Biophysical Reconstruction of the Signal Conduction Underlying Cortical Evoked Potentials Generated by Subthalamic Deep Brain Stimulation

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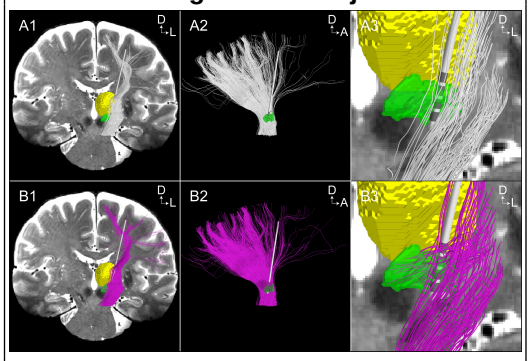
Introduction

Direct stimulation of the hyperdirect pathway has been linked to therapeutic benefit in subthalamic deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). Cortical evoked potentials generated by subthalamic DBS represent an electrophysiological signal that can be associated with hyperdirect pathway activation and represent possible biomarkers for use in closed-loop DBS control systems [Walker et al., 2012]. The objective of this study was to quantify the axonal conduction biophysics of corticofugal axons directly stimulated by subthalamic DBS and reconcile those findings with clinical cortical evoked potential results. Subthalamic DBS typically generates cortical evoked potentials in motor cortex with a very fast component occurring ~1 ms after the stimulus pulse, as well as a slower component that reaches its peak in ~6 ms.

Methods

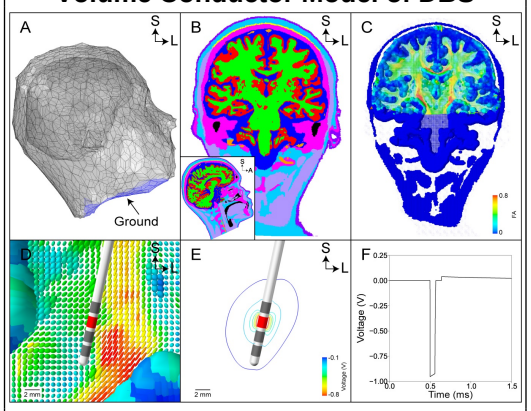
The 1 and 6 ms short latency evoked potentials signals seen clinically are expected to result from antidromic activation of cortical pyramidal neurons. We set out to evaluate the plausibility of that hypothesis using a detailed biophysical model of human subthalamic DBS. We used the Gunalan et al. [2017] model of human subthalamic DBS to quantify axonal activation and conduction. Signal propagation to cortex was quantified for medium (5.7 µm), large (10.0 µm), and exceptionally large (15.0 µm) diameter corticofugal axons.

Corticofugal Axon Trajectories



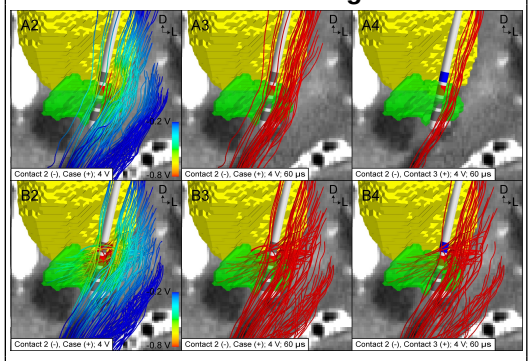
Internal capsule fibers of passage (white streamlines) and hyperdirect pathway axons (pink streamlines), which exhibit a collateral to the subthalamic nucleus.

Volume Conductor Model of DBS



Tissue anisotropy and inhomogenity influence the voltage distribution generated by subthalamic DBS

Activation of Corticofugal Axons

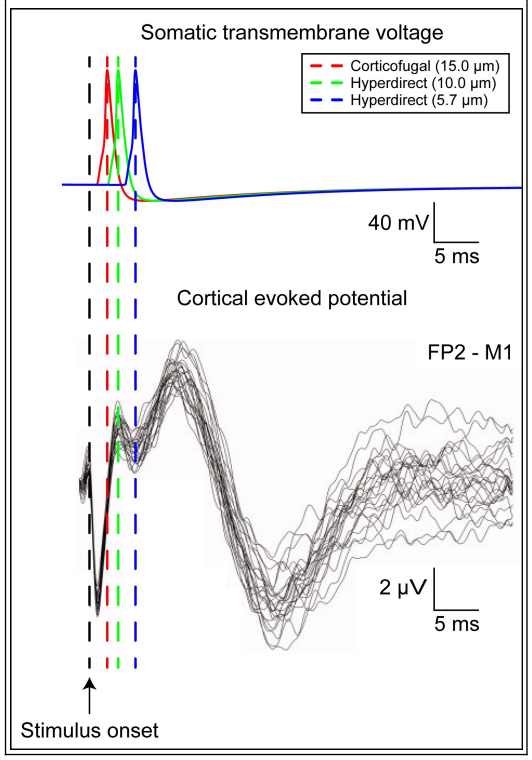


Application of the DBS voltage distribution to the axon models enables prediction of the individual streamlines that are suprathreshold for action potential initiation and propagation

Results

Our results suggest that the 1 ms peak is unlikely to be generated by direct activation of hyperdirect axon collaterals in the STN, but could possibly be the result of directly activating corticofugal axons in the internal capsule. However, such a fast response requires axonal conduction velocities, and underlying axon diameters, that are extreme for the internal capsule. In addition, the extra time delay needed to generate a somatic action potential spike and polarization of the apical dendrites casts further doubt on the 1 ms signal being derived specifically from antidromic activation of hyperdirect neurons. However, our simulation results demonstrate that the 6 ms signal is consistent with the biophysics of hyperdirect axon collateral activation in the STN and propagation to cortex.

Action Potential Conduction to Cortex



References

Walker et al. Short latency activation of cortex during clinically effective subthalamic deep brain stimulation for Parkinson's disease. Mov Disord. 27(7):864-73, 2012.

Gunalan et al. Creating and parameterizing patient-specific deep brain stimulation pathway-activation models using the hyperdirect pathway as an example. PLoS One. 12(4):e0176132, 2017.

Acknowledgements

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