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# Influence of the decay time of the GABAergic postsynaptic current on the spatial spread of network activity

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**Abstract**

The subunit composition of the $GABA_A$ receptor determines the decay time of the GABAergic inhibitory postsynaptic current (IPSC). In mice in which the α1 subunit is deleted, the decay time is longer than in wild-type mice, while the spatial spread of activity in the visual cortex following local stimulation is reduced. Using a simple network model of the visual cortex, we show that this reduced spread of activity could be accounted for by the longer IPSC decay time. After local stimulation of the network, a patch of activity develops, the equilibrium size of which depends on the IPSC decay time.


*Keywords:* $GABA_A$ receptor; α1 subunit; IPSC decay time; Network activity; Spatiotemporal patterns

## 1. Introduction

The $GABA_A$ receptor is the main inhibitory receptor in the mammalian brain. GABA synapses are present in all layers of the neocortex and on virtually all types of neurons. GABAergic inhibition prevents excessive firing, is involved in the synchronization of firing, and plays an important role in the fine tuning of synaptic efficacies. Impaired GABAergic transmission has been associated with several pathological conditions, such as epilepsy and anxiety.

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The $GABA_A$ receptor is composed of five subunits, which can be of different classes. The $\alpha, \beta, \gamma$, and $\delta$ classes are the most abundant ones. Each class consists of a number of different types; for example, there are six types of the $\alpha$ subunit ($\alpha 1$ through $\alpha 6$). In the neonatal visual cortex, the most abundant $\alpha$ subunit in layers II and III is $\alpha 3$. During postnatal development, between postnatal days 6 and 21 (around the time of eye opening), $\alpha 1$ expression is highly upregulated, so that in adult neurons, $\alpha 1$ is the most abundant $\alpha$ subunit.

The subunit composition of the $GABA_A$ receptor affects the deactivation and desensitization times and consequently also the synaptic response. The naturally occurring upregulation of the $\alpha 1$ subunit during development is correlated with faster inhibitory postsynaptic currents (IPSCs) [3]. In line with this, the decay time of the IPSC is longer in mice in which the $\alpha 1$ subunit is deleted ($\alpha 1 -/-$ mice) than in wild type mice ($\alpha 1 +/+$ mice). In $\alpha 1 -/-$ mice the ability of neurons in the visual cortex to fire synchronously at $\gamma$-frequencies is significantly reduced [1]. Furthermore, the spatial spread of network activity following stimulation of the cortex is much smaller in $\alpha 1 -/-$ mice than in $\alpha 1 +/+$ mice (as observed with voltage-sensitive dyes). Using a simple model of the visual cortex, we tested whether this reduced spatial spread of network activity could be a direct result of the longer decay time of the IPSC.

## 2. Model

The model described in [2] is used to construct a network with integrate-and-fire neurons and roughly the same connectivity pattern as in the cortex.

### 2.1. Network model

The network is composed of excitatory (e) and inhibitory (i) cells, which are randomly placed on a two-dimensional grid, the boundaries of which are connected to each other (torus). Given the distribution of excitatory and inhibitory cells, each cell is connected to a number of target cells, which are randomly chosen with uniform probability within a circular field (see Fig. 1). The radius of this field depends on the type of outgoing connection. The e to e connections are short range, the e to i connections are long range, and the i to e and i to i connections are medium range. For each cell, the strength and number of outgoing connections also depend on the type of connection.

### 2.2. Neuron model

The membrane potential of a neuron at time $t$, $V(t)$, is expressed relative to the resting potential $E_r$ and is calculated using

$$V(t) = \frac{S_e(t)M_e + S_i(t)M_i}{1 + S_e(t) + S_i(t)}, \tag{1}$$

where $S_e = G_e/G_r$ and $S_i = G_i/G_r$ represent the strengths of the excitatory and inhibitory inputs, respectively, expressed as ratios of the synaptic conductances $G_e$ and $G_i$ to the

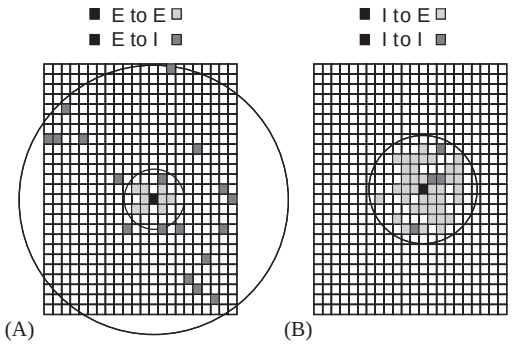


Fig. 1. Network connectivity. The target cells of an excitatory cell (black square in A) and an inhibitory cell (black square in B). The target cells can be excitatory (E) or inhibitory (I). (For display purposes, the radii of the fields are not exactly the same as in the simulations.)

resting conductance $G_r$; and $M_e = E_e - E_r$ and $M_i = E_i - E_r$, where $E_e$ and $E_i$ are the excitatory and inhibitory driving potentials, respectively. The values of $S_e$ and $S_i$ are taken to decay according to the time courses of EPSC and IPSC, respectively:

$$S_e(t+1) = D_e S_e(t) + I_e(t), \tag{2}$$

$$S_i(t+1) = D_i S_i(t) + I_i(t), \tag{3}$$

where $D_e$ and $D_i$ are constants and $I_e(t)$ and $I_i(t)$ are the total excitatory and inhibitory inputs at time $t$, with time partitioned into discrete intervals. The generation of an action potential is reduced to a threshold rule: if $V(t)$ exceeds the firing threshold $\theta$, the cell fires. After firing, $\theta$ is put up to $M_e$ for two time intervals (absolute refractory period) and then decreases in two time intervals (relative refractory period) to the default value. Each time interval in the model corresponds to about 1 ms.

### 2.3. Parameters

The network is composed of 80 x 80 cells, 30% inhibitory (i) and 70% excitatory (e). In Fig. 2, the following parameter values are used. For the e to e connections: number = 24, radius = 2, and strength = 0.06. (Note that a target cell can be innervated by multiple connections from the same neuron.) For the e to i connections: number = 20, radius = 15, and strength = 0.05. For the i to e connections: number = 74, radius = 5, and strength = 0.06. For the i to i connections: number = 6, radius = 5, and strength = 0.06. (Radius is expressed in number of cells; connection strength is expressed as ratio of the synaptic conductance to the resting conductance; see Section 2.2.) $M_e = 73$ mV, and $M_i = 0$ mV (shunting inhibition). The value of $D_e$ is such that $S_e$ decays with a time constant $\tau$ of 5 ms (EPSC decay time). In Fig. 3, $M_i = -10$ mV, the number of i to e connections is 55, and $D_i$ is such that $S_i$ decays with a time constant of 6 ms (IPSC decay time); for the rest, the parameter values are as in Fig. 2.

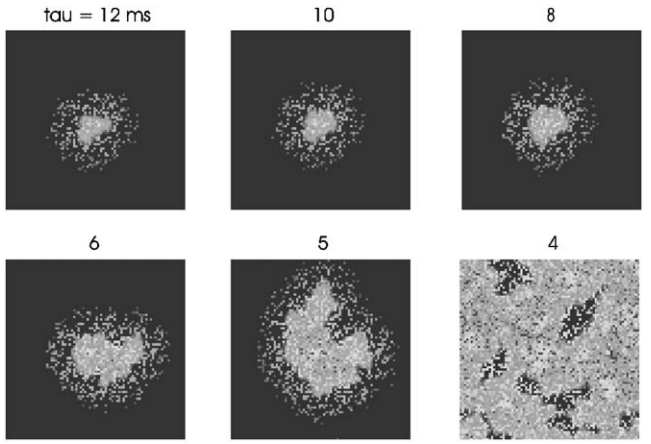


Fig. 2. For different values of the IPSC decay time, the patch of active cells in the network at equilibrium. Light gray values denote strongly depolarized neurons.

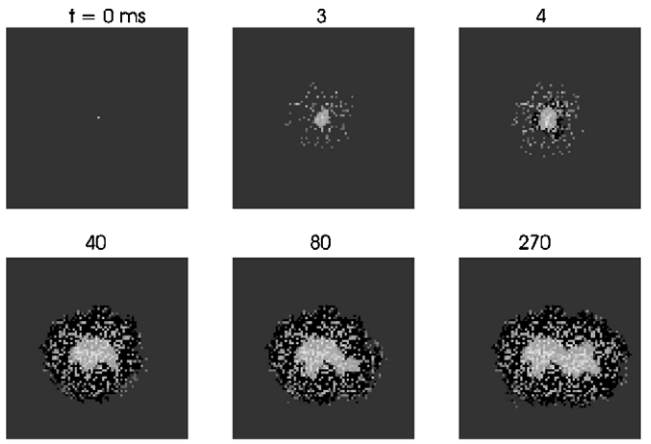


Fig. 3. Development of a patch of active cells. To show the effect of inhibition on excitatory cells, the inhibitory driving potential is here different from the resting potential. At $t = 0$ ms, an excitatory cell in the middle of the network is stimulated, after which stimulation is stopped. Activity expands, and the patch of active cells becomes surrounded by a ring of inhibited excitatory cells. Black indicates a hyperpolarized cell. At $t = 270$ ms, there is no further expansion of activity (equilibrium).

## 3. Results

A small patch of cells in the network is stimulated for a number of time steps, after which stimulation is stopped. The strengths of the connections are such that the network remains active without external stimulation. Activity in the network spreads out until an equilibrium state is reached in which a patch of cells is active that does no

longer expand. The size of this patch depends on the decay time of the IPSC (Fig. 2). The longer the decay, the smaller the size of the patch of active cells, in accordance with what has been found experimentally.

When excitatory cells are stimulated, they recruit other cells in their neighborhood (the e to e connections are short range), so that activity expands. But at the same time, inhibitory cells farther away become activated (the e to i connections are long range), which in turn project back to excitatory cells (the i to e connections), inhibiting them (see Fig. 3). Thus, the active patch of cells becomes surrounded by a ring of inhibited excitatory cells (and active inhibitory cells), which, if the ring is closed, prevents further expansion of activity. A longer IPSC decay time means that the i to e connections are effectively stronger, so that the excitatory cells become more inhibited and the expansion of activity is stopped earlier. Note that the IPSC decay time influences inhibitory input not only on excitatory cells but also on inhibitory cells (the i to i connections). A long IPSC decay time means that also the i to i connections are effectively stronger, so that the inhibitory cells become less active and the excitatory cells become less inhibited. With the connectivity pattern and number of connections used, the overall result of these two opposing effects is that inhibition becomes stronger and the spread of activity is reduced.

## 4. Conclusions

In mice in which the $\alpha 1$ subunit of the $GABA_A$ receptor is deleted, the decay time of the IPSC is longer and the spatial spread of network activity following local stimulation of the visual cortex is reduced. Using a simple network model of the visual cortex, we have shown that this reduced spread of activity could be a direct result of the longer IPSC decay time. In the model, the longer the IPSC decay time, the smaller the patch of active cells at equilibrium. The longer the IPSC decay time, the earlier the expanding patch of activity is stopped by a surrounding ring of inhibited excitatory cells.

Essential in this mechanism are the presence of short-range e to e connections, long-range e to i connections, and medium-range i to e connections. The latter should be strong and numerous enough to build up a ring of inhibited excitatory cells that at some point can prevent further expansion of activity.

To test if the mechanism suggested by the model is indeed operative in the cortex, we are planning experiments in which we monitor whether a patch of active cells becomes surrounded by a ring of strongly inhibited excitatory cells.

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