Multi-scale modeling of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons

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Background
Transcranial magnetic stimulation is a noninvasive technique to modulate brain activity for both clinical and research applications, but its mechanisms of action at the neural level are still unknown. Fundamental questions remain about the neural types and elements it activates and how stimulation parameters affect the neural response. We developed a multi-scale model of TMS-induced neuronal activation to quantify the effect of stimulation parameters on the direct neural response to TMS in a population of cortical neurons.

Methods
We integrated layer-specific, morphologically-realistic neuronal models (1) in NEURON (2) with TMS-induced electric fields computed in an finite element model (FEM) of a human head in SimNIBS (3) and determined activation thresholds for several combinations of TMS pulse waveforms and directions. The neurons were placed in a 32x34x50 mm^3 region containing the M1 hand knob on the pre-central gyrus and the portion of the postcentral gyrus opposite to it.

Results
TMS activated with lowest intensity layer 5 pyramidal cells at their intracortical axonal terminations in the superficial gyral crown and lip regions. Layer 2/3 pyramidal cells and inhibitory basket cells may be activated too, whereas direct activation of layers 1 and 6 was unlikely. Neural activation was largely driven by the field magnitude, contrary to theories implicating the field component normal to the cortical surface. Varying the induced current's direction caused a waveform-dependent shift in the activation site and provided a mechanistic explanation for experimentally observed differences in thresholds and latencies of muscle responses. Using homogeneous conductivity for the intracranial tissues (cerebrospinal fluid, gray matter, and white matter) in the FEM resulted in weaker and more diffuse E-field distribution and thus higher thresholds and less focal activation, in addition to reducing the sensitivity of the neuronal thresholds to current direction. We also simulated intrinsic, subthreshold polarization before TMS, which indicated somatic depolarization (hyperpolarization) can reduce (increase) thresholds via passive axonal polarization.

Conclusions
This biophysically-based simulation provides a novel method to elucidate mechanisms and inform parameter selection of TMS and other forms of cortical stimulation.

References
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