Modeling Deep Brain Stimulation in the Nucleus Accumbens as a Potential Treatment for Addiction

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Abstract

The nucleus accumbens is an important nucleus in the brain for reward and conditioning. In addiction, however, the nucleus accumbens is coopted to reinforce addictive behavior, creating a destructive influence in many lives. Recent research has shown that electrically stimulating the nucleus accumbens directly by deep brain stimulation (DBS) has potential to treat addiction [1-2]. However, the mechanisms by which DBS modulates nucleus accumbens are not well understood. In this study, we created a computational neuron model of the nucleus accumbens using the programming language, NEURON [3], to test how DBS affects the neuronal activity patterns. Here we suggest that decoupling the action potentials of axons from those of the cell bodies is a possible mechanism through which DBS might treat addiction.

Introduction

The Nucleus Accumbens (NAcc) (Fig 1). The NAcc regulates conditioning and stimulus reaction by combining inputs from several key areas [4-7]. Excitatory input from the prefrontal cortex (PFC), amygdala, and hippocampus send the NAcc important environmental stimuli filtered by past memories and emotion. If a burst of cortical input arrives at the same time, neurons in the NAcc will enter an excited state and generate action potentials.

Deep Brain Stimulation (DBS). DBS uses subcortically implanted electrodes to stimulate nuclei involved in the pathophysiology of a particular brain disorder. The electrical stimuli produce extracellular tissue voltages that through an activating function modulate neuronal membrane potentials [8].

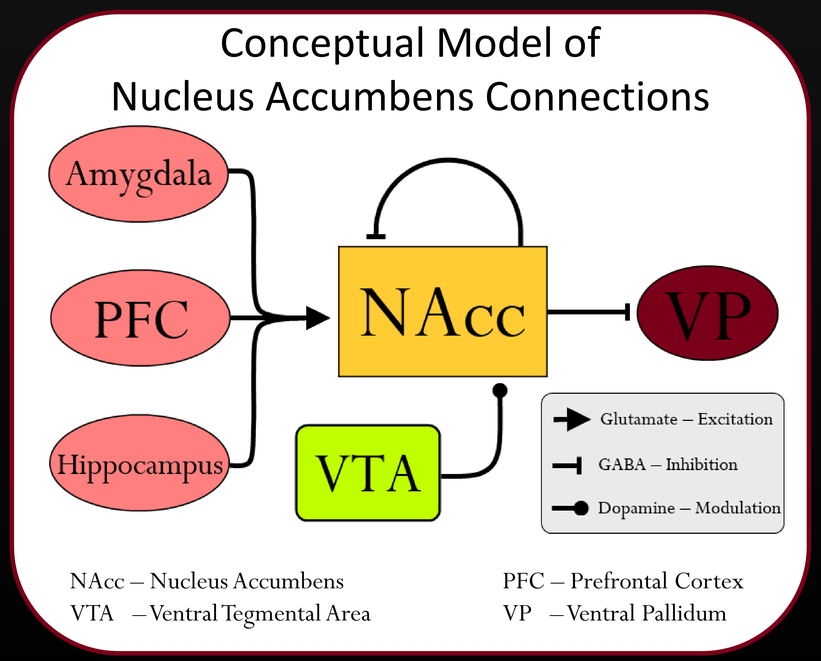

Figure 1

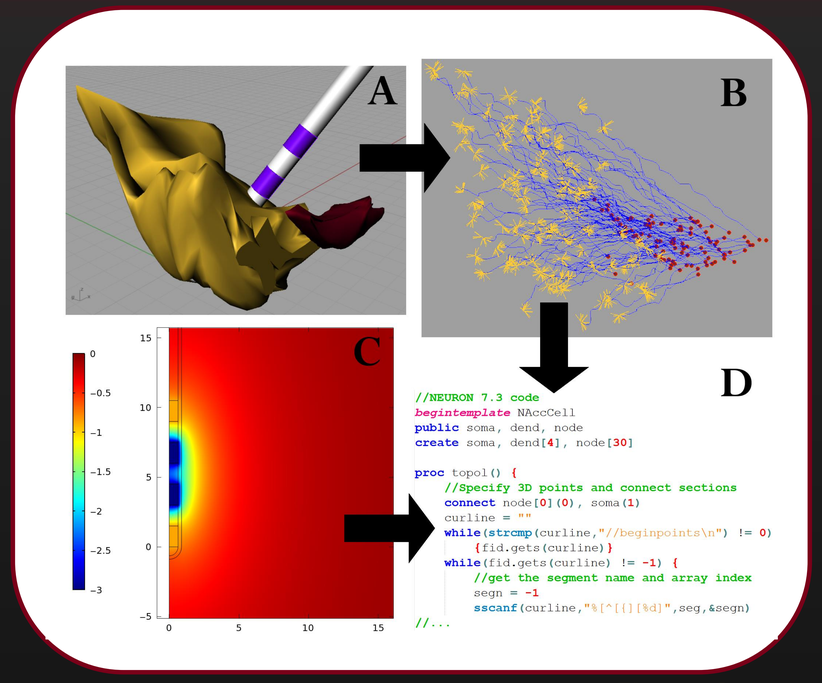

Figure 2

Methods

Creating a 3D NAcc (Fig 2A). Using scans of a human brain atlas, we traced out the curves for each slice of the NAcc and VP in a 3D modelling program called Rhinoceros. Then, after aligning them properly in 3D space, we "lofted" a surface over them to create a mesh of the nuclei. Additionally, we placed a DBS lead in the 3D space according to trajectories from human implants [1].

Generating Neuron Positions (Fig 2B). We exported the 3D model to MATLAB and used the Jordan Curve Algorithm to generate 100 points each in both the NAcc and VP. Using a directed random walk, we generated axons that traveled from points in the NAcc to a paired point in the VP. Additionally, four branching dendrites were procedurally generated for each neuron.

Modeling DBS Effects (Fig 2C). A reconstruction of the human DBS lead (Medtronic 3389) was created in the finite element modeling (FEM) program, COMSOL. Tissue voltages were solved for varying radial and axial distances from the lead in brain tissue (0.3 S/m) using amplitudes and electrode configurations consistent with [1].

Creating and Testing the Model (Fig 2D). Interpolated extracellular potentials were applied to a neuron model of NAcc as perturbations in the form of the activating function [8]. The differential equations governing the equivalent circuit model of the NAcc neuron was then solved to investigate the effects of DBS on the membrane voltage.

Results

Propagation of Action Potentials (Fig 3). With all of the biophysical properties inserted in the model, a current clamp was attached to the soma and action potentials were evoked, resulting in propagation of action potentials down the axon in approximately 1.7 ms.

Response to Dopamine. Changing dopamine levels in the model had no discernable effect on ion flow or action potential behavior.

Response to DBS. Work is ongoing to couple the activating function to the neuron model.

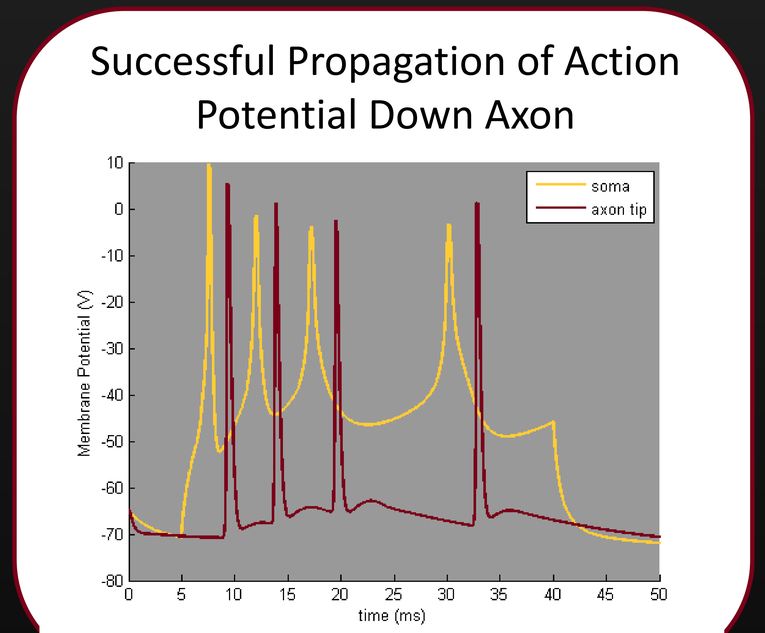

Figure 3

Discussion

The overall model integrates a range of smaller models. Since these models were spliced together, some parameters still need debugging to interact smoothly. We hypothesize that DBS will cause the axon and soma to become decoupled in their spike activity such that spikes will not occur in one-to-one pairs. We further hypothesize that this will occur because the threshold for activating the axon is smaller than the soma, and activation of GABAergic input will have an inhibitory effect on somatic activity.

References

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