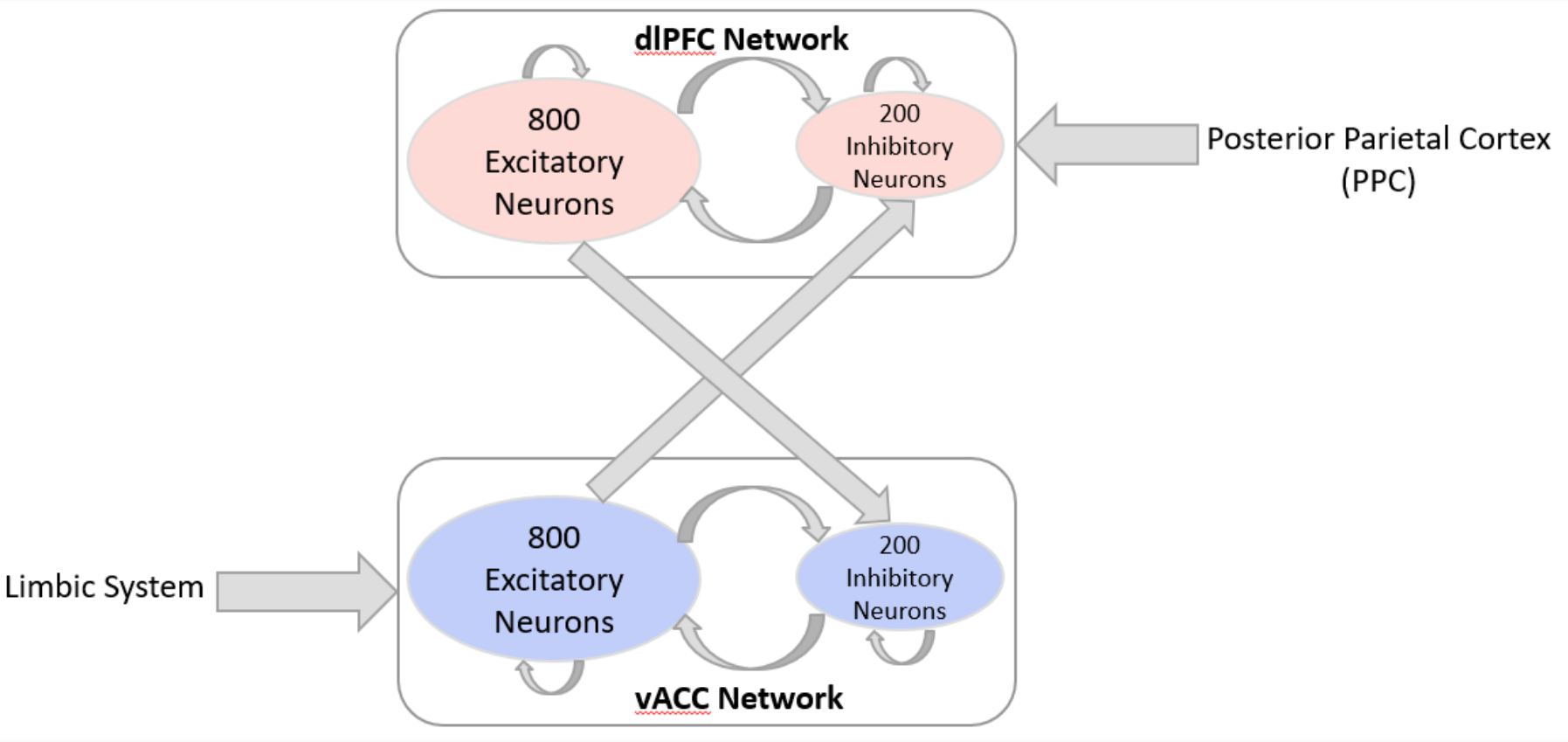


Figure 2 - Network diagram.

DYNAMICS OF THE MODEL

The membrane potential of each one of the neurons followed

$$C_m \frac{dV_m}{dt} = -g_m(V_m(t) - V_L) - I_{syn}(t) \tag{1}$$

with resting potential $V_L = -70mV$, leak conductance g_m and membrane capacitance C_m. The total synaptic current $I_{syn}(t)$ was given by

$$I_{syn}(t) = I_{AMPA,rec}(t) + I_{NMDA,rec}(t) + I_{GABA}(t) + I_{AMPA,ext}(t) \tag{2}$$

Where the conductance-based postsynaptic currents were modeled according to

$$I_{syn}(t) = g_{syn} s(V_m(t) - V_{syn}) \tag{3}$$

where $g_s$yn is the synaptic conductance, s is a synaptic gating variable and $V_s$yn is the synaptic reversal potential. The synaptic gating variable was modeled as

$$\frac{ds}{dt} = \frac{-1}{\tau_{receptor}} s + \alpha_s x(1 - s) \tag{4}$$

with

$$\frac{dx}{dt} = \frac{-1}{\tau_x} x + \sum_i \delta(t - t_i) \tag{5}$$

For the NMDA synapses, the conductance was voltage dependent, so the current for NMDA synapes was given by

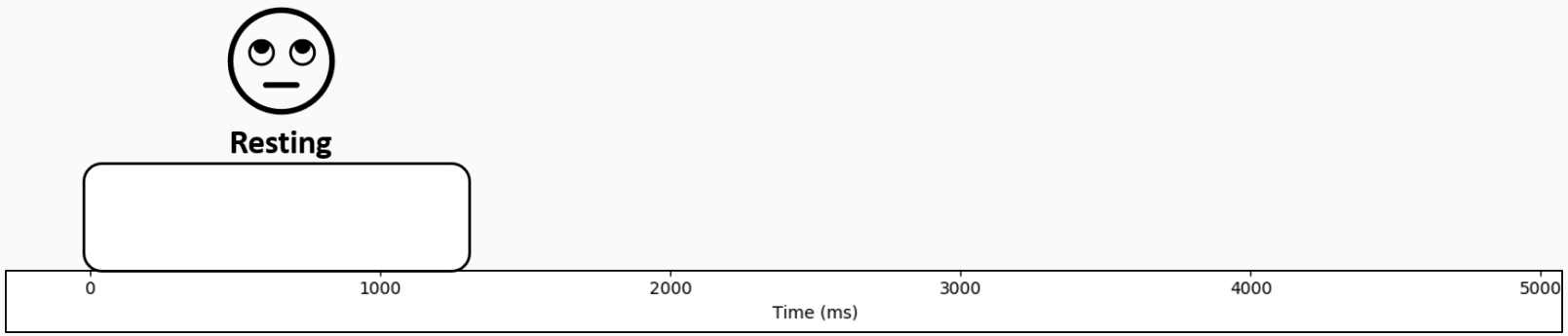
$$I_{NMDA}(t) = g_{NMDA} s \frac{V(t)}{1 + Mg^{2+} \frac{e^{-0.062V(t)}}{3.57}} \tag{6}$$

DYNAMICS OF THE MODEL

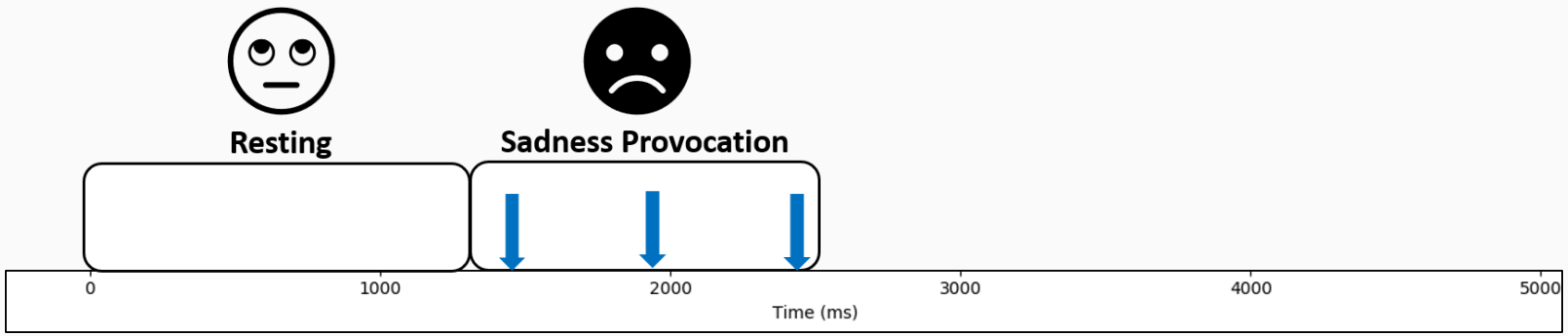
In MDD networks, we simulated deficient glutamate reuptake by increasing the time constant of synaptic glutamate decay τ_{AMPA}, $\tau_{\text{AMPA}} = 2.05\text{ms}$ (mild MDD), $\tau_{\text{AMPA}} = 2.1\text{ms}$ (moderate MDD), and $\tau_{\text{AMPA}}2.15\text{ms}$ (severe MDD).

NUMERICAL RESULTS

SIMULATION TASKS



SIMULATION TASKS



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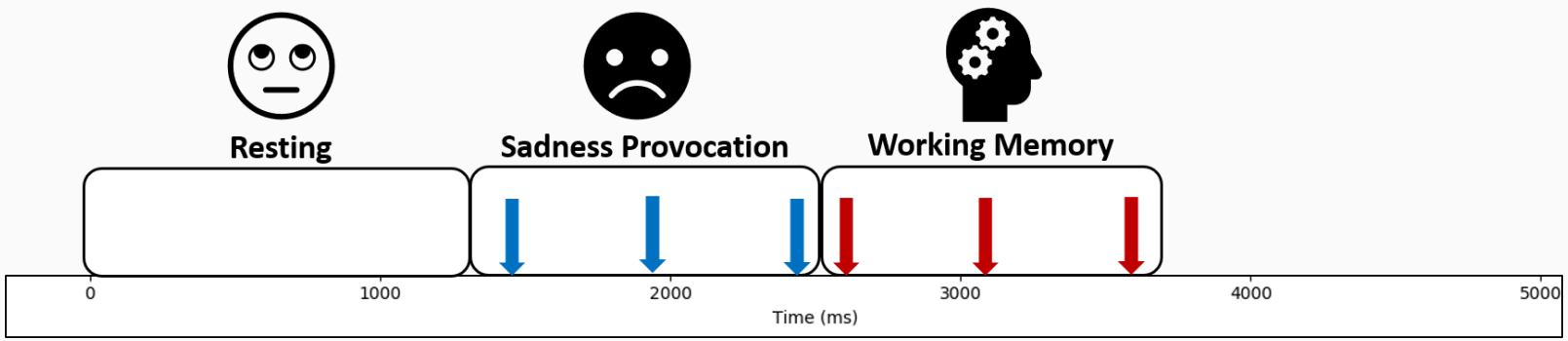

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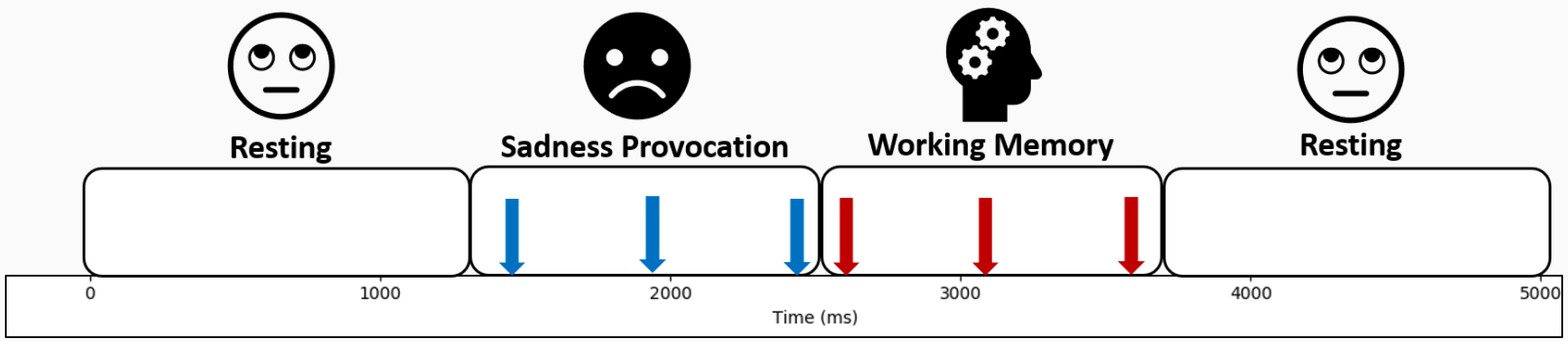


SIMULATED CASES

The four simulated cases are:

- Healthy
- Mild MDD: 2.5% slow-down in glutamate decay in the vACC.
- Moderate MDD: 5% slow-down in glutamate decay in the vACC.
- Severe MDD: 7.5% slow-down in glutamate decay in the vACC.

SIMULATION OF HEALTHY CASE

Figure 3 - Healthy network operation.

SIMULATION OF MILD MDD

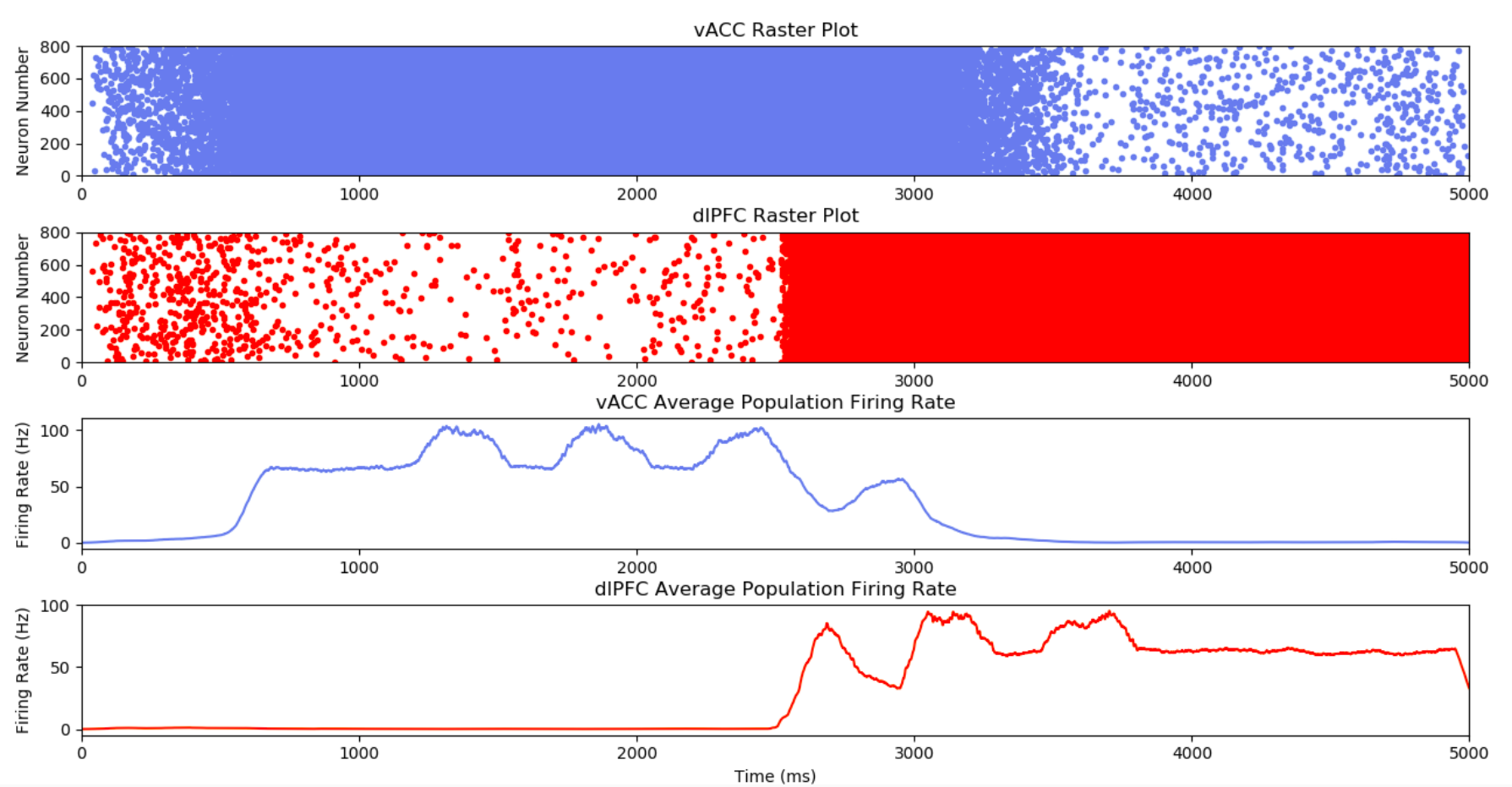


Figure 4 - Mild MDD network operation.

SIMULATION OF MODERATE MDD

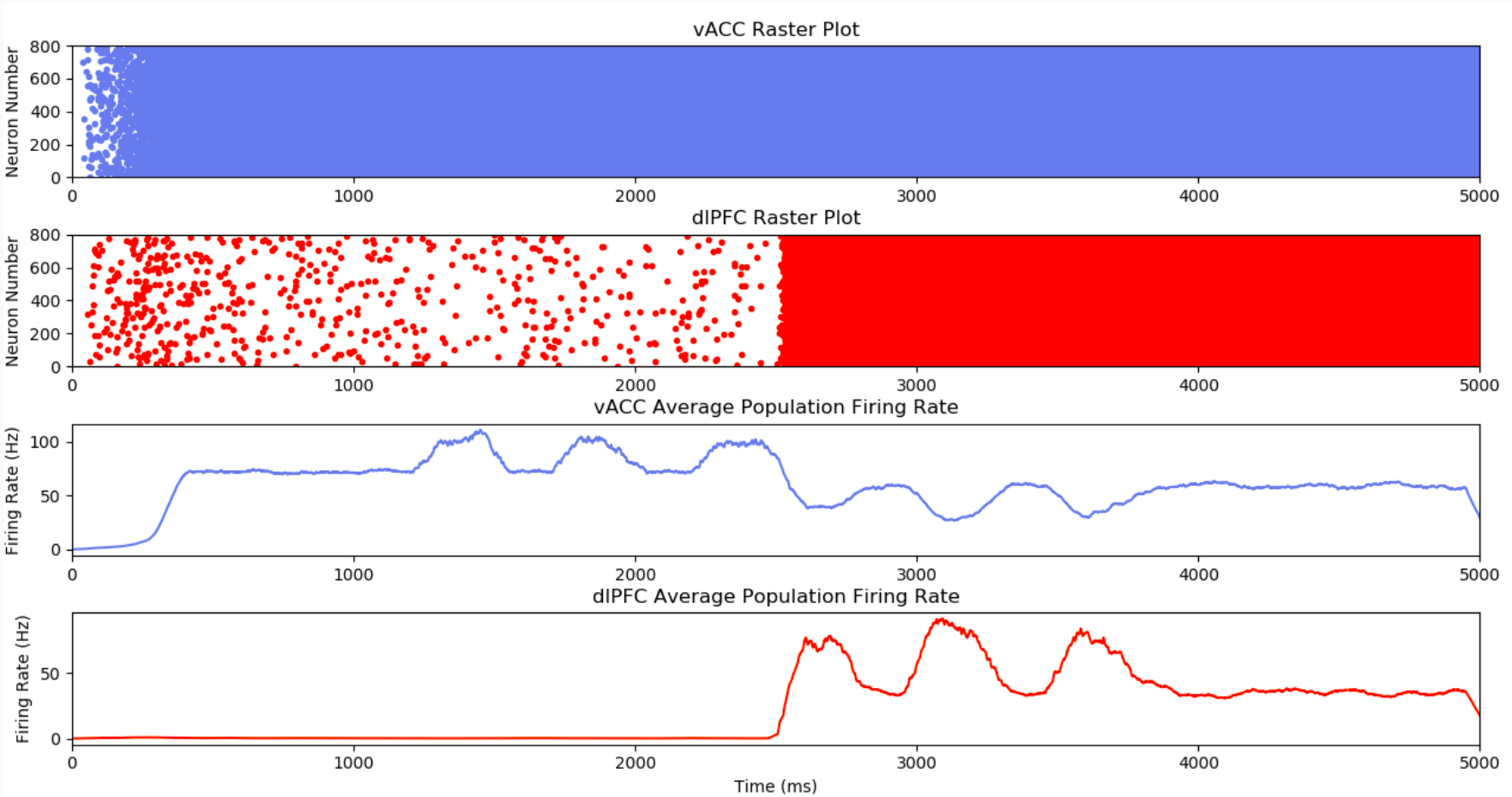


Figure 5 - Moderate MDD network operation.

SIMULATION OF SEVERE MDD

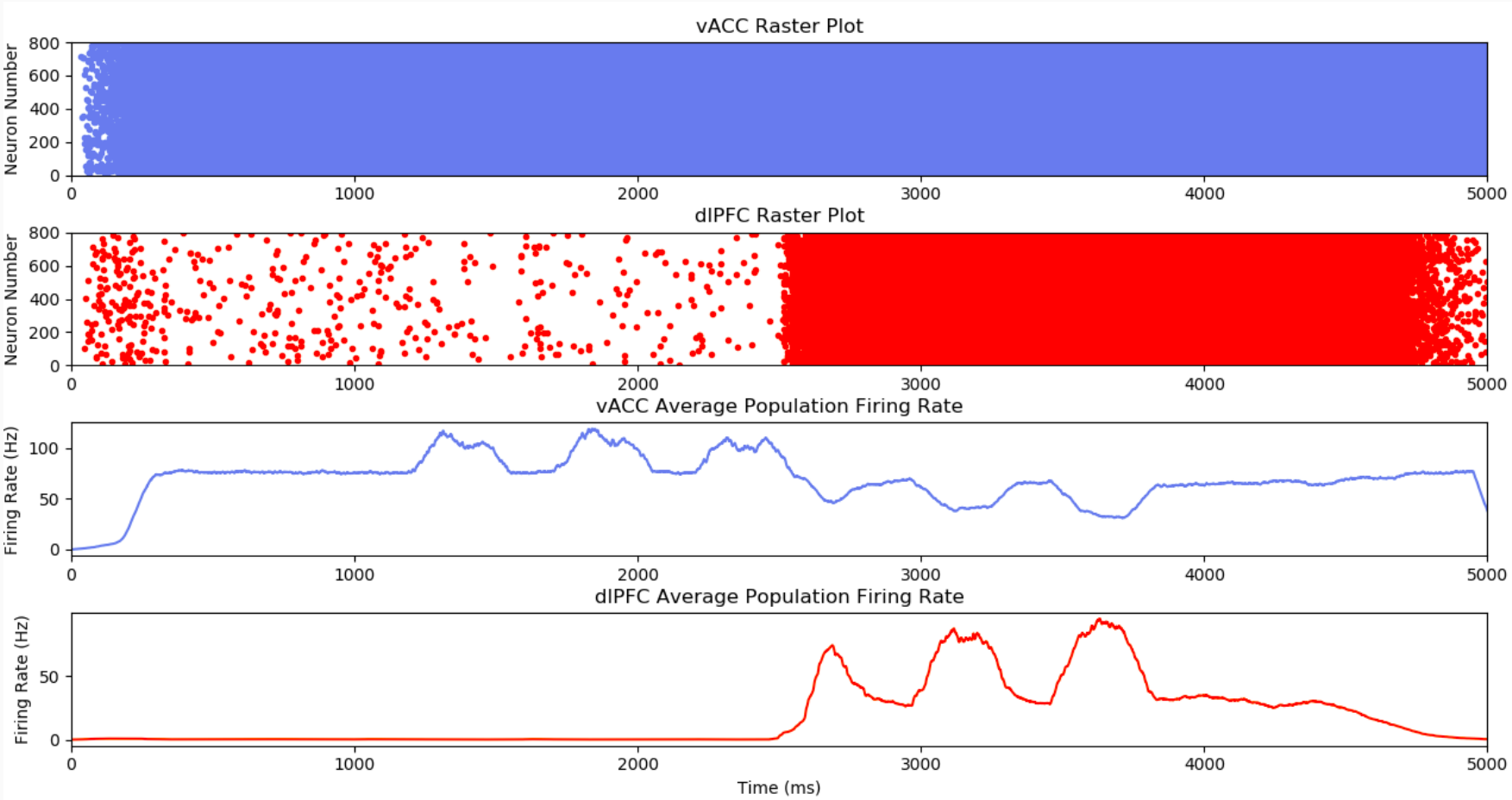
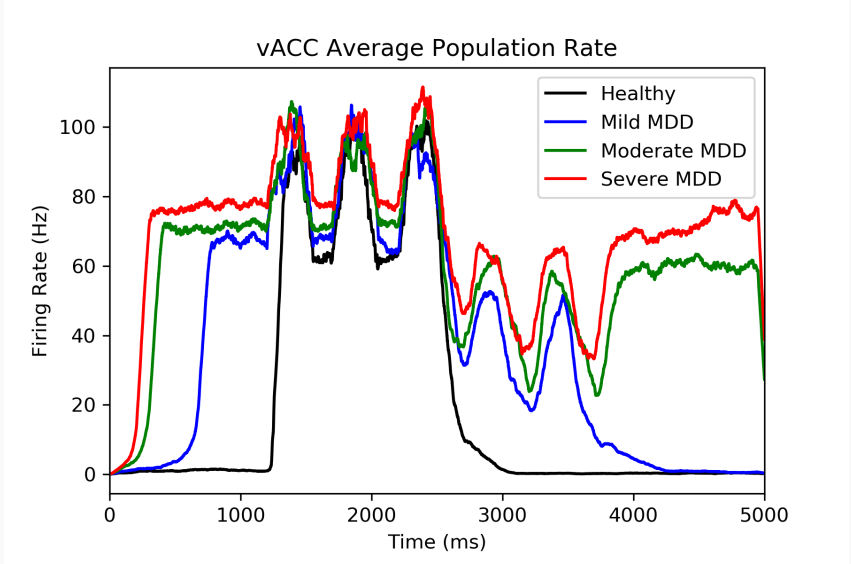


Figure 6 - Severe MDD network operation.

POPULATION RATES



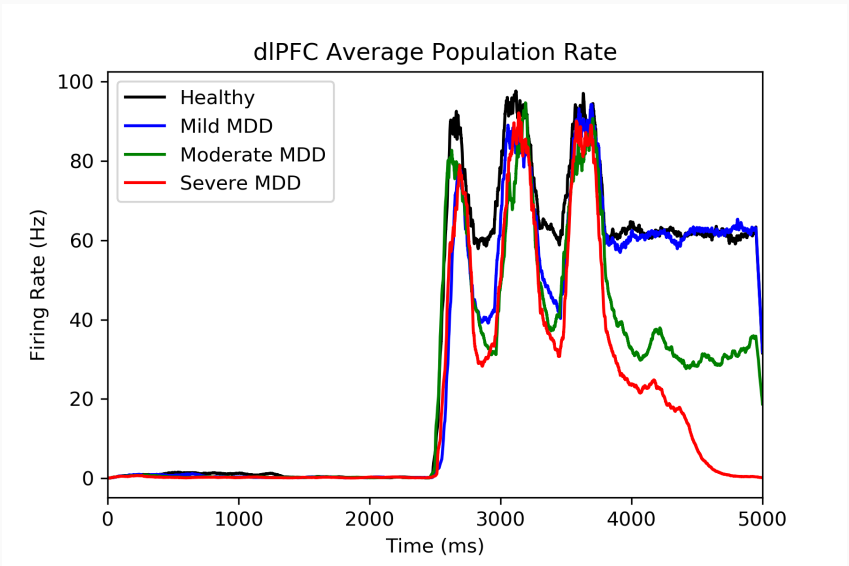


Figure 7 - Average population rates of networks.

TREATMENTS

We simulated two types of treatments:

- Selective Serotonin Reuptake Inhibitor (SSRI): Small hyperpolarization of vACC excitatory neurons.
- NMDA Receptor Antagonist: Decrease in the strength of the NMDA synaptic conductance of the vACC excitatory neurons by a factor of 10 %.

TREATMENT RESULTS OF MILD MDD

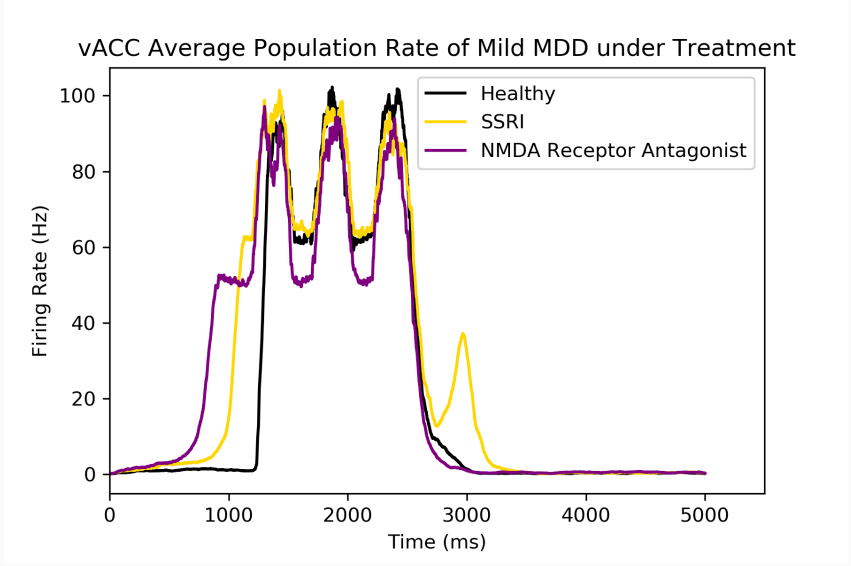
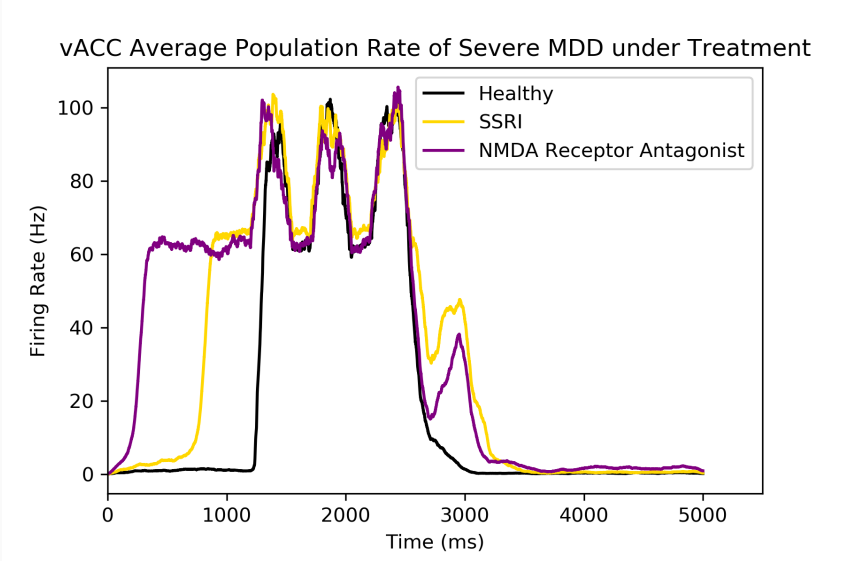


Figure 8 - Treatment results for a mild MDD case.

TREATMENT RESULTS OF SEVERE MDD



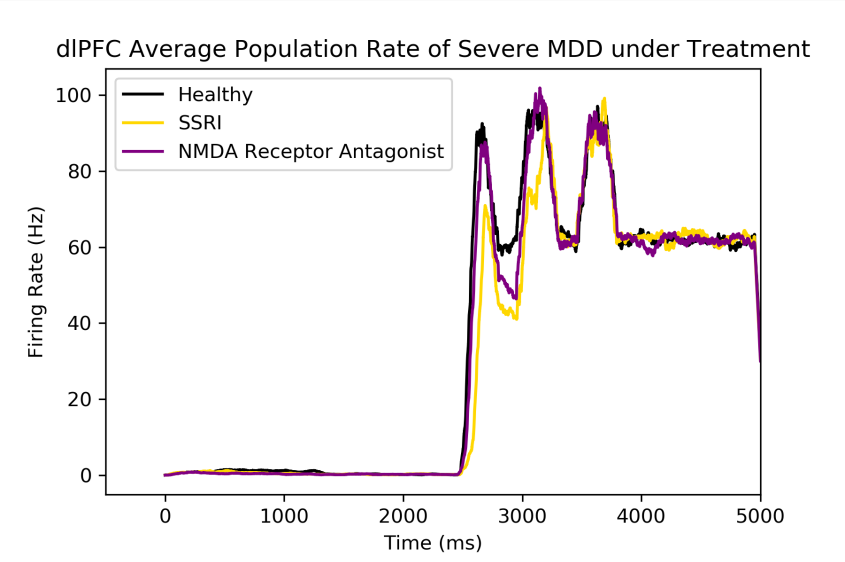


Figure 9 - Treatment results for a severe MDD case.

We analyze the synchronization of the membrane potentials in the network using the Kuramoto order parameter, which is given by

$$R(t) = \left| \frac{1}{N} \sum_{i=1}^{N} (\cos(\theta_i) + i\sin(\theta_i)) \right| \tag{7}$$

where θ_i is the phase associated to the i-neuron, and N is the number of neurons considered.

SYNCHRONIZATION PATTERNS

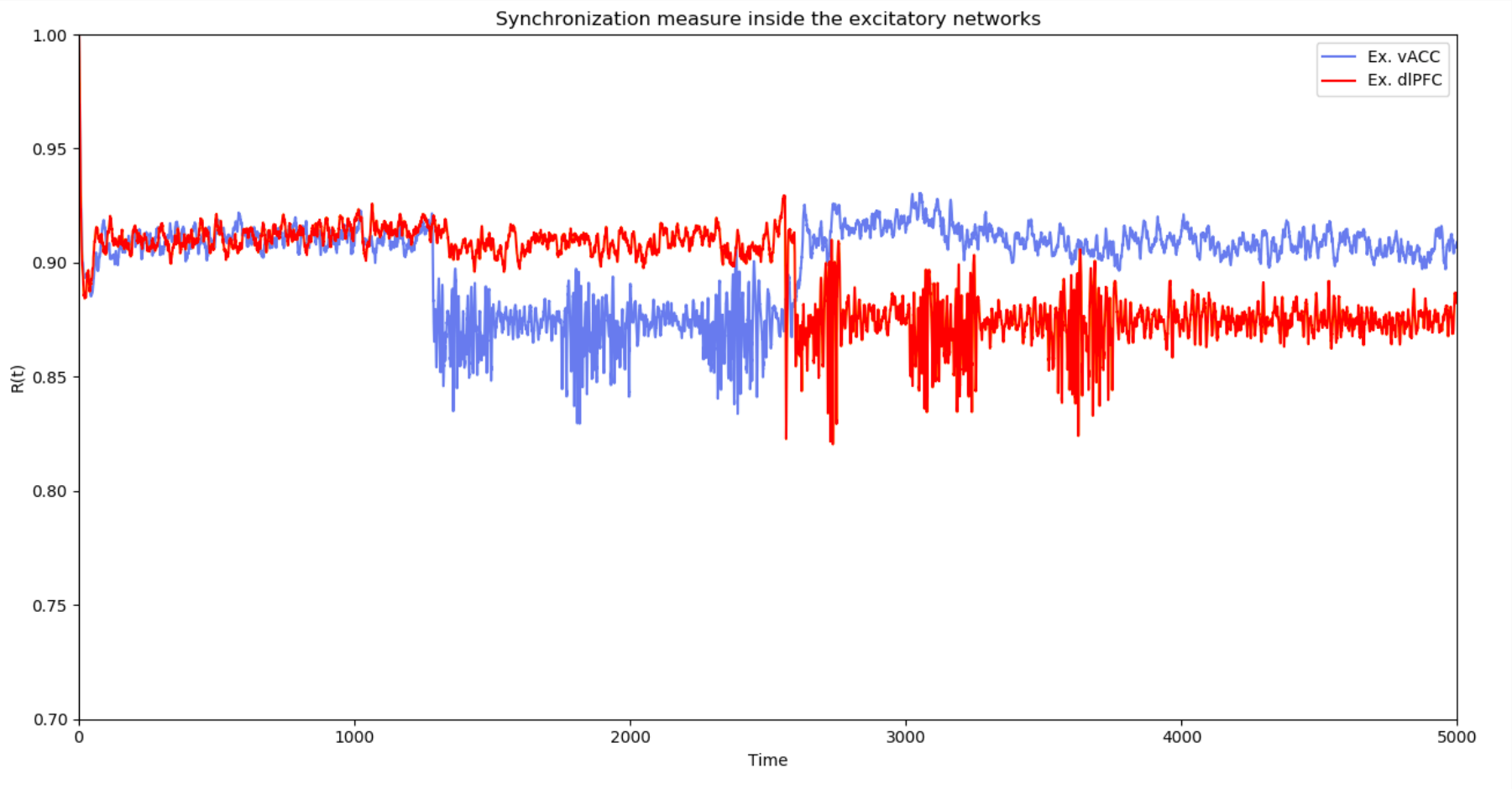


Figure 10 - Kuramoto order parameter for a healthy network.

SYNCHRONIZATION PATTERNS

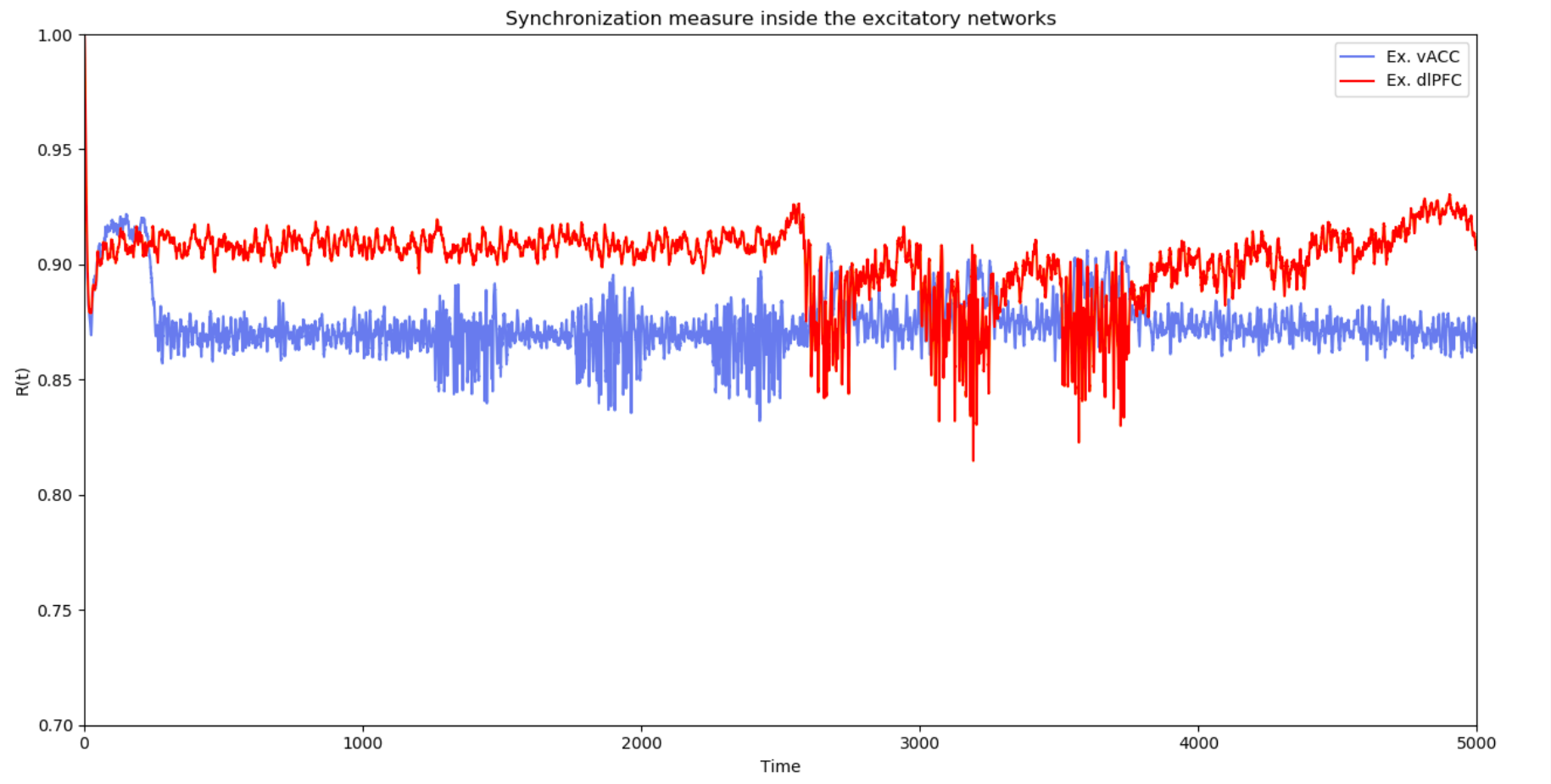


Figure 11 - Kuramoto order parameter for a severe MDD network.

CONCLUSIONS

SUMMARY

- A model was implemented to describe the glutamate dysfunction in the cingulo-frontal network.

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- Both of the treatments, SSRI and NMDA receptor antagonist, showed good results.

SUMMARY

- A model was implemented to describe the glutamate dysfunction in the cingulo-frontal network.
- This model was able to reproduce the symptoms caused by glutamate dysfunction such as the hyperactivity in the vACC and the lack of ability to switch from emotional to cognitive processing.
- Both of the treatments, SSRI and NMDA receptor antagonist, showed good results.
- Finally, we conclude that the synchronization patterns is also affected by the glutamate dysfunction.

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Thank you for your attention!

Questions?