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Rational modulation of neuronal processing with applied electric fields

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Abstract— **Traditional approaches to electrical stimulation, using trains of supra-threshold pulses to trigger action potentials, may be replaced or augmented by using 'rational' sub-threshold stimulation protocols that incorporate knowledge of single neuron geometry, inhomogeneous tissue properties, and nervous system information coding. Sub-threshold stimulation, at intensities (well) below those sufficient to trigger action potentials, may none-the-less exert a profound effect on brain function through modulation of concomitant neuronal activity. For example, small DC fields may coherently polarize a network of neurons and thus modulate the simultaneous processing of afferent synaptic input as well as resulting changes in synaptic plasticity. Through 'activity-dependent plasticity', sub-threshold fields may allow specific targeting of pathological networks and are thus particularly suitable to overcome the poor anatomical focus of noninvasive (transcranial) electrical stimulation. Additional approaches to improve targeting in transcranial stimulation using novel electrode configurations are also introduced.**

I. Introduction

The use of (brief) trains of supra-threshold electrical pulses to trigger action potentials in targeted central and peripheral neuronal structures is an established and effective theraputic tool. Here several complimentary approaches are presented and reviewed that a) target inhibitory neurons and non-neuronal cells; or b) modulate neuronal structures in a sub-threshold manner (i.e. without directly triggering action potentials). In addition, approaches to increase focality using multiple electrodes are discussed in this context. These approaches are not proposed as substitutes in applications where supra-threshold stimulation of neurons has been proven effective, rather these novel stimulation paradigms may be used to expand the clinical possibilities, efficacy, and safety of electrical stimulation. These un-traditional approaches are termed 'rational' because they generally require specific knowledge of the target structure's anatomical and biophysical properties, as well as the nature of information processing by that region. Approaches to suppress epileptiform activity, including sub-threshold DC stimulation [1], have been reviewed elsewhere [2] and are not explicitly discussed here. Approaches to modulate the dynamics [3], plasticity [4]-[6], or information content [7] of a neuronal network using *supra-threshold* stimulation are also not addressed here.

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II. Non-neuronal stimulation targets

Potential non-neuronal electrical stimulation targets include: 1) glia cells, the most abundant cell type in the brain; and 2) endothelial cells, whose tight junctions form the blood brain barrier. These cell types do not generate action potentials and are thus traditionally not considered 'electrically excitable'. Moreover, because neurons are considered the information processing units of the brain, electrical stimulation studies have largely ignored other cell types. However, polarization of either glia cells or endothelial cells can induce profound change in neuronal function including through changes in the extracellular micro-environment.

The blood-brain barrier (BBB) represents the site of exchange between blood, in the central nervous capillaries, and the brain extracellular fluid; the barrier is formed by tight-junctions between endothelial cells. Even moderate changes in barrier permeability can lead to profound changes in the chemical composition of the extracellular brain fluid and hence in neuronal function. Numerous studies have demonstrated that electric fields can modulate endothelial cell membrane permeability through electroporation [8]-[10]. Electroporation, like conventional neuronal activation, follows the polarization of cell membranes due to induced extracellular field gradients along the cells. However, electroporation requires significantly higher membrane polarization (~500 mV from rest) [11]; than that sufficient to trigger action potential in neurons (~15 mV from rest), and thus significantly stronger electrical stimulation. However, we propose that relatively low-intensity electrical stimulation may induce 'electro-permeation' of the blood-brain barrier through action on the tight-junctions *between* endothelial cells (Figure 1).

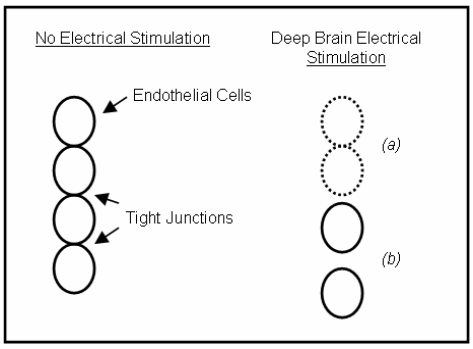

Fig. 1. Electroporation and electro-permeation induced by electrical stimulation (e.g. DBS). We propose an increase in blood-brain barrier permeability occurs through electroporation of endothelial cell membranes (A) and electro-permeation of tight-junctions between cells (B).

Consistent with this proposition, preliminary data using a monolayer system has demonstrated increased permeability of blood-brain barrier model systems by fields <200 mV/mm (Figure 2).

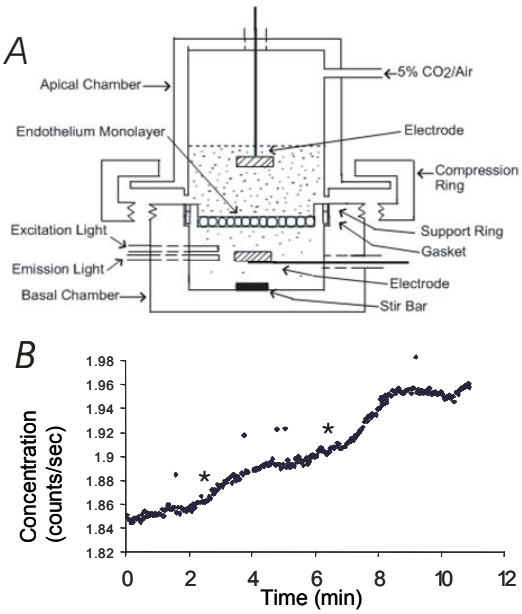

Fig. 2 A) Diagram of system for evaluating electro-permeation of BBB model systems. B) Increase in permeability following stimulation (at stars).

Glia cells may be modulated through both electroporation and through activation of voltage-gated membrane properties. As an example of the latter, polarization of glia cell membranes produces large changes in extracellular potassium concentration [12]; such changes will exert a profound effect on the excitability of neighboring neurons and have been suggested to play a role in clinical Deep Brain Stimulation [13]. Figure 3 illustrates the generation of potassium transients during electrical stimulation in a sub-thalamic nuclei (STN) brain slice, and the correlation of potassium concentration changes with unit activity after stimulation (during stimulation the unit activity was not monitored due to the stimulation artifact).

As noted above, (controlled) extracellular ionic transients may also be generated through stimulation of the BBB. Because extracellular ionic transients (generated by neurons, glia, and/or through the BBB) are ubiquities during high-intensity stimulation of nervous tissue, they should be considered in any quantitative and safe neuro-rehabilitation system incorporating high-intensity stimulation.

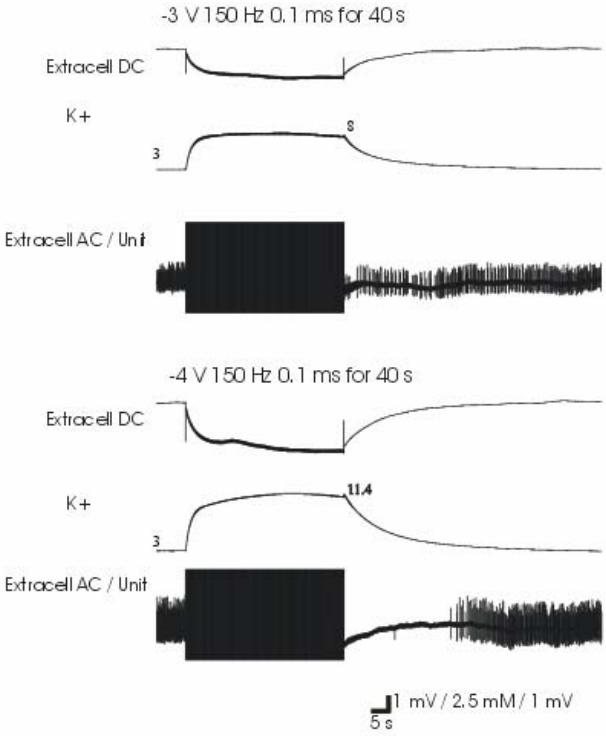

Fig. 3 Simultaneous monitoring of the extracellular 'DC' field shift, extracellular potassium concentration, and unit activity during high-frequency electrical stimulation of a STN brain slice. Two stimulation intensities are shown. Note the correlation between unit activity and recovery of the potassium transient post-stimulation. The extracellular DC trace is shown because of the clinical potential of using this signal as a simple indirect indicator of ionic transient generation and recovery.

Finally, the electroporation of neuronal cells should be considered, especially in the context of neurons adjacent to implanted stimulating electrodes. Preliminary data suggest that electric fields generated during clinical Deep Brain Stimulation protocols are sufficiently large near the electrodes to induce local electroporation. In all the above cases, electroporation/electro-permeation should be considered not only in designing *safe* stimulation protocols but also in designing novel *efficacious* protocols that take advantage of membrane/barrier permeability changes. A ready example is electroporation for controlled (systemically injected) drug delivery into local cell populations (e.g. electro-chemotherapy) [11], [14].

III. Inhibitory Neurons as Functional Stimulation Targets

Inhibitory neurons are ubiquities through the central

nervous system, exert a critical role on excitatory neuron function, and have been shown to be effected by extracellular electrical stimulation. Protocols do not currently exist to *specifically* target inter-neurons (or glia cells) but the activation of these cells during any realistic CNS stimulation paradigm should be considered (Vreugdenhil et al. 2005).

IV. Modulation of Neurons with Sub-threshold Fields

Sub-threshold electric fields polarize neurons, but not sufficiently to trigger action potentials. Sub-threshold stimulation thus employs lower peak amplitude stimulation which is advantageous from the perspective of electrochemical safety [15]. However, the sub-threshold stimulation protocols outlined below generally require relatively longer stimulation durations. The specific advantage of sub-threshold stimulation protocols relates to the ability to modulate neuronal function through fundamentally different mechanisms then supra-threshold stimulation (which triggers action potentials), thus suggesting novel therapeutic stimulation approaches. In addition, sub-threshold modulation is particularly relevant to environmental exposure concerns, where induced fields are generally small.

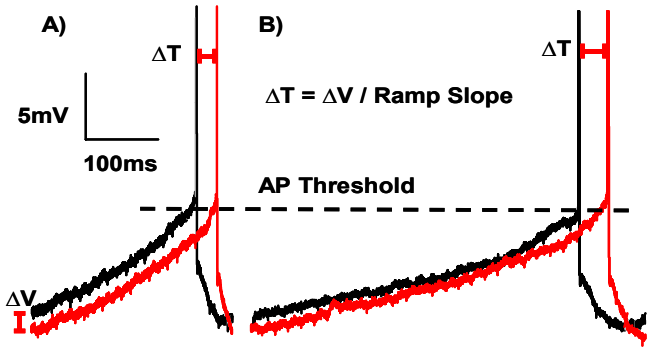

Fig. 4. Intracellular recordings of CA1 pyramidal cell response to depolarizing current ramps. A) Response to a .6nA/S intracellular current ramp. B) Response to a .4nA/S intracellular current ramp. In both cases hyperpolarization (ΔV) delayed the AP firing time. The change (ΔT), is inversely proportional to depolarizing ramp slope, $\Delta T_A < \Delta T_B$). Action potentials clipped.

Sub-threshold stimulation mechanisms may be considered in the context of 1) single neurons effects, or 2) synaptic/network function effects; though the two are evidentially related. One class of effects of sub-threshold fields on single neuron function is illustrated in Figure 4. The *timing* of neuronal firing in response to a depolarizing ramp (e.g. an EPSP) may be modulated by a small sub-threshold extracellular field. Moreover, the change is timing is effectively amplified as the slope of the depolarizing ramp decreases. Indeed, temporal coding is emerging as an important concept of information processing in the central nervous system [16]-[19]; thus protocols designed to modulate neuronal timing can potentially exert a functional.

We propose an additional level of amplification effecting spike timing, resulting from populations of neurons being coherently (synchronously) polarized by an extracellular electric field [20]. This results from these neurons being tightly coupled through recurrent synaptic mechanisms. The two synergistic single neuron/network amplification mechanisms presented above may provide an explanation for the observed effect of very small (sub-threshold) electric fields on gamma oscillation timing *in vitro* [21]. These *in vitro* experimental findings also reiterate the importance of considering timing (e.g. oscillation phase) when designing electric stimulation protocols.

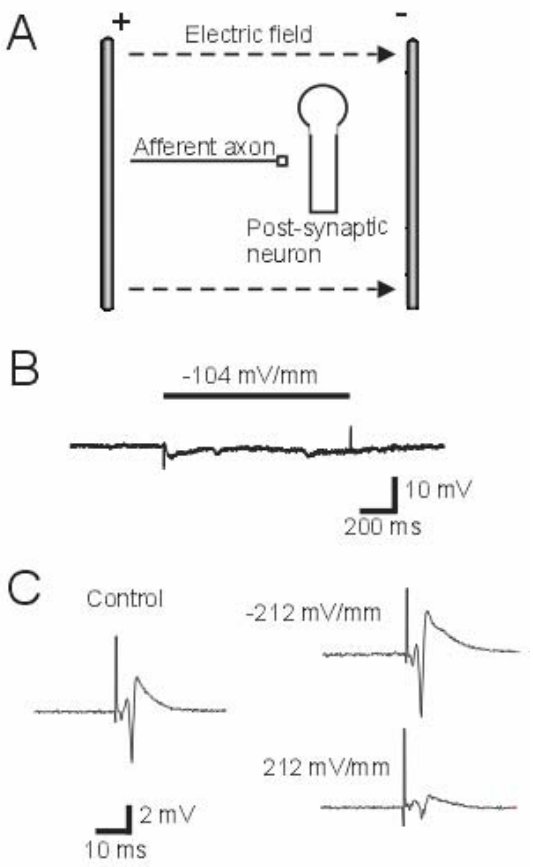

Fig. 5. Modulation of synaptic function through putative synaptic polarization. A) Experimental paradigm. Note that uniform electric fields are applied in a direction that would be expected to polarize synaptic terminal of afferent axons but not the post-synaptic neurons. B) Intracellular recording from a post-synaptic neuron during application of an electric field (bar). Though there was an increase in 'membrane noise' (see text) the soma was not directly polarized by the applied field. C) Population spike recording from post-synaptic cells in response to orthodromic activation of the afferent axons. Simultaneous application of either positive or negative electric fields modulate the response of the post-synaptic cells, presumably by changing synaptic efficacy.

Sub-threshold fields may exert a profound effect on neuronal excitability by modulating synaptic efficacy. At the single neuron level, sub-threshold fields will change the

membrane potential of neurons and thus modulate if any given simultaneous synaptic input is supra- or sub-threshold [22] [23].

At the network level, electric fields will effects synaptic efficacy through polarization of nerve terminals (Figure 5). In both cases, especially when fields are applied for extended durations (minutes), changes in synaptic plasticity may follow. These induced changes in synaptic plasticity (e.g. LTP) may exert a therapeutic or functional effect [24]-[27].

Both these mechanisms are adaptable to activity-dependent-plasticity stimulation paradigms. Namely, a given sub-threshold electrical stimulation protocol may polarize a (poorly localized) population of neurons, however, only those neurons receiving concomitant synaptic input will be 'targeted'.

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