Paroxysm potentiation: synaptic potentiation enhances repetitive epileptiform discharge without enhancing evoked response

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Abstract

We have explored a rat model of the human photoparoxysmal response (PPR), a high amplitude epileptiform response to repetitive strobing. This rat PPR is acquired and is likely to involve potentiation at multiple sites in the circuit. The thalamocortical synapse is known to show long-term potentiation and is likely to be one of the sites involved. However, in our preparation, spike amplitude increased substantially in the late PPR without increasing in the first response cycle, suggesting no augmentation at this site. We performed network simulations to explore this paradox. We found that mild increases in synaptic strength at the thalamocortical synapses did not significantly alter response to single stimulation but nonetheless produced substantial amplitude augmentation during an epileptiform oscillation.

Summary

We studied a robust, strobe-triggered, generalized photoparoxysmal response (PPR) in rat that resembles the human PPR. PPR in humans is a brief epileptiform response to photic stimulation that typically generalizes and is associated with epileptic syndromes. Photically-induced seizures have come into recent public attention with reports of seizures associated with viewing Pokemon and with playing video games.[4, 7] The production of an epileptiform discharge after repeated exposure to the high intensity stimulation makes this a form of seizure kindling.

The high amplitude stimulation of a strobe can be expected to produce strong firing in all elements of the thalamocortical circuit, including excitatory and inhibitory cells in cortex, thalamocortical cells and reticularis neurons. As a consequence, we would predict synaptic potentiation at thalamic and cortical sites that are capable of plasticity in response to strong activation. One such site is the thalamocortical synapse itself. This synapse has been shown to be a site of long term potentiation in the juvenile[2] and in the adult.[5]

Rats of several strains were implanted with epidural electrodes for chronic electrocorticography and exposed to repeated 2 s 8 Hz trains of intermittent strobe stimulation. A feature detection algorithm was used to identify strobe-related spikes and measure voltage and sharpness. A computer model was developed based on prior models of the thalamocortical augmenting response.[1, 3] The network had 31 columns. Each consisted of a cortical pyramidal cell, a cortical interneuron, a thalamocortical cell and a reticularis cell. Individual neurons were single compartments except for the pyramidal cell which had somatic and dendritic compartments. Connectivity footprint between cell types was varied from 3-15 in size (Fig. 1). Simulations were run in Neuron on a 54 node IBM 1300 cluster.[6]

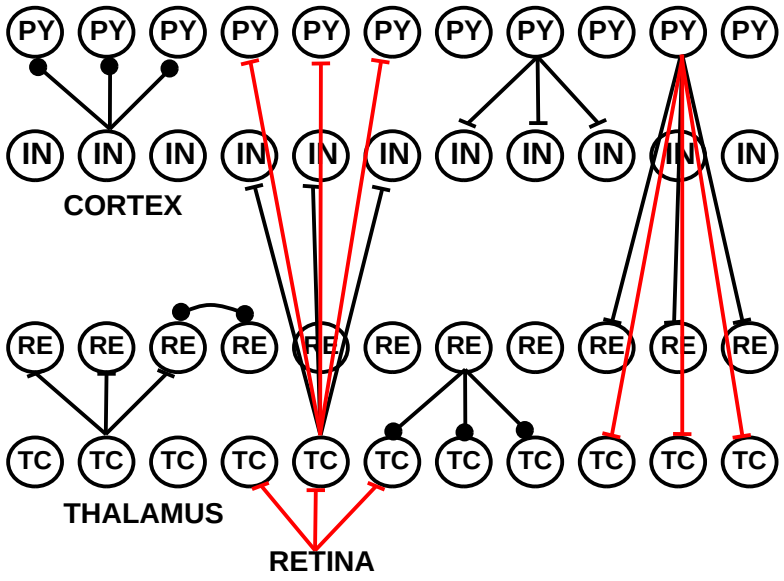

Fig. 1: Simulated circuitry: representative synapses are shown. Synapses in red were augmented.

Following exposure over 1-2 days, the visual responses changed over time. Initially, most strobe episodes produced only low amplitude evoked potentials. Over the course of the first day of repeat strobe exposure, increasing numbers of high amplitude paroxysmal responses were seen (Fig. 2). By day 3, 81%(214/263) of the stimulation trains produced PPRs of 4 or more consecutive spikes, compared to only 46%(121/263) during the day of acquisition. This was associated with a significant increase in spike amplitude (3.4→4.0 ?mV; p<e1e-5) and in average number of cycles of response (7.7→9.2 cycles; $p<1 \cdot 10^{-4}$; the PPR rarely lasted for the entire 16 cycles of strobe stimulation). The response to the first strobe of the sequence showed a small, non-significant decrease in average amplitude, remaining at about half the size of an average PPR spike (1.8→1.7 ?mV).

In simulo, we assessed the effects of 65% potentiation at the thalamocortical synapse. This produced a mild augmentation in simulated field potential (Fig. 3). The must pronounced difference was in a secondary spike (oblique arrow) rather than in the initial large spike that followed each stimulation.

We assessed the sensitivity of the simulated cortical response to augmentation at other sites by co-varying synaptic strength at retinogeniculate (stim→TC), thalamocortical (TC→CX) and corticothalamic (Cx→TC) synapses (red lines in Fig. 1). We found that stim→TC synaptic strength had to be above a minimum level in order to get the coordinated pyramidal cell firing that we assume underlies the spike-and-wave field response. The bottom row of Fig. 4 shows that low stim→TC strengths do not result in substantial responses at any level of Cx→TC (columns) or TC→Cx (oblique axis). This is expected since the corticothalamic circuitry must be engaged by strong input in order to produce high amplitude activity. Fig. 4 demonstrates that TC→Cx synaptic augmentation

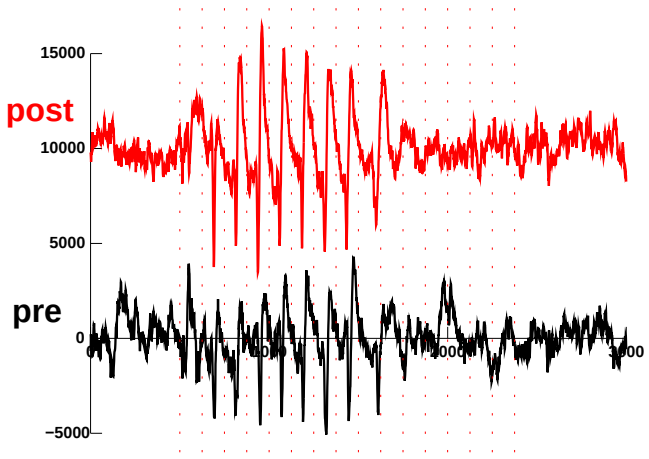

Fig. 2: Physiology: PPR spikes are generally larger following full acquisition at days 2-3. The evoked response to the first strobe does not show augmentation and has a distinct morphology.

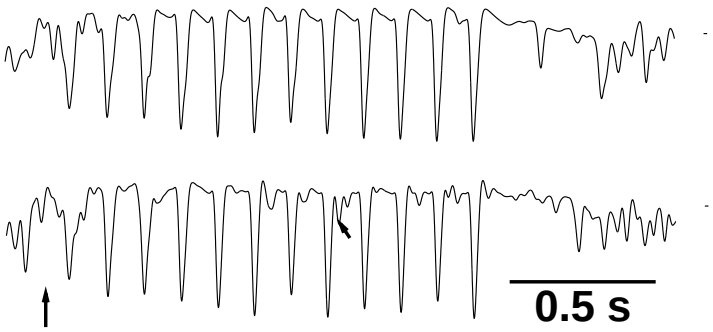

Fig. 3: Simulated field potentials before (above) and after (below) augmentation at the TC→CX synapse. Vertical arrow shows onset of stimulation. Oblique arrow shows augmented secondary spike. Spike wave duration matches duration of stimulation.

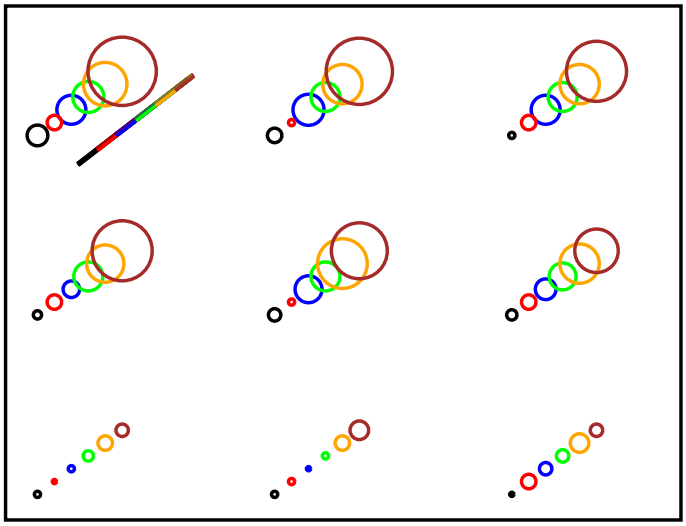

Fig. 4: Alteration in population spike response with location in synaptic strength parameter space. Circle diameter represents response strength as measured by number of pyramidal cell spikes grouped around time of maximum firing following a stimulation averaged over all cycles.

does produce significant increase in spike-wave amplitude while Cx→TC synaptic augmentation has inconsistent effects, sometimes producing augmentation and sometimes diminution, depending on the location in synaptic parameter space.

We then looked at the sensitivity of the initial population response to changes in the same parameters (Fig. 5). First-response strength still showed some increase with TC→Cx synaptic augmentation but this increase was much less than seen in in Fig. 4 and was not nearly as consistent across parameter space.

The augmentation in strobe response following a period of exposure likely reflects alterations in synaptic responses in multiple locations, quite possibly involving diminution in inhibition (either through reduction of activation of inhibitory cells or reduction in the strength of the inhibitory projections themselves) in addition to changes in excitatory pathways. Further alterations could also occur in cellular dynamics, with alterations in channel properties enhancing tendency for neuron bursting. In this study we have focused on a possible role of 3 major excitatory synapses which make up the input pathway (retinothalamic) and the reciprocal connections between thalamus and cortex. We found that augmentation at the TC→Cx synapse was particularly effective in increasing the repetitive population response as measured by near-simultaneous spiking of pyramidal cells, reflected in the simulated population spike-wave. Despite the fact that this synapse lies on the direct pathway connecting stimulus (the strobe) to response (the population spike), the single stimulation response was not consistently increased by augmentation at this location. Since the repetitive epileptiform response augments and the single response does not, this suggests that this epileptiform response emerges from the interaction of the

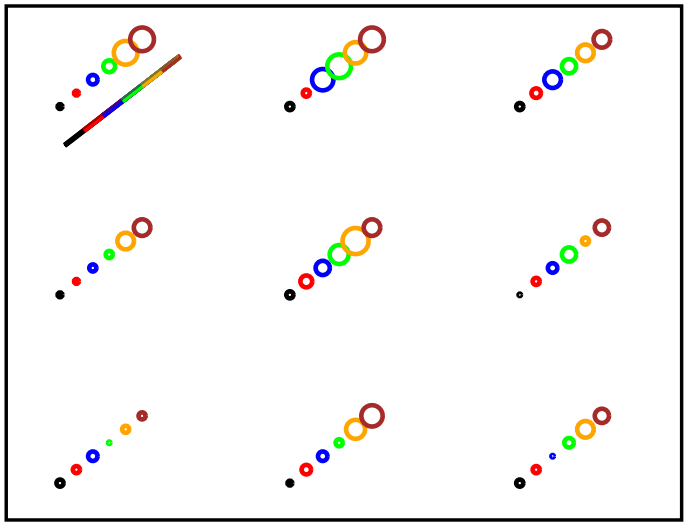

Fig. 5: Alteration in initial population spike response with location in synaptic strength parameter space. Circle diameters are at same scale as in Fig. 4.

enhanced synapse and the network.

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