White Matter Network Architecture Guides Direct Electrical Stimulation Through Optimal State Transitions

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Introduction

Electrical brain stimulation is currently being investigated as a potential therapy for neurological disease. However, opportunities to optimize and personalize such therapies are challenged by the fact that the beneficial impact (and potential side-effects) of focal stimulation on both neighboring and distant regions is not well understood. Here, we hypothesize that the effects of simulation will propagate along white matter tracts to affect change in the activity of distal regions. Specifically, we use network control theory to build a formal model of brain network function that makes explicit predictions about how stimulation spreads through the brain's white matter network and influences large-scale dynamics. We test these predictions using combined electrocorticography (ECoG) and diffusion weighted imaging (DWI) (Fig 1A) data from patients with medically refractory epilepsy undergoing evaluation for resective surgery, and who volunteered to participate in an extensive stimulation regimen (Fig 1B). We posit a specific model-based manner in which white matter tracts constrain stimulation, defining its capacity to drive the brain to new states, including states associated with successful memory encoding (as defined by a previously trained and validated classifier). In a first validation of our model, we find that the true pattern of white matter tracts can be used to more accurately predict the state transitions induced by direct electrical stimulation than the artificial patterns of a topological or spatial network null model. We then use a

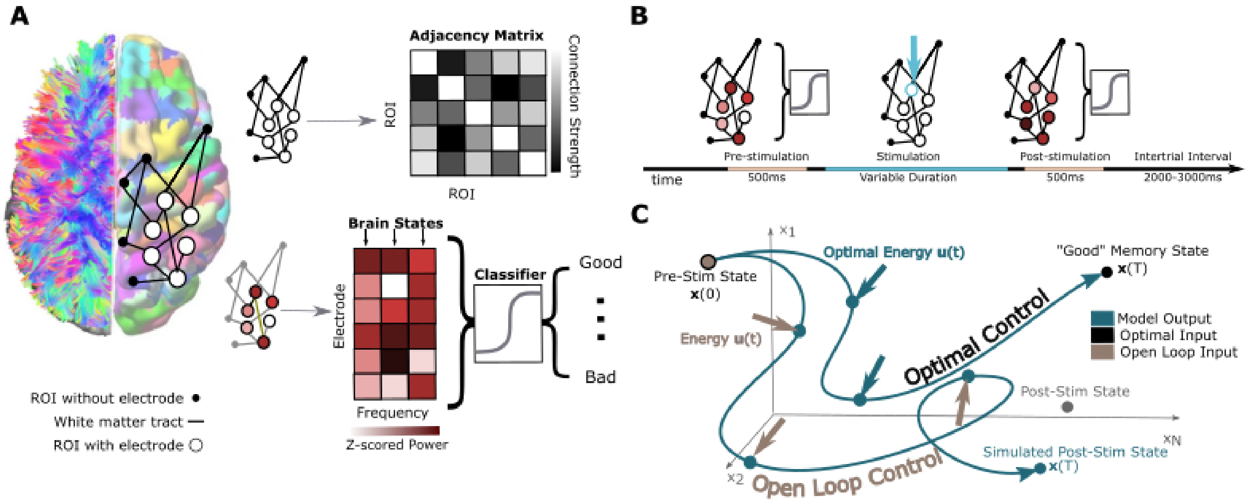

Figure 1: (A) Depiction of network construction and definition of brain state. (Left) We segment subjects' diffusion weighted imaging data into *N=234* regions of interest using a Lausanne atlas. We treat each region as a node in a whole-brain network, irrespective of whether or not the region contains an electrode. Edges between nodes represent mean quantitative anisotropy along the streamlines connecting them. (Right, Top) Practically, we summarize the network in an *NxN* adjacency matrix. (Right, Bottom) A brain state is defined as the *Nx1* vector comprising activity across the N regions. Any element of the vector corresponding to a region with an electrode is defined as the band-limited power of ECoG activity measured by that electrode. Each brain state is also associated with an estimated probability of being in a good memory state, using a previously validated machine learning classifier approach. (B) A schematic of a single stimulation trial. First, ECoG data is collected for 500 ms. Then, stimulation is applied to a given electrode for a variable duration. Finally, ECoG data is again collected after the stimulation. (C) A schematic of the open loop and optimal control paradigms. In the open loop design, energy *u(t)* is applied in silico at the stimulation site to the initial, pre-stimulation brain state *x(0)*. The system will travel to some other state *x(T)* as stipulated by our model of neural dynamics, and we will measure the similarity between that predicted state and the empirically observed post-stimulation state. In the optimal control design, the initial brain state *x(0)* has some position in space that evolves over time towards a predefined target state *x(T)*. At every time point, we calculate the optimal energy (*u(t)*) required at the stimulating electrode to propel the system to the target state.

targeted optimal control framework to solve for the optimal energy required to drive the brain to a given state (Fig 1C). We show that, intuitively, our model predicts larger energy requirements when starting from states that are farther away from a target memory state. We then suggest testable hypotheses about which structural properties will lead to efficient stimulation for improving memory based on energy requirements. We show that the strength and homogeneity of edges between controlled to uncontrolled nodes, as well as the persistent modal controllability of the stimulated region, predict energy requirements. Our work demonstrates that individual white matter architecture plays a vital role in guiding the dynamics of direct electrical stimulation, more generally offering empirical support for the utility of network control-theoretic models of brain response to stimulation.

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