Influence of NMDA and GABA synaptic dysfunction on the evoked gamma oscillations in a computational model of schizophrenia

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Background. Schizophrenia is a psychiatric disorder which is characterized by delusions and hallucinations, and affects thoughts, behaviour and emotions. Major neuronal degeneration is not observed in schizophrenic patients, but abnormalities in cortical circuits are present. These abnormalities are reflected in impaired EEG gamma frequency (30–80 Hz), being crucial for many processes including sensation, perception, working memory, and attention. NMDA and GABA synaptic dysfunction is proposed as one of the possible mechanisms underlying the gamma oscillatory deficits in schizophrenia.

Materials and Methods. We used a computational modeling approach to investigate the joint influence of NMDA and GABA synaptic dysfunction on gamma oscillations in cortex. We employed a computational model of a spiking neural network composed of 800 pyramidal neurons, 150 regular-spiking interneurons, and 50 fast-spiking interneurons. All cells were randomly interconnected. Network neurons received independent Poisson noise input at 4 Hz and 40 Hz drive excitatory stimulation. Fast-spiking interneuron GABA receptor-gated channel time constant was increased and NMDA receptor-gated channel synaptic conductance was decreased to represent synaptic dysfunction in schizophrenia.

Results. Reducing NMDA conductance enhanced gamma power, and increasing decay time constant of GABA receptor-gated channel attenuated gamma generation in a network. The effect of synaptic GABA alteration was more profound.

Conclusions. NMDA and GABA synaptic dysfunction leads to the impaired gamma frequency oscillations in a spiking neural network of cortex. Computational modeling approach is a powerful tool to understand complex non-linear dynamical systems and intrinsic mechanisms of neuronal network activity in healthy and diseased brain.

Keywords: schizophrenia, spiking-neural network, gamma oscillations, NMDA receptor, GABA receptor

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Computational modeling of schizophrenia

INTRODUCTION

Schizophrenia is a disabling chronic mental illness that affects one percent of the general population. Schizophrenic patients suffer from hallucinations, delusions, thought and movement disorders, apathy, neurocognitive deficits such as poor attention, distractability, and impaired working-memory (Mueser, McGurk, 2004). Morphological abnormality in the temporal cortex, the limbic and frontal cortex are commonly observed in schizophrenia (Lewis et al., 2005; Iritani, 2013). Impaired cortical network processing is reflected in altered oscillatory gamma frequency (30–80 Hz) response during sensory stimulation and spontaneous neuronal activity (Gallinat et al., 2004; Uhlhaas and Singer, 2013). For example, physiological experiments show that altered gamma rhythm response in schizophrenic patients is most evident when given periodic click train stimuli at 20 Hz and 40 Hz: the oscillation power is increased at 20 Hz and decreased at 40 Hz (Vierling-Claassen et al., 2008; Griskova-Bulanova et al., 2012).

N-methyl-D-aspartate (NMDA) receptor and γ-aminobutyric (GABA) acid receptor dysfunction of cortical networks, reduced connectivity, and deficient neuromodulation are proposed as the possible mechanisms underlying the gamma oscillatory deficits in schizophrenia. The NMDA receptor hypofunction model of schizophrenia was inspired by the observation that NMDA agonists induce transient symptoms of psychosis and hallucinations (e.g., Olney et al., 1999; Coyle, 2012; Cohen et al., 2017). The NMDA receptors are also critical for the development and function of cortical GABAergic interneurons that are responsible for recurrent inhibition to the pyramidal neurons and play an important role in gamma frequency generation (Gonzalez-Burgos, Lewis, 2012). In addition, post mortem studies of schizophrenic patients showed that GABAergic interneurons have altered properties, captured by the extended synaptic decay time constant (Lewis et al., 2005; Vierling-Claassen et al., 2008).

Theoretical models of prefrontal cortex networks have been developed to understand the symptoms and intrinsic neuronal mechanisms of schizophrenia (review Rolls et al., 2008; Gonzalez-Burgos et al., 2005; Vierling-Claassen et al., 2008; Spencer, 2009; Spencer, 2009; Kirli et al., 2014; Anticevic et al., 2015; Jadi et al., 2016; Metzner et al., 2016). In particular, modeling of impairment of evoked gamma oscillations in the auditory cortex received considerable attention: Vierling-Claassen et al. (2008) analysed the effect of GABA deficits; Kirli et al. (2014) evaluated the effect of NMDA deficits; Metzner et al. (2016) included GABA hypofunction and impaired connectivity. Spencer (2009) addressed the influence of reduced cortical connectivity and NMDA synaptic hypofunction in a resting state.

We use a computational model of auditory cortex to investigate the joint influence of NMDA and GABA synaptic dysfunction on the gamma oscillations in a resting state and in sensory stimulation conditions.

MATERIALS AND METHODS

A model of a spiking neural network was composed of 800 pyramidal neurons (PCs), 150 regular-spiking interneurons (RSIs) and 50 fast-spiking interneurons (FSIs) (Spencer et al., 2009). All neurons were randomly interconnected and received excitatory background inputs and sensory drive stimuli (Fig. 1). All cells had excitatory NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) acid synapses and inhibitory GABA synapses. Leaky-integrated and fire model was used to describe PCs, RSIs and FSIs dynamics. Membrane potential of PCs, RSIs and FSIs was expressed as:

$$\frac{dV}{dt} = \frac{g_{in}(E_{in} - V) + g_{stim}(E_{stim} - V) + g_{PC}(E_{PC} - V) + g_{RIS}(E_{RIS} - V) + g_{FSI}(E_{FSI} - V)}{C_m}$$

where $V$ is membrane potential, $g_{in}$ is synaptic conductance of the AMPA synapse receiving independent noise input, $g_{stim}$ is synaptic conductance of the AMPA synapse stimulated by sensory drive stimulus, $g_{PC}$ is synaptic conductance
of AMPA synapse receiving input from pyramidal cells, $\mathcal{G}_{\text{RSI}}$ is synaptic conductance of the GABA synapse receiving input from regular spiking interneurons, $\mathcal{G}_{\text{FSI}}$ is synaptic conductance of the GABA synapse receiving input from fast spiking interneurons, $E_e$ and $E_i$ are reversal potentials of excitatory and inhibitory synapses, respectively, $E_{\text{rest}}$ is the membrane time constant, $C_m$ is membrane capacitance, $\text{area}$ is the membrane area. Parameter values are presented in Table 1.

AMPA and GABA synaptic conductances are modeled as a double exponential function:

$$g_{\text{syn}} = \frac{\tau_{\text{rise}}}{\tau_{\text{rise}} - \tau_{\text{fall}}} \left( e^{-t_{\text{syn}}/\tau_{\text{rise}}} - e^{-t_{\text{syn}}/\tau_{\text{fall}}} \right),$$

where $\tau_{\text{rise}}$ is the rising time constant, $\tau_{\text{fall}}$ is the decay time constant, $g_{\text{syn}}$ is a peak synaptic conductance, $t_{\text{syn}}$ is the time of the synaptic activation.

The NMDA receptor mediated synaptic response is expressed:

$$g_{\text{syn}} = \frac{\tau_{\text{rise}}}{\tau_{\text{rise}} - \tau_{\text{fall}}} \left( e^{-t_{\text{syn}}/\tau_{\text{rise}}} - e^{-t_{\text{syn}}/\tau_{\text{fall}}} \right) \nonumber$$

$$\cdot \left( 1 + \mu [\text{Mg}^{2+}] \right)^{\nu},$$

where $\tau_{\text{rise}}$ is the rising time constant, $\tau_{\text{fall}}$ is the decay time constant, $g_{\text{syn}}$ is a peak synaptic conductance, $t_{\text{syn}}$ is the time of the synaptic activation, $[\text{Mg}^{2+}]$ is extracellular Mg concentration, $\mu$ and $\nu$ are the parameters describing the influence of Mg concentration and membrane potential. Time constants, peak synaptic conductances, reversal potentials, $\mu$ and $\nu$ parameters are presented in Table 1. Probabilities and peak synaptic conductances of each connection type between PCs, FSIs, RSIs are given in Table 2.

The background activity in the cortex is represented by an independent Poisson noise input to the network neurons at 4 Hz. Sensory drive stimulus is modeled as excitatory input to the network neurons at 40 Hz. Peak synaptic conductances for a resting state have been estimated using a genetic algorithm and are presented in Table 1.

The synaptic dysfunction in the schizophrenic state is modeled by altering synaptic properties of FSIs: GABA receptor-gated channel decay time constant is increased from 5 ms to 15 ms, and NMDA receptor-gated channel synaptic conductance is decreased from 100% to 10%.

To characterize network activity, power spectrum of the average membrane potential for each cell population was computed with a Fast Fourier Transform. Frequency resolution was chosen at 2 ms.

The network was simulated for 1000 ms. The model was implemented in the Brian Spiking Neural Simulator environment (Goodman DF, Brette, 2009; Stimberg et al., 2014). Data analysis was performed in Matlab, The MathWorks, Inc.

RESULTS

Activity of the network in a resting state is shown in Fig. 2. Raster plot of 800 PCs, 150 RSIs, and 50 FSIs indicated that the network was synchronized after approximately 100 ms after the simulation onset in response to the background Poisson noise input at 4 Hz (Fig. 2A).
Table 1. Parameters of the pyramidal cells (PCs), regular spiking interneurons (RSIs), fast spiking interneurons (FSIs), AMPA, NMDA, GABA synapses

<table>
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<tr>
<th>Cells</th>
<th>Value</th>
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<tbody>
<tr>
<td>Network size</td>
<td></td>
</tr>
<tr>
<td>PCs (pyramidal cells)</td>
<td>800</td>
</tr>
<tr>
<td>RSIs (regular-spiking interneurons)</td>
<td>150</td>
</tr>
<tr>
<td>FSIs (fast-spiking interneurons)</td>
<td>50</td>
</tr>
<tr>
<td>Firing threshold</td>
<td>−52 mV</td>
</tr>
<tr>
<td>After-spike reset potential</td>
<td>−59 mV</td>
</tr>
<tr>
<td>Resting potential $E_{rest}$</td>
<td>−70 mV</td>
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<tr>
<td>Spike transmission time</td>
<td>2 ms</td>
</tr>
<tr>
<td>PCs and RSIs membrane time constant $\tau_m$</td>
<td>20 ms</td>
</tr>
<tr>
<td>FSIs membrane time constant $\tau_m$</td>
<td>10 ms</td>
</tr>
<tr>
<td>Refractory time period constant</td>
<td>2 ms</td>
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<tr>
<td>Membrane capacitance $C_m$</td>
<td>1.0 $\mu$F/cm$^2$</td>
</tr>
<tr>
<td>Membrane area $area$</td>
<td>400 $\mu$m$^2$</td>
</tr>
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</table>

<table>
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<th>Synapses</th>
<th>Value</th>
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</thead>
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<tr>
<td>Reversal potential of excitatory synapse $E_e$</td>
<td>0 mV</td>
</tr>
<tr>
<td>Reversal potential of inhibitory synapse $E_i$</td>
<td>−70 mV</td>
</tr>
<tr>
<td>AMPA rise and decay time constants $\tau_{rise}, \tau_{decay}$</td>
<td>0.5 ms, 2 ms</td>
</tr>
<tr>
<td>NMDA rise and decay time constant $\tau_{rise}, \tau_{decay}$</td>
<td>2 ms, 100 ms</td>
</tr>
<tr>
<td>GABA rise and decay time constant $\tau_{rise}, \tau_{decay}$</td>
<td>0.5 ms, 5 ms</td>
</tr>
<tr>
<td>NMDA/AMPA receptor conductance strength ratio for PCs</td>
<td>0.45</td>
</tr>
<tr>
<td>NMDA/AMPA receptor conductance strength ratio for RSIs and FSIs</td>
<td>0.1</td>
</tr>
<tr>
<td>$[\text{Mg}^{2+}]$ $\text{Mg}^{2+}$ concentration</td>
<td>1 mM</td>
</tr>
<tr>
<td>$\mu$ ($\text{Mg}^{2+}$ concentration constant)</td>
<td>0.33/mM</td>
</tr>
<tr>
<td>$\gamma$ constant</td>
<td>0.062/mV</td>
</tr>
</tbody>
</table>

Table 2. Probability and relative weights of PCs, FSIs, RSIs connections. Each relative weight was scaled by a factor of 8.25 nS to obtain $g_{syn}$ (Spencer, 2009)

<table>
<thead>
<tr>
<th></th>
<th>PC-PC</th>
<th>PC-RSI</th>
<th>PC-FSI</th>
<th>RSI-PC</th>
<th>RSI-RSI</th>
<th>RSI-FSI</th>
<th>FSI-PC</th>
<th>FSI-RSI</th>
<th>FSI-FSI</th>
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<tr>
<td>Probability</td>
<td>0.1</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.15</td>
<td>0.5</td>
<td>0.5</td>
<td>0.35</td>
<td>0.6</td>
</tr>
<tr>
<td>Relative weight</td>
<td>1.0</td>
<td>0.8</td>
<td>1.9</td>
<td>0.8</td>
<td>0.8</td>
<td>1.9</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

The membrane potential of individual neurons and averaged across PCs, RSIs, FSIs populations is presented in Fig. 2B, C. The oscillation power, computed from the average membrane potential for each cell group, had a peak at 40 Hz for PCs, RSIs and FSIs (Fig. 3A).
Fig. 2. Network activity in a resting state. (A) Raster plot of pyramidal cells (PCs, no. 1-800), regular spiking interneurons (RSIs, no. 801-950) and fast spiking interneurons (FSIs, no. 950-1000). (B) Membrane potential of PC, RSI, FSI. (C) Averaged membrane potential of PCs, RSIs, FSIs populations

Fig. 3. Power spectral density of pyramidal cells (PCs), regular-spiking interneurons (RSIs), and fast-spiking interneurons (FSIs) in a resting state. (A, B) GABA receptor-gated channel decay time constant is 5 ms. (C, D) GABA receptor-gated channel decay time constant is 15 ms. (A, C) NMDA synaptic weight is 100%. (B, D) NMDA synaptic weight is 10%
Schizophrenic condition was modeled by altering NMDA and GABA synaptic properties of FSIs: synaptic conductance of NMDA receptor-gated channels was decreased up to 10% of its initial value (Fig. 3B, D), and GABA receptor-gated channel decay time constant was increased from 5 ms up to 15 ms (Fig. 3C, D).

In a resting state, weak NMDA synapses onto FSIs decreased oscillation power at 40 Hz in FSIs (from 1.1 mV$^2$ to 2.4 mV$^2$) and increased oscillation power at 40 Hz in PCs (from 1.9 mV$^2$ to 2.35 mV$^2$), when GABA functioned normally (Fig. 3A, B). Prolonged decay time constant of GABA receptor-gated channels led to the abolished gamma oscillations in PCs, FSIs and RSIs (Fig. 3C), when NMDA was unaffected. Deficits of both NMDA and GABA synapses increased oscillation power at 40 Hz in all cell populations (Fig. 3D), however, only slightly (up to 0.03 mV$^2$ in PCs and 0.16 mV$^2$ in FSIs), and introduced oscillations at lower frequencies (10–30 Hz).

40 Hz-drive stimulus increased oscillation power of PCs (up to 2.4 mV$^2$) and FSIs (up to 1.2 mV$^2$) at 40 Hz in a so-called healthy neural network (Fig. 4A). The raster plot of the network activity illustrates population syn-

**Fig. 4.** Power spectral density (A, C) and raster plots (C, D) of pyramidal cells (PCs, no. 1-800), regular-spiking interneurons (RSIs, no. 801–950) and fast-spiking interneurons (FSIs, no. 950–1000) for 40 Hz drive case. NMDA synaptic weight is 100%. (A, B) GABA receptor-gated channel decay time constant is 5 ms. (C, D) GABA receptor-gated channel decay time constant is 15 ms.
chronization approximately after 75 ms after the simulation onset and rhythm generation at 40 Hz (Fig. 4B). Increased decay time constant of GABA receptor-gated channels onto FSIs diminished the oscillation power at 40 Hz (0.4 mV²) and enhanced at 20 Hz (0.75 mV²) in PCs; similar effects were observed in FSIs and RSIs activity. Thus, 20 Hz oscillations became dominant in all three cell populations (Fig. 4B).

NMDA deficits had only a mild effect on network activity in 40 Hz-drive conditions: PCs oscillation power slightly decreased for normal FSIs GABA synapse (Fig. 5A), and was not affected if GABA decay time constant was prolonged to 15 ms (Fig. 5B).

DISCUSSION

Synaptic dysfunction in schizophrenia was modeled by reducing NMDA synaptic conductance and increasing GABA decay time constant on FSIs of a cortical network model. The effect of synaptic GABA impairment was more profound in both conditions.

In a resting state, impaired NMDA synapses onto FSIs increase the oscillation power at 40 Hz in PCs as noise inputs provided weaker excitation for FSIs, and PCs were less inhibited. Similar observations on the influence of NMDA synaptic hypofunction in a resting state were reported by Spencer (2009). Prolonged decay time constant of GABA channels impairs network activity as FSIs-provided GABA inhibition of PCs and RSIs becomes more effective. Weak NMDA synapses onto FSIs enhance network oscillations, when GABA synapses are affected by illness. In 40 Hz-drive stimulation case NMDA dysfunction effect is mild and does not influence network rhythm substantially. Kirli et al. (2014) found that varying NMDA conductance led to an inverted U relation with network gamma oscillation. In our study NMDA influence is relatively small as inputs are strong and overpower NMDA dysfunction. GABA impairment decreases oscillation power at 40 Hz and increases at 20 Hz in PCs, FSIs and RSIs, as in the computational modeling study by Vierling-Claassen et al. (2008).

Fig. 5. Power spectral density of pyramidal cells (PCs), regular spiking interneurons (RSIs) and fast spiking interneurons (FSIs) for 40 Hz drive case. NMDA synaptic weight is 10%. (A) GABA receptor-gated channel decay time constant is 5 ms. (B) GABA receptor-gated channel decay time constant is 15 ms
Influence of NMDA deficit is not evident if GABA is impaired.

CONCLUSIONS

NMDA and GABA synaptic dysfunction leads to the altered gamma frequency oscillations in a spiking neural network of cortex in a resting state and in 40 Hz-drive case. Our simulation study shows that effect of synaptic GABA impairment is more profound in both conditions.

One of the recent trends in neuroscience is to develop computational models of psychiatric and neurological disorders and integrate the available knowledge at the molecular, cellular and system-levels (Friston et al., 2014; Adams et al., 2016; Huys et al., 2016; Raymond et al., 2017). This newly emergent field of computational psychiatry gives a new perspective on mental illness, serves as a bridge from neuroscience to clinical applications and advances understanding, prediction and treatment of psychiatric disorders. Computational modeling approach provides a powerful tool to study complex interactions, time courses and dynamics of multiple mechanisms underlying neuronal network activity in health and disease.

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NMDA IR GABA SINAPSIŲ DISFUNKCIJOS POVEIKIS GAMA DAŽNIO OSCILIACIJOMS ŠIZOFRENIJOS LIGOS ATVEJU: KOMPIUTERINIŲ MODELIAVIMAS

Santrauka
Šizofrenija – tai psichikos liga, pasireiškianti su svokimo, mąstymo bei elgesio ir emocijų pokyčiais. Šizofrenija sergančiųjų smegenyse neuronų nykimas nėra aptinkamas, tačiau smegenų žievėje pažymėti gebėjimai patologiniai signalų perdavimo pokyčiai, t. y. pakitus EEG gama dažnis (30–80 Hz), kuris yra išskirtinai tokioms procesams kaip pojūčiai, suvokimas, atmintis ir dėmesys. Pastaruoju metu manoma, kad NMDA ir GABA sinapsių disfunkcija yra vienas iš galimų priežasčių šių pokyčių sukurti. Šiame darbe taikant kompiuterinio modeliavimo metodą siekiama ištirti NMDA ir GABA sinapsių disfunkcijos poveikį gama ritmo sutrikimams sergant šizofrenija. Šiame darbe taikant kompiuterinio modeliavimo metodą siekiama ištirti NMDA ir GABA sinapsių disfunkcijos poveikį gama ritmo sutrikimams sergant šizofrenija. Šiame darbe taikant kompiuterinio modeliavimo metodą siekiama ištirti NMDA ir GABA sinapsių disfunkcijos poveikį gama ritmo sutrikimams sergant šizofrenija. Šiame darbe taikant kompiuterinio modeliavimo metodą siekiama ištirti NMDA ir GABA sinapsių disfunkcijos poveikį gama ritmo sutrikimams sergant šizofrenija. Šiame darbe taikant kompiuterinio modeliavimo metodą siekiama ištirti NMDA ir GABA sinapsių disfunkcijos poveikį gama ritmo sutrikimams sergant šizofrenija.