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Cortical and thalamic components of augmenting responses: A modeling study

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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 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

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 (de)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_A 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]).

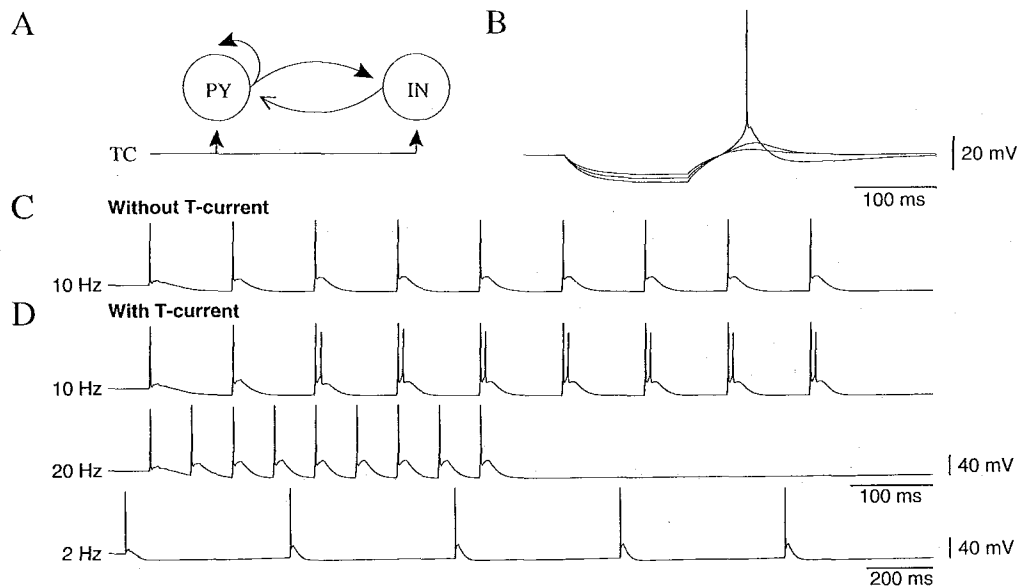


Fig. 1. (A) Schematic of the reduced cortical network model. (B) Rebound response of the PY cell at different strengths of hyperpolarization when a T-current was included ($pT = 20 \text{ nm/s}$). (C) PY cell response to nine cortical shocks at 10 Hz in the model without T-current. (D) PY cell responses 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 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 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 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 $> 11 \text{ Hz}$ and $< 3 \text{ Hz}$ responses were not

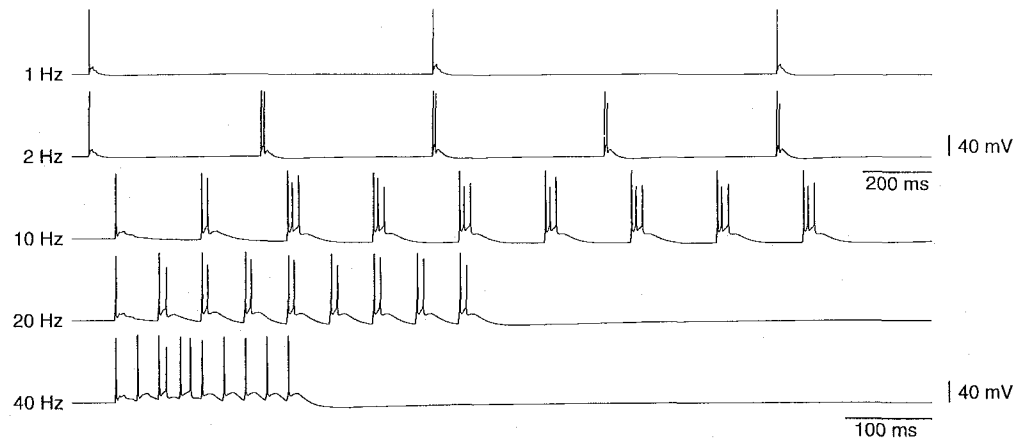


Fig. 2. PY cell responses to cortical shocks at different frequencies in the model including short-term synaptic plasticity.

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 deinactivation 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

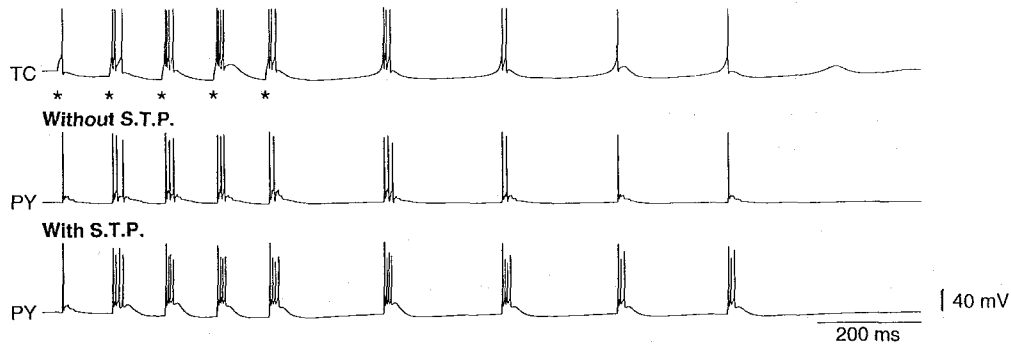


Fig. 3. PY cell responses to five thalamic shocks (indicated by *) at 10 Hz. TC cell response (upper), PY cell response in the model without short-term synaptic plasticity (S.T.P.) (middle), and PY cell response in the model with short-term synaptic plasticity (lower).

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 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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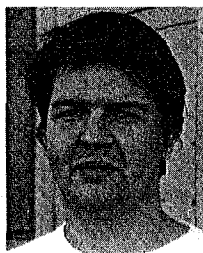
References

- [1] L.F. Abbott, J.A. Varela, K. Sen, S.B. Nelson, Synaptic depression and cortical gain control, *Science* 275 (1997) 220–224.
- [2] M.C. Angulo, J. Rossier, E. Audinat, Excitatory unitary synaptic inputs to GABAergic fast-spiking interneurons in the rat neocortex, *Eur. J. Neurosci.* 10 (10) (1998) 84.
- [3] M. Bazhenov, I. Timofeev, M. Steriade, T.J. Sejnowski, Cellular and network models for intrathalamic augmenting responses during 10-Hz stimulation, *J. Neurophysiol.* 79 (5) (1998) 2730–2748.
- [4] M. Bazhenov, I. Timofeev, M. Steriade, T.J. Sejnowski, Computational models of thalamocortical augmenting responses, *J. Neurosci.* 18 (16) (1998) 6444–6465.
- [5] M.A. Castro-Alamancos, B.W. Connors, Short-term plasticity of a thalamocortical pathway dynamically modulated by behavioral state, *Science* 272 (1996) 274–277.
- [6] M.A. Castro-Alamancos, B.W. Connors, Spatiotemporal properties of short-term plasticity in sensorimotor thalamocortical pathways of the rat, *J. Neurosci.* 16 (8) (1996) 2767–2779.
- [7] M.A. Castro-Alamancos, B.W. Connors, Cellular mechanisms of the augmenting response: short-term plasticity in a thalamocortical pathway, *J. Neurosci.* 16 (23) (1996) 7742–7756.
- [8] R.A. Deisz, D.A. Prince, Frequency-dependent depression of inhibition in guinea-pig neocortex in vitro by GABAB receptor feed-back on GABA release, *J. Physiol.* 412 (1989) 513–541.
- [9] A. Destexhe, T. Bal, D.A. McCormick, T.J. Sejnowski, Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices, *J. Neurophys.* 76 (1996) 2049–2070.
- [10] D. Ferster, S. Lindstrom, Augmenting responses evoked in area 17 of the cat by intracortical axon collaterals of cortico-geniculate cells, *J. Physiol.* 367 (1985) 217–232.
- [11] Z. Gil, B.W. Connors, Y. Amitai, Differential regulation of neocortical synapses by neuromodulators and activity, *Neuron* 19 (3) (1997) 679–686.
- [12] Z. Gil, B.W. Connors, Y. Amitai, Quantal properties and release characteristics of thalamocortical and intracortical synapse in layer 4 of neocortex, *Eur. J. Neurosci.* 10 (10) (1998) 137.
- [13] M.L. Hines, N.T. Carnevale, The NEURON simulation environment, *Neural Comput.* 9 (6) (1997) 1179–1209.
- [14] A.R. Houweling, M. Bazhenov, I. Timofeev, M. Steriade, T.J. Sejnowski, Intra cortical augmenting responses mediated by short-term depression of cortical synapses, submitted.
- [15] J.R. Huguenard, D.A. McCormick, Simulation of the currents involved in rhythmic oscillations in thalamic relay neurons, *J. Neurophysiol.* 68 (4) (1992) 1373–1383.
- [16] Z.F. Mainen, T.J. Sejnowski, Influence of dendritic structure on firing pattern in model neocortical neurons, *Nature* 382 (1996) 363–366.
- [17] H. Markram, Y. Wang, M. Tsodyks, Differential signaling via the same axon of neocortical pyramidal neurons, *Proc. Natl. Acad. Sci. USA* 95 (9) (1998) 5323–5328.
- [18] R. Metherate, J.H. Ashe, Facilitation of an NMDA receptor-mediated EPSP by paired-pulse stimulation in rat neocortex via depression of GABAergic IPSPs, *J. Physiol.* 481 (2) (1994) 331–348.
- [19] D. Morin, M. Steriade, Development from primary to augmenting responses in the somatosensory system, *Brain Res.* 205 (1) (1981) 49–66.
- [20] R.S. Morison, E.W. Dempsey, Mechanism of thalamocortical augmentation and repetition, *Am. J. Physiol.* 138 (1943) 297–308.
- [21] A. Nunez, F. Amzica, M. Steriade, Electrophysiology of cat association cortical cells in vivo: intrinsic properties and synaptic responses, *J. Neurophysiol.* 70 (1) (1993) 418–430.

- [22] D. Pare, E.J. Lang, Calcium electrogenesis in neocortical pyramidal neurons in vivo, *Eur. J. Neurosci.* 10 (10) (1998) 3164–3170.
- [23] D.P. Purpura, R.J. Shofer, F.S. Musgrave, Cortical intracellular potentials during augmenting and recruiting responses. II. Patterns of synaptic activities in pyramidal and nonpyramidal tract neurons, *J. Neurophysiol.* 27 (1964) 133–151.
- [24] S. Song, J.A. Varela, L.F. Abbott, S.B. Nelson, A quantitative description of synaptic depression at monosynaptic inhibitory inputs to visual cortical pyramidal neurons, *Soc. Neurosci. Abstr.* 23 (1997) 2362.
- [25] M. Steriade, G. Iosif, V. Apostol, Responsiveness of thalamic and cortical motor relays during arousal and various stages of sleep, *J. Neurophysiol.* 32 (2) (1969) 251–265.
- [26] M. Steriade, I. Timofeev, Short-term plasticity during intrathalamic augmenting responses in decorticated cats, *J. Neurosci.* 17 (10) (1997) 3778–3795.
- [27] M. Steriade, I. Timofeev, F. Grenier, N. Durmuller, Role of thalamic and cortical neurons in augmenting responses and self-sustained activity: dual intracellular recordings in vivo, *J. Neurosci.* 18 (16) (1998) 6425–6443.
- [28] K.J. Stratford, K. Tarczy-Hornoch, K.A. Martin, N.J. Bannister, J.J. Jack, Excitatory synaptic inputs to spiny stellate cells in cat visual cortex, *Nature* 382 (1996) 258–261.
- [29] K. Tarczy-Hornoch, K.A. Martin, J.J. Jack, K.J. Stratford, Synaptic interactions between smooth and spiny neurones in layer 4 of cat visual cortex in vitro, *J. Physiol.* 508 (2) (1998) 351–363.
- [30] A.M. Thomson, J. Deuchars, D.C. West, Single axon excitatory postsynaptic potentials in neocortical interneurons exhibit pronounced paired pulse facilitation, *Neuroscience* 54 (2) (1993) 347–360.
- [31] A.M. Thomson, Activity-dependent properties of synaptic transmission at two classes of connections made by rat neocortical pyramidal axons in vitro, *J. Physiol.* 502 (1) (1997) 131–147.
- [32] I. Timofeev, M. Steriade, Cellular mechanisms underlying intrathalamic augmenting responses of reticular and relay neurons, *J. Neurophysiol.* 79 (5) (1998) 2716–2729.
- [33] M.V. Tsodyks, H. Markram, The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability, *Proc. Natl. Acad. Sci. USA* 94 (2) (1997) 719–723.
- [34] J.P. Turner, T.E. Salt, Characterization of sensory and corticothalamic excitatory inputs to rat thalamocortical neurones in vitro, *J. Physiol.* 510 (3) (1998) 829–843.



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Terrence Sejnowski is an Investigator with the Howard Hughes Medical Institute and a Professor at The Salk Institute for Biological Studies where he directs the Computational Neurobiology Laboratory. He is also Professor of Biology at the University of California, San Diego, where he is Director of the Institute for Neural Computation. Dr. Sejnowski received B.S. in physics from the Case-Western Reserve University, M.A. in physics from Princeton University, and a Ph.D. in physics from Princeton University in 1978. In 1988, Dr. Sejnowski founded Neural Computation, published by the MIT Press. The long-range goal of Dr. Sejnowski's research is to build linking principles from brain to behavior using computational models. This goal is being pursued with a combination of theoretical and experimental approaches at several levels of investigation ranging from the biophysical level to the systems level.

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[4] S.E. Fahlman and C. Lebiere, The cascade-correlation learning architecture, Report CMU-CS-90-100, School of Computer Science, Carnegie Mellon University, Pittsburgh, PA, 1990.

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