Mechanisms of spike inhibition in a cortical network induced by transcranial magnetic stimulation

Yoichi Miyawaki [a,1] Masato Okada [b,a]

[a] *PRESTO JST c/o RIKEN Brain Science Institute, 2-1, Hirosawa, Wako, Saitama 351-0198, JAPAN*

[b] *Graduate School of Frontier Sciences, The University of Tokyo, 5-1-5, Kashiwanoha, Kashiwa, Chiba 277-8561, JAPAN*

Abstract

We propose mechanisms of neural interference induced by transcranial magnetic stimulation (TMS). TMS is widely used as a powerful and unique experimental tool to stimulate the human brain noinvasively, which typically induces inhibitory effect on the cortical functions. However, the fundamental mechanism of TMS-induced suppression is still unclear. In this paper, we computationally demonstrate that TMS induces sustained spike inhibition in a conductance-based network model without the ion channel which is necessary for spike inhibition in an isolated single neuron, suggesting that each individual neuron is not necessarily suppressed by TMS; rather, a collapse of excitatory and inhibitory input balance in the cortical network is crucial for TMS-induced suppression.

Key words: TMS; Spike inhibition; Conductance-based model; Perturbation; AHP channel

1 Introduction

Transcranial magnetic stimulation (TMS) is an experimental tool to stimulate the human brain noninvasively with high temporal resolution through a brief magnetic pulse yielded by a coil placed on the scalp. TMS typically causes inhibitory effect on the cortical functions; e.g. a part of visual field can be erased by the occipital stimulation [1], and peripheral electromyogram can be

[1] Corresponding author, E-mail address: yoichi_miyawaki@brain.riken.jp

suppressed by the motor cortical stimulation [2]. These striking results have appealed to various applications in cognitive neuroscience fields. However, the neural mechanisms of TMS-induced effect are still unclear.

A few past studies discussed the TMS effect on the isolated single neuron level. They used multicompartment model of a cortical neuron and modeled the TMS effect as an additional current input produced by the induced electric field on each compartment [3][4][5]. They showed a brief magnetic pulse could inhibit spiking activity of the single neuron and suggested that after-hyperpolarization (AHP) channel plays a critical role in TMS-induced spike inhibition in a single neuron level [5]. On the other hand, our previous studies demonstrated that the simplest one-population rate network model without any adaptation mechanisms could be suppressed by a TMS-like brief perturbation, and the temporal properties of the suppression were totally consistent with various experimental data [6][7]. This fact suggests that TMS-induced suppression might be mediated by inhibitory interaction in the cortical network rather than a particular membrane mechanism in a single neuron level. In this paper, we use a conductance-based network model, in which each neuron has Hodgkin-Huxley type ion channel mechanisms but excludes AHP mechanisms. We analyze TMS effect on the spiking network and elucidate the critical mechanisms for spike inhibition induced by TMS.

2 Model

We used a single compartment model as an individual neuron,

$$C_m \frac{dV_i(t)}{dt} = g_i^{\text{leak}}(E_i^{\text{leak}} - V_i(t)) - I_i^{\text{ion}}(t) + I_i^{\text{syn}}(t) \tag{1}$$

where I_i^{ion} is the active ion current of the i-th neuron including the fast sodium, delayed rectifier, and A-current. Each ion current obeys Hodgkin-Huxley type kinetics, whose details are in [8]. I_i^{syn} is the sum of the synaptic input current given from the other neurons inside the network and from the afferent terminal,

$$I_i^{\text{syn}}(t) = \sum_{\alpha=\text{E,I}} \sum_{j=1}^{N} g_{ij}^{\alpha}(t)(E_j^{\alpha} - V_i(t)) + g_i^{\text{aff}}(t)(E^{\text{aff}} - V_i(t)) \tag{2}$$

$$g_{ij}^{\text{E}} = J_2[1 + \cos 2(\theta_i - \theta_j)], \quad g_{ij}^{\text{I}} = J_0, \quad (\theta_i = -\frac{\pi}{2} + i\frac{\pi}{N}) \tag{3}$$

$$\frac{dg^{\alpha}}{dt} = -\frac{g^{\alpha}}{\tau^{\alpha}} + G^{\alpha} \sum_{t_j} \delta(t - t_j), \quad (\alpha = \text{E, I, aff}). \tag{4}$$

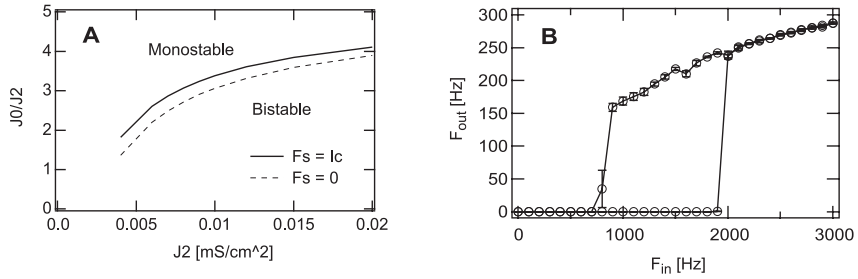

Fig. 1. A) Phase diagram of the rate model whose structure is the same as the conductance-based network model. B) An example of bistability of the conductance-based model showing hysteresis for the afferent input intensity. The synaptic weights were calculated by the phase diagram of the rate model. Note that the afferent firing rate, $F_{\rm in}$, is modeled as the sum of all presynaptic input, equivalently 100 presynaptic Poisson input at $F_{\rm in}/100$ Hz. The parameters used here were, $J_0 = 0.021$ mS/cm^2, $J_2 = 0.008$ mS/cm^2, $N = 100$, and the others were the same as [8].

We used a network model that has been well analyzed as a model of orientation tuning function in the primary visual cortex [8][9], with a Mexican-hat type synaptic structure consisting of the uniform inhibition J_0 and the orientation-specific interaction J_2. The afferent input firing rate was modeled as $f^{\rm aff}(\theta_i - \theta_0) = F[1 - \epsilon + \epsilon \cos 2(\theta_i - \theta_0)]$ to be weakly modulated according to difference between the preferred feature of a neuron and the stimulus orientation θ_0. The network shows a local excitation around θ_0.

We assumed that TMS-induced effect would be constant for all neurons in the local network because the spatial extent of the neural population is very small compared with the spatial gradient of the induced electric field. The previous modeling works showed that the external electric field causes difference in local current flow inside the cell, equivalently causes the transmembrane current in each dendritic element as if applying an additional current input to the cell [3][4][5][7]. Thus we can simply add the TMS current, $I^{\rm TMS}(t)$, on the right side of Eq. 1 as an additional current input. Here we employ a simple rectangular pulse input with 1 ms duration as a TMS-like perturbation.

3 Results

Our previous studies suggest that the network needs to exhibit bistability to induce a sustained suppression by TMS [6][7]. However, it is difficult to search the proper network parameters for the bistable mode directly from the complicated conductance-based network model. Thus, we applied Shriki's method [8] to link the parameter space of the rate model to that of the conductance-based model. First, we calculated the f-I curve for the conductance-based neuron model and fitted the effective input-output gain and the threshold value by the formula $f = \beta[I - I_c] - \gamma[I - I_c]^2$ for $I > I_c$. Second, we computed

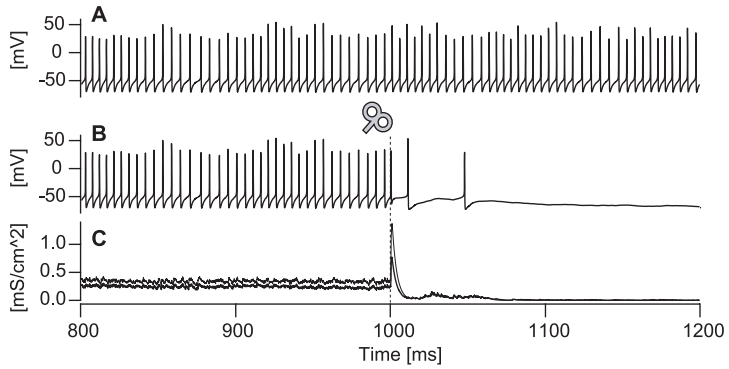

Fig. 2. A) The spiking activity of the neuron $\theta_i = \theta_0$ in the conductance-based network model. B) Suppression of the spiking activity by the TMS-like perturbation. C) Excitatory (thick line) and inhibitory (thin line) input conductance. The parameters used here were $F^{\mathrm{T}} = 2800$ Hz, $D^{\mathrm{T}} = 200$ ms, $F^{\mathrm{S}} = 1000$ Hz, $\theta_0 = 0$, $I^{\mathrm{TMS}} = 36$ uA/cm^2, and the others were the same as Fig. 1.

the phase diagram in the fitted rate model and determined inhibitory and excitatory synaptic weight by which the network exhibits bistability (Fig. 1A). Third, we converted the parameter set into that of the conductance-based model. Using this method, we could easily find the proper parameter region in which the conductance-based model showed bistability (Fig. 1B). Finally, we employed a simple afferent input model consisting of suprathreshold transient (mean rate: $F^{\mathrm{T}} > F_{\mathrm{thres}}$, duration: D^{T}) and subthreshold sustained (mean rate: $F^{\mathrm{S}} < F_{\mathrm{thres}}$) components. F_{thres} was 1900 Hz in this case. This is the simplest input model that leads the network into the bistable regime, yet it still captures the common properties of neural signals in brain areas such as the LGN and visual cortex.

Fig. 2A illustrates an example of a spiking pattern when the network was driven in the bistable regime. After the output firing frequency became stable, we applied the TMS-like perturbation to the network and could observe sustained spike inhibition (Fig. 2B). The minimum intensity of the perturbation was in the same order as the sum of the total synaptic input current ($10^1 - 10^2$ uA/cm^2). The reduction of the firing rate took more than 50 ms. The slow relaxation was also clearly observed in the change of excitatory and inhibitory input conductance (Fig. 2C). The balance between excitatory and inhibitory input conductance were collapsed by the perturbation, and the network could not maintain the stable firing pattern and converged to the quiescent state. These basic properties of spike inhibition were consistently observed regardless of the induction timing of the perturbation if it was applied after the output firing frequency became stable.

We then examined the effect of TMS on an isolated single neuron by using a multicompartment model with the reconstructed dendritic arborization [10]. Major differences between our conductance-based model and this multicompartment model were calcium-related ion mechanisms: high-threshold Ca

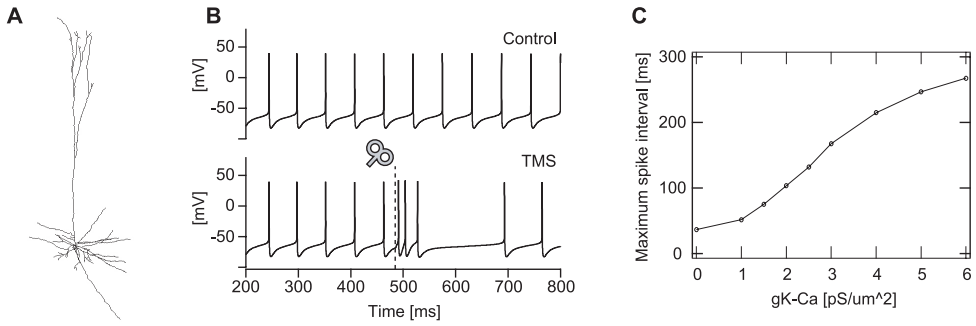

Fig. 3. A) Layer V pyramidal cell used in the simulation. B) The spiking activity could be suppressed by the perturbation, but C) the duration strongly depended on K-Ca channel properties.

channel, K-Ca channel, and Ca pump were included in the soma and dendrite in only the multicompartment model. We injected a constant somatic current and generated a specific spiking pattern depending on its morphology (Fig. 3B). TMS-induced current was calculated by the dot product of the applied electric field and the direction vector of each compartment multiplied by the axial conductance of the compartment. (see detail in [5][7]). We could find spike inhibition for over 100 ms after a brief bursting period with Ca rush-in and increase in K-Ca conductance as reported in [5], and the duration of the inhibition strongly depended on the maximum conductance of K-Ca channel. Under the condition that K-Ca channel was completely blocked, no spike inhibition was observed by TMS that could induce intracellular current even ten times stronger than the somatic injection current, indicating that K-Ca channel is necessary to induce spike inhibition in a single neuron level. Note that this spike inhibition could be observed in the very limited condition. It was selective about cellular morphology; e.g., no spike inhibition was observed in layer IV stellate cell and bushier layer V pyramidal cell. Even using the most susceptible morphology, that is the cell in Fig. 3A, it was hard to suppress the spike train if the current input was strong and the cell fired at high frequency more than about 40 Hz. On the other hand, the network model showed spike inhibition by TMS in a wide range of firing frequency, though K-Ca channel was not included as a member of ion channel. We also successfully observed that subthreshold weak TMS could induce sustained inhibitory effect, whose duration agrees with experimental data of occipital TMS examining the relationship between phosphene threshold and the paired-pulse TMS interval [11].

4 Discussion

We constructed the conductance-based spiking network model and investigated the effect of TMS. The results were totally consistent with the predic-

tion from the rate model [6][7]. In the network model, all the neurons were excited by the TMS modeled as a brief current pulse, resulting in suppressive effect on the original local excitation via inhibitory synaptic connections from the neurons far from the afferent stimulus center θ_0. Because we set the synaptic weight so that the network showed the bistability, the TMS-like perturbation could stop the spiking activity if such a suppressive effect was large enough, and finally the network converged to the quiescent state. The point is that these mechanisms were independent of the spike inhibition processes in an isolated single neuron mainly mediated by conductance increase in K-Ca channel. In addition, the temporal properties of the spike inhibition by a weak subthreshold TMS observed in the network model agree with experimental data of the occipital TMS [11]. These results suggest that each single neuron is not necessarily suppressed directly by TMS but the collapse of the excitatory and inhibitory input balance and transsynaptic inhibitory interaction in the local network might play a critical role in TMS-induced suppression.

Acknowledgement

We greatly appreciate technical support in programming by Takashi Shinozaki.

References

[1] Kamitani Y, Shimojo S, *Nat Neurosci* **2** (1999) 767-71.

[2] Inghilleri M, Berardelli A, Cruccu G, Manfredi M, *J Physiol* **466** (1993) 521-34.

[3] Roth BJ, Basser PJ, *IEEE Trans Biomed Eng* **37** (1990) 588-97.

[4] Nagarajan SS, Durand DM, Warman EN, *IEEE Trans Biomed Eng* **40** (1993) 1175-88.

[5] Kamitani Y, Bhalodi VM, Kubota Y, Shimojo S, *Neurocomputing* **38-40** (2001) 697-703.

[6] Miyawaki Y, Okada M, *Neural Comput* **16** (2004) 309-31.

[7] Miyawaki Y, Okada M, *Adv Neural Inf Process Syst* **16** (2004) 1295-302.

[8] Shriki O, Hansel D, Sompolinsky H, *Neural Comput* **15** (2003) 1809-41.

[9] Ben-Yishai R, Bar-Or RL, Sompolinsky H, *PNAS* **92** (1995) 3844-8.

[10] Mainen ZF, Sejnowski TJ, *Nature* **382** (1996) 363-6.

[11] Ray PG, Meador KJ, Epstein CM, Loring DW, Day LJ, *J Clin Neurophysiol* **15** (1998) 351-7.