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# Cortical and thalamic components of augmenting responses: A modeling study

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## Abstract

Augmenting responses in neocortical pyramidal cells can be elicited by cortical or thalamic repetitive stimulation around 10 Hz. A realistic model of a cortical pyramidal (PY) cell and an interneuron (IN) was developed to explore possible intracortical mechanisms. The interaction between strong feedforward hyperpolarizing inhibition, deinactivation of a low-threshold  $\text{Ca}^{2+}$  current and depression of fast inhibitory currents in the PY cell resulted in only weakly augmented responses. The incremental nature and frequency dependence of intracortical augmenting responses was reproduced in the model pair of cortical cells that included short-term plasticity of inhibitory, lateral and thalamocortical synapses. Hyperpolarization-activated currents were not needed in the model to obtain these effects. Thalamic stimulation in a simplified thalamocortical model with short-term plasticity of cortical connections resulted in a small additional cortical augmentation of the already augmented thalamocortical inputs. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* Augmenting response; Short-term synaptic plasticity; Neocortex; Thalamus; Computational model

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## 1. Introduction

When thalamically stimulated at frequencies between 5 and 15 Hz cortical responses grow in size and may carry an increased number of action potentials. These

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‘augmenting’ responses [20] have been reported in motor cortex [5–7,23,27], somatosensory cortex [19] and association cortex [21], as well as in visual cortex [10] and auditory cortex [18]. Cortical augmenting responses can be evoked by stimulation of specific thalamic nuclei, white matter [7,19], ipsilateral [7,27] and contralateral cortical areas [21], but not from prethalamic stimulation sites [4]. Augmenting responses are modulated by behavioral state [5,25] and may develop into seizure-like self-sustained oscillatory activity in cortical neurons [27].

Recent evidence indicates there are two separate components contributing to augmenting responses: an intrathalamic and an intracortical component. The intrathalamic component was recently investigated in decorticated animals [26,32] and the underlying mechanisms have been explored in computer models of the thalamus [3]. The possible role of thalamically generated augmenting responses in the development of cortical incremental responses was investigated *in vivo* [27] and in a modeling study [4]. The occurrence of incremental responses in cortical slices [7] and in thalamus-lesioned animals [19] corroborates an additional purely intracortical component.

In this paper we test two possible mechanisms underlying intracortical augmenting responses. The first mechanism involves the interaction between strong feedforward hyperpolarizing inhibition and (dein)activation of hyperpolarization-activated currents in layer 5 cells [7]. The second mechanism depends on short-term synaptic plasticity of cortical connections. Growing evidence indicates short-term synaptic plasticity is a ubiquitous property of neocortical circuitry: connections between various excitatory cortical cell types display short-term depression [1,31,33], connections from excitatory cells onto inhibitory cells either facilitate [17,30] or depress [2,29], inhibitory currents in excitatory cells depress [7,8,24,29], and thalamocortical synapses depress [11,12,28]. If short-term plasticity is a common characteristic of cortical synapses, cortical networks are expected to display use-dependent phenomena when electrically or naturally stimulated.

## 2. Methods

Model description and parameters are given in detail elsewhere [14]. Briefly, neocortical pyramidal cells (PY) and interneurons (IN) were described using a two-compartment model [16] including voltage-dependent currents described by Hodgkin–Huxley type of kinetics. Our cortical model was a reduced network version consisting of a single PY-IN cell pair (Fig. 1A). The PY cell was connected to itself and the IN cell through an AMPA synapse, the IN cell was connected to the PY cell with a GABA<sub>A</sub> synapse. Both cells received a thalamocortical AMPA synapse. Maximal synaptic conductances in the model were  $\bar{g}_{py-in} = 0.06 \mu\text{S}$ ,  $\bar{g}_{in-py} = 0.10 \mu\text{S}$ ,  $\bar{g}_{tc-py} = 0.05 \mu\text{S}$ ,  $\bar{g}_{tc-in} = 0.02 \mu\text{S}$ ,  $\bar{g}_{py-py} = 0.04 \mu\text{S}$  with and  $\bar{g}_{py-py} = 0.01 \mu\text{S}$  without short-term plasticity of the PY-PY synapse. To model short-term synaptic plasticity we used a phenomenological description of the synaptic conductance [1,33]. Parameters of synaptic plasticity were estimated from experimental data (see [14]).

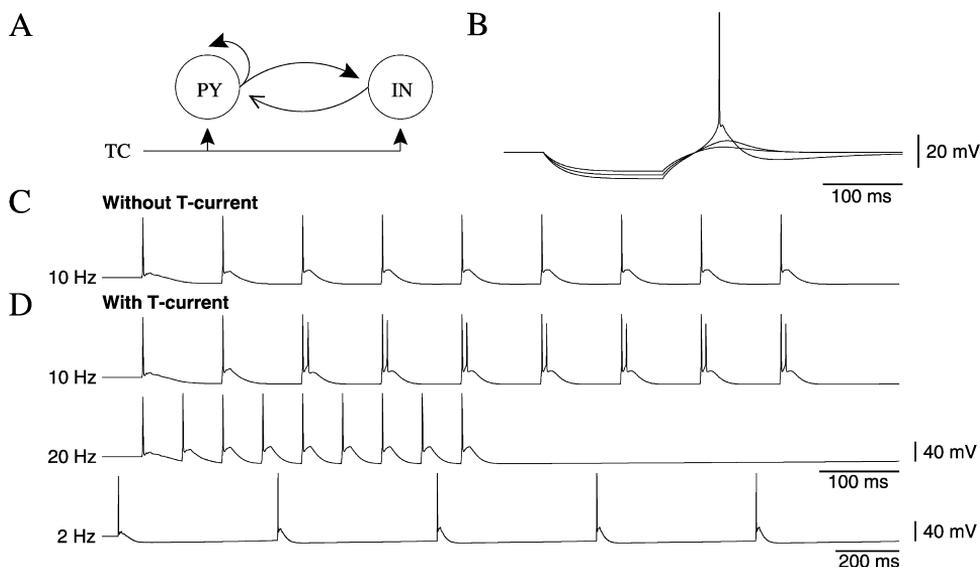


Fig. 1. (A) Schematic of the reduced cortical network model. (B) Rebound response of the PY cell at different strengths of hyperpolarization when a T-current was included ( $pT = 20$  nm/s). (C) PY cell response to nine cortical shocks at 10 Hz in the model without T-current. (D) PY cell responses at different frequencies of stimulation in the model with T-current.

Electrical stimulation of the cortex was modeled as a brief activation of all synapses in the model. Activation of the thalamocortical synapses alone gave similar results. As a thalamic model we used an interconnected thalamocortical (TC) cell and nucleus reticularis (RE) cell described elsewhere [3]. All simulations were run using NEURON [13].

### 3. Results

To test the proposal that the initiation of augmenting responses depends on intrinsic properties of layer 5 cells [7] we added a low-threshold  $\text{Ca}^{2+}$  (T-) current [15] to the dendrite of the PY cell. The permeability of the T-channel was of intermediate strength such that a 150 ms hyperpolarization toward  $-85$  mV resulted in a single sodium spike upon release from inhibition (Fig. 1B). We added a  $\text{GABA}_B$  component [9] to the IN-PY synapse to obtain a slow IPSP that hyperpolarized the PY cell 15 mV from rest ( $\bar{g} = 0.01 \mu\text{S}$ ). None of the synapses displayed short-term plasticity except the inhibitory  $\text{GABA}_A$  synapse, which depressed. The model without T-current did not show augmentation upon 10 Hz stimulation (Fig. 1C). In contrast, when the T-current was added 10 Hz stimulation resulted in weakly incremented responses (Fig. 1D). At frequencies  $> 11$  Hz and  $< 3$  Hz responses were not

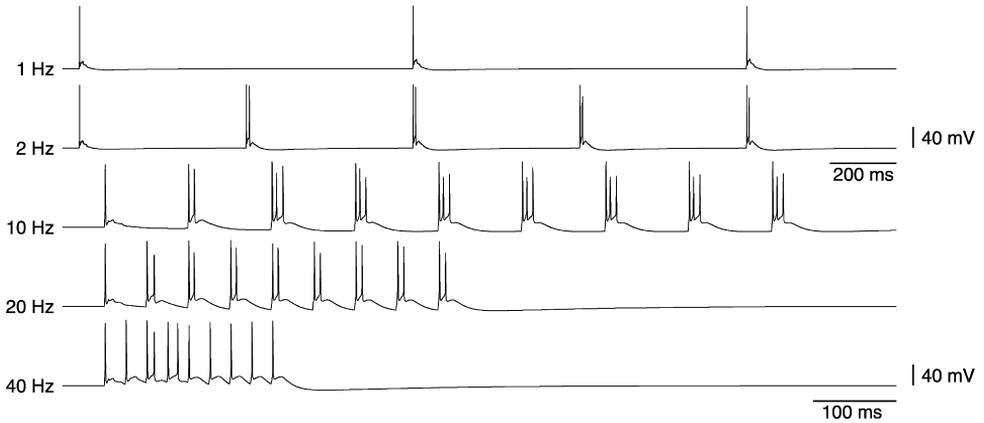


Fig. 2. PY cell responses to cortical shocks at different frequencies in the model including short-term synaptic plasticity.

augmented (Fig. 1D). When the inhibitory synapse did not depress, addition of the T-current did not result in incremental responses for any value of the inhibitory conductance (data not shown).

Next, we tested whether short-term plasticity of cortical synapses without T-current could generate incremental responses. In this model of cortical short-term plasticity the inhibitory synapse depressed with a paired-pulse depression of 30% at short intervals and a slow time constant of recovery ( $U_{se} = 0.3$ ,  $\tau = 1000$  ms) [7,24]. The PY-PY excitatory synapse depressed strongly at short intervals and recovered fast ( $U_{se} = 0.75$ ,  $\tau = 50$  ms) [31] and similar dynamics governed the thalamocortical synapses ( $U_{se} = 0.4$ ,  $\tau = 100$  ms) [11,28]. No T-current was present in the model. At 10 Hz stimulation PY cell responses augmented strongly carrying one, two and three spikes for the first three shocks respectively (Fig. 2). After the third shock responses stabilized to three spikes per shock. At high frequencies of stimulation incremental responses were reduced. For example, at 20 Hz a steady-state response of two spikes per shock was reached after the second shock, and at 40 Hz the steady-state was not augmented. At frequencies  $< 4$  Hz augmentation was either reduced (at 2 Hz) or absent (at 1 Hz). IN cell responses were augmented similarly (data not shown). Frequency-dependent incremental responses were observed for a wide range of plasticity parameter values.

Finally, we tested whether thalamic stimulation could support cortical augmenting responses in the short-term plasticity model. A reciprocally coupled pair of RE-TC cells was stimulated at 10 Hz and the spike train of the TC cell was taken as an input to the cortical cells (Fig. 3, upper trace). The response of the TC cell was strongly augmented as a result of the deactivation of the low-threshold  $Ca^{2+}$  current in this neuron and displayed characteristic poststimulus oscillations around 4 Hz [3]. In the cortical model without short-term plasticity the PY cell responded by closely reproducing the input pattern of spikes (Fig. 3, middle trace; see also [4]). In the cortical

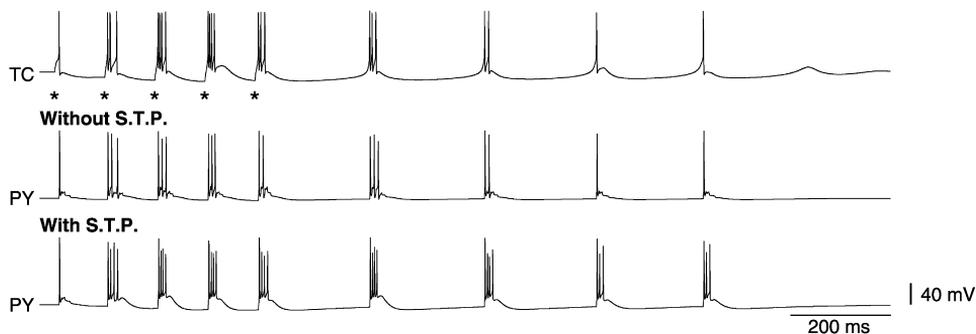


Fig. 3. PY cell responses to five thalamic shocks (indicated by \*) at 10 Hz. TC cell response (upper), PY cell response in the model without short-term synaptic plasticity (S.T.P.) (middle), and PY cell response in the model with short-term synaptic plasticity (lower).

model with short-term plasticity, the PY cell responded to each shock with an equal or increased number of spikes compared to the thalamocortical input train (Fig. 3, lower trace), and the thalamic poststimulus oscillations were amplified.

#### 4. Discussion

We tested two possible mechanisms underlying intracortical augmenting responses in a computational model of a pair of cortical cells. The first mechanism involved the deinactivation of a low-threshold  $\text{Ca}^{2+}$  current as a consequence of strong hyperpolarizing inhibition in pyramidal cells. This mechanism resulted in weakly augmented pyramidal cell responses for reasonably strong conductance values of the T-current. Small amplitude low-threshold spikes were obtained in only 15% of neocortical pyramidal cells [22]. Moreover, cells displaying augmenting responses often lack the strong hyperpolarization needed to deinactivate the T-current. These findings suggest this mechanism may contribute to cortical augmenting responses although it probably is not the most prominent one.

The incremental nature and frequency dependence of intracortical augmenting responses was reproduced in the model pair of cortical cells that included short-term plasticity of inhibitory, lateral and thalamocortical synapses. Hyperpolarization-activated currents were not needed in the model to obtain these effects. In a forthcoming paper we explore this mechanism in a large cortical network model [14]. Thalamic stimulation in a simplified thalamocortical model with short-term plasticity of cortical connections resulted in a small additional cortical augmentation of the already augmented thalamocortical inputs. Given the facilitory nature of corticothalamic feedback connections [34], thalamic and cortical circuits are likely to reciprocally reinforce thalamocortical oscillatory activity around 10 Hz.

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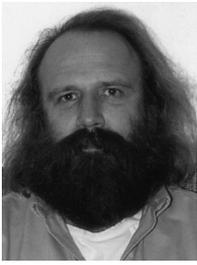
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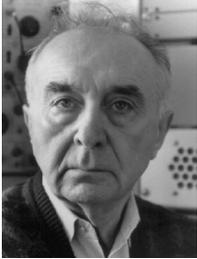
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