Dose-Response in Non-Invasive Brain Stimulation - Animal/Cellular Level
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Notes on the limits of electric field sensitivity

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Lots of references (by PMID) for those who want to dig in.

The polarization of a neuron membrane is linear with electric field.

$$V_{tm} = A * EF$$

Change in membrane potential of a given compartment of the neurons. (in mV)

A number
"Coupling constant": mV change in membrane potential per mV/mm Electric Field
"Polarization length": in mm

The Electric Field (in mV/mm) the neuron is exposed to*

Shown for spheroids (PMID: 1278928; PMID: 10920001) and axons transverse to field (PMID: 34077366)

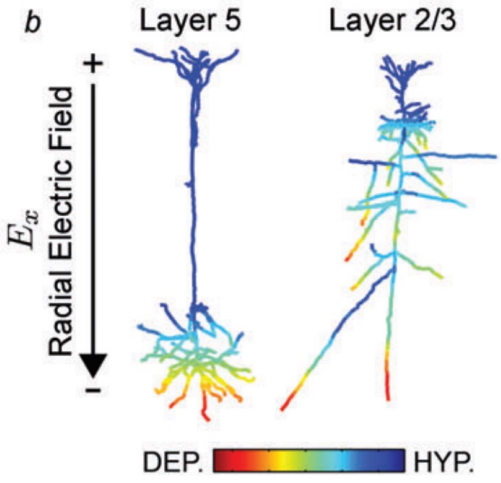
Shown for semi-infinite terminating axons or bent axons (PMID: 8244426; PMID: 1278925)

Shown for "compact" neurons (PMID: 19413956; PMID: 14978199; PMID: 3801574)

Shown (sometimes) for "not compact" axon/dendrite terminals (PMID: 23366946; PMID: 31611014)

*Quasi-unform assumption (PMID: 23290681)

Not the case for long axons / not compact neurons in non-uniform fields (PMID: 1487287, PMID: 9609941; PMID: 9929489)



PMID: 23478132

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Change in membrane potential of a given compartment of the neurons. (in mV)

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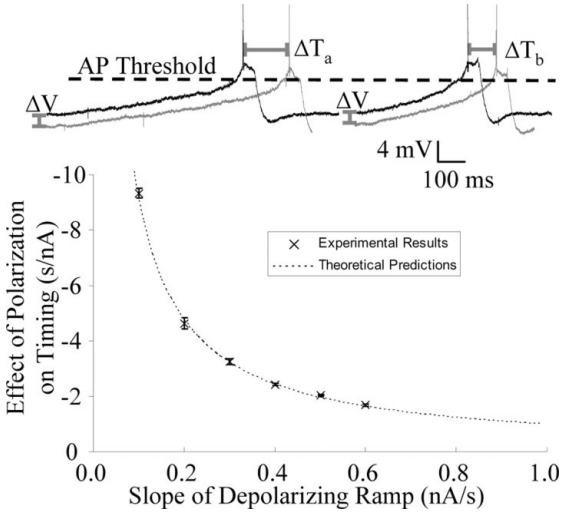
The Electric Field (in mV/mm) the neuron is exposed to*

- There is no minimum Electric Field that has no effect. No matter how small the Electric Field some membrane polarization will be produced.
- Since membrane potential governs neuronal function, is there than no limit to how small an Electric Field is "effective?



PMID: 17360926

The “how low can you go” game.

$$V_{tm} = A * EF$$

In animal models, the ability to detect the effect of an Electric Field (either directly on membrane potential or secondary changes in neuronal/network function) is limited only by S/N.

So over many (hundreds) of trials, the effects of very low-intensity Electric Fields can be “shown”.

(PMID: 20624597; PMID: 21068312; PMID: 12917358; PMID: 36044976)

(Its also possible to experimentally NOT “show” effects for given Electric Field)

The Journal of Neuroscience, November 10, 2010 • 30(45):15067–15079 • 15067

Cellular/Molecular

Low-Intensity Electrical Stimulation Affects Network Dynamics by Modulating Population Rate and Spike Timing

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Clinical effects of transcranial electrical stimulation with weak currents are remarkable considering the low amplitude of the electric fields acting on the brain. Elucidating the processes by which small currents affect ongoing brain activity is of paramount importance for the rational design of noninvasive electrotherapeutic strategies and to determine the relevance of endogenous fields. We propose that in active neuronal networks, weak electrical fields induce small but coherent changes in the firing rate and timing of neuronal populations that can be magnified by dynamic network activity. Specifically, we show that carbachol-induced gamma oscillations (25–35 Hz) in rat hippocampal slices have an inherent rate-limiting dynamic and timing precision that govern susceptibility to low-frequency weak electric fields (<50 Hz; <10 V/m). This leads to a range of nonlinear responses, including the following: (1) asymmetric power modulation by DC fields resulting from balanced excitation and inhibition; (2) symmetric power modulation by lower frequency AC fields with a net-zero change in firing rate; and (3) half-harmonic oscillations for higher frequency AC fields resulting from increased spike timing precision. These underlying mechanisms were elucidated by slice experiments and a parsimonious computational network model of single-compartment spiking neurons responding to electric field stimulation with small incremental polarization. Intracellular recordings confirmed model predictions on neuronal timing and rate changes, as well as spike phase-entrainment resonance at 0.2 V/m. Finally, our data and mechanistic framework provide a functional role for endogenous electric fields, specifically illustrating that modulation of gamma oscillations during theta-modulated gamma activity can result from field effects alone.

(Animal studies of) Low electric field effects should develop explanations for low-intensity tES

$$V_{tm} = A * EF$$

Can neurons be modulated without triggering action potentials? (PMID: 10077317; PMID: 14978199)

Why are oscillations especially sensitive to electric fields? (PMID: 24167483; PMID: 21068312; PMID: 25129402; PMID: 30504921; PMID: 31189931; PMID: 34035240)

How is plasticity modulated modulated by electric fields and under what conditions is it very sensitivity to small electric fields? (PMID: 34749007; PMID: 20434997)

How can (weak) electric fields influence one neuronal function and not another, supporting targeted outcomes? (PMID: 31668982; PMID: 24155708)

When is more intensity not “more” outcomes? (PMID: 29258808)

What non-linear neuronal properties support a “supra-linear” sensitivity” (PMID: 17947123; PMID: 28655149)

Can other cell types such as glia (PMID: 27000523) or endothelial cells of the BBB be stimulated (PMID: 29915178, PMID: 33962079) - with distinct dose response?