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Disruptive effects on neocortical processing by pulsed fMRI gradients: A Modeling study in the auditory cortex

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Introduction and rationale

Functional Magnetic Resonance Imaging (fMRI) has, in recent years, gained wide usage in "non invasive" studies of the human brain. For example at the 2012 SfN conference in New Orleans, numerous papers deploying the fMRI approach were presented --- often by graduate students or other "volunteers' who had also served as test subjects in the reported studies. One of us (HW) had the opportunity to query several fMRI poster presenters as to their understanding of the biophysical basis of fMRI -- and its possible long term neural effect on "volunteer" subjects such as themselves . We also tried to get a feeling for how well understood the possibility of artifacts (due to the magnetically induced currents in the brain) were. We were surprised to discover that the majority of these student presenters (and in some cases, the PIs on the study as well) had little or no understanding of how fMRI works -- and the fact that it involves the "invasion" of several forms of electromagnetic energy into the brain. However, most of them were able to cite the Food and Drug Administration (FDA) ruling that fMRI was safe and efficacious to use in volunteer studies.

The FDA stance on fMRI safety and efficacy is based largely on the notion that intra-cranial currents induced by the rapid switching of the applied magnetic field are below the levels required to fire action potentials (APs) in central neurons. Indeed the induced currents from fMRI exposure are below levels used deliberately in Transcranial Magnetic Stimulation (TMS) devices to fire neuronal APs -- but that does not mean that they can not modulate ongoing signal processing patterns -- especially in neurons that are already active. Such neural modulations could have several detrimental consequences, including:

1. The activity patterns that are being observed using fMRI field exposure would be different than the unperturbed ones -- i.e. there is a substantial artifact possibility.

2. Repeated and/or prolonged changes in neural activity due to fMRI exposures could pose a safety issue to the "volunteer" subjects used -- especially those involved in multiple studies.

It therefore behooves the Neuroscience community to better understand and quantify the possible neuro - modulatory effects of fMRI -- and to better educate "volunteer" subjects as to these limitations and hazards. As a step in this direction, we are herein reporting the use of GENESIS models of cortical neuron networks to study modulatory effects of fMRI induced fields.

To our knowledge, this study is the only attempt to analyze the effect of these fields on a model of a neocortical network that contains morphologically detailed and realistically firing pyramidal cells.

Questions to be answered by this study:

1. What effect, if any, do these pairs of E pulses have on cortical network activity and the generation of action potentials (APs)?

2. For a given set of pulse parameters, what is the minimum E field (E_{thresh}) needed to produce a measurable effect?

3. The maximum value of E is proportional to dB/dt, which is inversely proportional to t_r. Thus E is larger when there is a fast rise time, but it lasts for a proportionally shorter time. Is the product of E_{thresh} and t_r a constant?

4. What fMRI pulse parameters result in the largest influences on cortical network activity or lowest E_{thresh}?

5. Does the network produce a “stochastic resonance” effect that magnifies the E field effects beyond those seen when the E field is applied to a single cell, or when it is applied to a network with no ongoing activity?

6. Depending on whether a depolarizing E field precedes or follows a hyperpolarizing one, the pulse pairs have the potential to accelerate or delay the generation of action potentials. Do positive B_{grad} pulses have a greater or lesser effect on network activity than negative ones?

7. How do these E_{thresh} values compare with those fields that are likely to be produced at the location of the auditory cortex during an fMRI experiment?

Previous studies

- Were on unwanted peripheral nerve stimulation (PNS) during full-body MRI.
- On intended transcranial magnetic stimulation (TMS) of cortical areas (Reilly 1989).
- Models used modified Hodgkin-Huxley cable equation or compartmental models of myelinated axons
- Identified two mechanisms leading to changes in membrane potential that could affect AP generation:

(1) E fields that are longitudinal to the cell membrane surface generate transmembrane currents that are proportional to the gradient of the field along the surface and inversely to the axial resistance of the section of dendrite or axon. (Roth and Basser 1990)

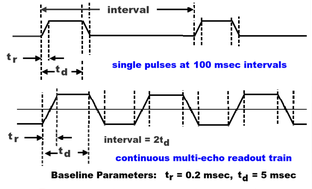
(2) E fields that are transverse to the cell membrane can produce nearly instantaneous shifts in the intracellular membrane potential that are proportional to the field strength and to the axon or cell diameter. (Ye et al. 2011)

In the context of PNS and generation of APs in axons, (1) has generally been shown to have the greatest effect, although (2) cannot be ignored. However, the situation is considerably different for cortical neurons.

The input model

The figure at the right shows the two standard pulse train models that were used. The rising sides of the B pulses generate positive E pulses of width t_r, and negative ones on the falling sides.

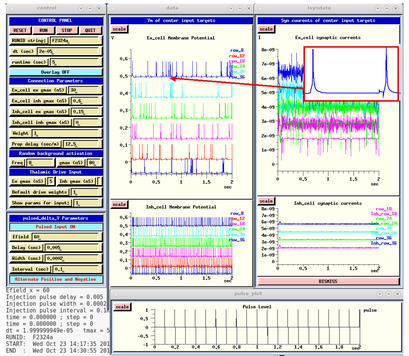
For the transverse field model, an instantaneous shift in Vm was applied to each cell compartment equal to its diameter times the transverse component of E.
For the longitudinal field model, each compartment received a current injection that is proportional to the gradient of the E field component along the compartment and inversely to the axial resistance (e.g. as for the oblique and basal dendrites).



Graphical User Interface

Typical simulations runs were for 5 sec. For the standard single B pulse spike train with a separation of 100 msec, the E pulse pairs are presented 50 times. This large separation of pulses is not used in a typical experiment, but it allows us to collect data on multiple presentations of a single pulse. An expected response would be some sign of a regular disturbance from normal activity at 100 msec intervals. To simulate the continuous spike train, the Interval would be set to twice the Delay t_d.

The simulation GUI at the right shows a run of 'fMRInet' with E = 60 V/m, or about 1.5 times the estimated E_{thresh}. The plots of pyramidal and basket cell soma membrane potential (Vm) and synaptic currents arising from other cells in the network are for several representative cells, and are shown for the first 2 sec.



Summary of principal results

1. The simulation results show that, when the amplitude and duration are sufficient, the pairs of positive and negative E pulses affect the timing of network activity by advancing or retarding the generation of APs.

2. With the default pulse parameters, E_{thresh} is 40 V/m for single E pulse pairs, and 5 V/m for a continuous train.

3. PSD values are nearly identical for values of E that are inversely proportional to t_r in the range 0.1 to 0.5 msec.

4. Beyond the effects of duration and amplitude, tests on single cell and network models showed a maximal effect on the timing of network activity when the delay t_d between the postive and negative E pulses was > 5 msec, or enough to "bracket" a developing AP.

5. In the absence of ongoing 8 Hz background activity, the thresholds for generating APs in the quiescent network were 5 times higher. Thresholds that caused measurable changes in the firing of single cell models were only slightly higher than for the network. This suggests that ongoing network activity can amplify an effect that is large enough to be present in a single cell, but it is unlikely to lower the threshold for the effect to occur.

6. When a positive E pulse precedes the negative one, E_{thresh} is lower than when the negative occurs first. This indicates that an initial hyperpolarizing stimulation has less of an effect on changing the timing of action potentials.

7. A crude "back of the envelope" calculation with Faraday's law, assuming $B_{grad}(z)$ is constant in the x-y plane at 0.05 * z T/m^2 with a rise time t_r = 0.1 msec, E would be about 0.35 V/m at the location of the auditory cortex. The simulated E_{thresh} values are 10 to 100 times larger, and are in the range reported for generation of APs in axons (Reilly 1989), well below those used in fMRI expriments.

Future work

In order to completely answer the final question of how these E_{thresh} values compare with those likely to be produced at the location of the auditory cortex:

It is necessary to more accurately determine the E field magnitudes and their gradients that would be expected at the auditory and visual cortices during typical EPI fMRI gradient pulse sequences.

Because the magnitudes of the B gradient fields vary with position along the direction of the gradient, this calls for a detailed calculation of the B and E field values at the cortex using finite difference time domain (FDTD) numerical methods to be performed, rather than the simple Faraday's law estimates made in this study.

The effects of E fields longitudinal to the membrane surface were not investigated in enough detail to conclude that they can be neglected. Any further development or use of this model should address these effects.