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Modulation of arousal regulation with central thalamic deep brain stimulation

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Abstract—**To investigate the effects of central thalamic deep brain stimulation (CT/DBS) on behavior and frontal cortical function, we conducted experiments in an awake, behaving macaque monkey performing tasks that required sustained attention and working memory. Results of this preliminary study revealed that CT/DBS can lead to an improvement, a decrement, a mixed or have no effect on behavior.**

I. Introduction

CENTRAL thalamic deep brain stimulation (CT/DBS) has been proposed as a therapeutic strategy for impaired cognitive function of patients with non-progressive brain injury. Few therapeutic options are available to the very large patient populations suffering from chronic cognitive function loss following head injuries and stroke. The facilitating effects of CT/DBS have been studied in intact [1] and brain-injured animals [2] and in one brain-injured human subject [3]. Although facilitating effects have been observed, the mechanism, control of effectiveness and expected outcomes of DBS remain to be studied.

Prior to conducting the CT/DBS experiments, we characterized single-unit activity in both the central thalamus (CT) and frontal cortex (FC) during tasks requiring sustained attention and working memory in a macaque monkey.

II. Background And Significance

A. Role of Central Thalamic neurons in forebrain arousal regulation.

The central thalamus (CT) is being considered as a target for deep brain stimulation based on several anatomical and physiological considerations including: 1) CT receives monosynaptic connections from the brainstem and basal forebrain 'arousal systems', 2) CT has reciprocal connections with mesial, lateral and pre-frontal cortices engaged in the organization of behavior, and 3) the grading of CT activity across varying levels of vigilance and in response to cognitive load and stressors suggests a role in regulation of overall level of cerebral activation [4]. The unique anatomical connections of the CT and their selective activation in response to demands on arousal regulation have been proposed as a physiological basis for the central thalamic role in cognitive control [5], [6].

Fluctuations of behavioral responses and deficits are consistently seen with both unilateral [7] and bilateral lesions [8] to the CT and frontal lobe lesions [9]. This is consistent with the strong anatomical connections between the central thalamus and frontal lobe, both through direct corticothalamic connections and indirectly through frontostriatal loop systems (cortico-striatopallidal-thalamocortical).

B. Human case study

The possible benefit of CT/DBS in treating cognitive impairments was recently revealed in the single-subject clinical trial of a 38-year old man in a minimally-conscious state (MCS) (6 years following a severe traumatic brain injury) [3] . Bilateral DBS electrodes were implanted in the anterior intralaminar thalamic nuclei (central lateral nucleus and adjacent paralaminar regions of the thalamus). The patient was evaluated according to the Coma Recovery Scale Revised (CRS-R), a validated psychometric tool used in patients with disorders of consciousness, and three tailored secondary measures developed during the clinical trial which employed a crossover design. The overall findings indicated significantly improved behavioral responsiveness in this patient as seen in comparison with pre-stimulation responses in all behavioral categories measured (attentive behavior, communication, functional limb movements, oral feeding, object naming). The evidence in this single-case study for both reproducible and sustained acute effects of DBS, as well as more enduring and slowly accumulating effects, suggests that biological mechanisms on multiple timescales may play a role in mediating the effects of DBS. Detailed logistic regression modeling of these behavioral data, including the time course of stimulation history and behavioral observations, demonstrated linkage between the observed functional improvements and stimulation history for both the cross-over data and effects seen during the initial evaluation of stimulation parameter effectiveness (titration).

III. Methods

A. Experimental Protocol

We used two tasks: 1) Sustained attention (SA) requires the ability to hold mental focus and resist distraction, and 2) Working memory (WM) requires short-term maintenance and goal-directed manipulation of information. Thus both tasks serve as testable components of executive function. In

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addition, these functions are strongly dependent upon the control of arousal regulation for a consistent behavioral response during continuous and repetitive activity over short and long time courses.

The SA task begins with the appearance of a visual cue (red cursor), followed by acquisition and visual fixation of the cue until the appearance of a GO signal (green cursor), and finishes with a bar release that remained held during the entire period from onset of the cue. In the experiments reported here the red cursor could appear in one of nine spatial locations chosen at random. The monkeys were required to maintain fixation for a variable *delay period* (uniform normal distribution with mean 1350 ms and standard deviation of 350ms). The bar release was required within 1000 ms after the GO signal to trigger a liquid reward.

The WM task requires the acquisition of a central fixation spot (red square) before the brief flashing of a peripheral cue. The animal continues to hold fixation for a variable *delay period* (uniform normal distribution with mean 1350 ms and standard deviation of 350ms). When the central fixation cue changes color (red to green), the animal is then required to saccade to the remembered target (peripheral cue) and receives a liquid award.

Failure to initiate or maintain even simple behavioral sets is emblematic of 'executive' function impairments and are viewed here as a proxy for more general executive function impairment.

B. Electrophysiological Recordings

We recorded extracellular action potentials and local field potentials from the central thalamus and frontal cortical regions (Frontal Eye Field (FEF), Anterior Cingulate (ACC) and Supplementary Motor Area (SMA)) of one monkey. Recording sites were identified in the monkey utilizing a 3-dimensional MRI/CT reconstruction prior to and following implantation surgery. An anatomical atlas was also consulted [14]. The extracellular recordings were obtained using epoxy insulated tungsten microelectrodes (FHC Corp., Bowdonham, Maine), with nominal impedance of 1-4 MOhms at 1 kHz. A plastic grid (Crist Instrument) inserted into the chamber provided a reproducible coordinate system for submillimeter consistency in electrode placement from day-to-day. The signals from each electrode were low-pass filtered at 7 KHz with a second-order Butterworth filter (12 dB per octave) to prevent aliasing of high frequency noise when sampled at 20 KHz. The signals were amplified by a gain of 8000.

C. Analysis of Single Unit Activity

Offline analysis of single unit activity (extracellular action potentials) was conducted using a spike-sorting algorithm proposed by Fee, Mitra and Kleinfeld [10]. For each neuron identified we computed the mean firing rate estimate (averaged across correct trials in each task separately), using a local regression algorithm (Locfit) that fits a curve to a given subset of the data (# of spikes/time window), and repeats that fit across the entire time period of interest. Jack-knife error bars for the rate estimates were also computed. Rate estimates were computed for 1.25 seconds of data, aligned to the start of the delay period, with 0.25 seconds prior. The start of the delay period was defined for each type of task as follows: 1) Sustained attention - acquisition of fixation cue, b) Working memory - completion of peripheral cue presentation. Modulation of neurons for each task was defined by the increase/decrease in firing rates during the delay period, when compared with the baseline (0.25 secs prior to start of delay).

D. Deep Brain Stimulation Experiments

Unilateral CT/DBS experiments were conducted with specially developed scaled down human DBS electrodes (2 contacts, surface area 0.020cm^2) to stimulate and record in between stimulation bouts. We stimulated with continuous current controlled, monopolar, 130 Hz, biphasic square waves (60 microseconds per phase pulse width), with amplitudes ranging from 1.8 mA to 8mA. Stimulation was conducted in the sites where preliminary studies had identified neurons that modulated to the tasks. Experiments were conducted by alternating between OFF and ON stimulation every 100 trials (~10 min OFF and ~10 min ON). Some of the experiments were conducted with both tasks, but most were restricted to just one task due to task related differences (even without stimulation). A few of the initial experiments were conducted using a MultiChannel Systems stimulator but due to a current amplitude ceiling of 3mA, the remaining experiments were run with a custom designed stimulator manufactured by IntElect Medical Systems, Inc.

E. Behavioral effect modeling:

The effects of stimulation on the behavioral performance of the animal were modeled using state-space modeling [11], [12].

IV. RESULTS

A. Single Unit Activity – CT and FC

We obtained a series of microelectrode recordings to sample multi-unit, single-unit and local field potentials in the CT and FC.

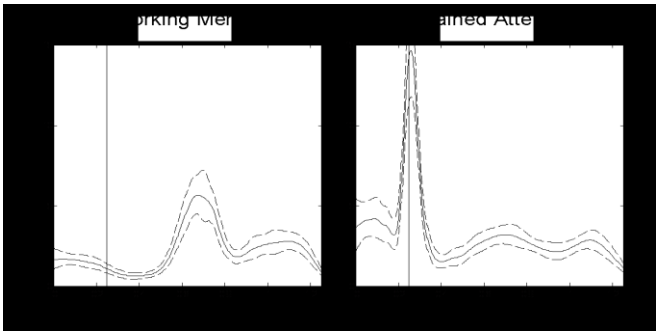

Fig. 1: A CT single unit firing rate response to a) Working memory; b) Sustained attention. The black vertical line represents the start of the delay period. Solid and dashed lines correspond to the means and jack-knifed confidence intervals, respectively.

Preliminary results of the recorded single unit (SU) activity from central thalamus and frontal cortex (FC) showed firing rate modulation in the delay period to both tasks (8/43 SU CT and 18/52 SU FC) or to only one task (8/43 SU CT and 8/52 SU FC).

Several important conclusions were drawn from these data:1) Firing rate profiles of a cell responding to both tasks could be similar or different, 2) Task specific responses could be recovered when switching between tasks, 3) Task responsive cells were recorded over a large area (6-9 mm in both regions), 4) Cells with varying single unit firing modulation profiles were recorded within 150um of each other, 5) Cells that responded to one task were more likely to respond to the other task and 6) An equal proportion of cells showed responses for either tasks in both regions.

B. Effects of CT/DBS on behavioral performance

The quantitative assessment of behavioral effects due to CT/DBS and their statistical linkage is characterized using a state space method illustrated in Fig. 2. In the example dataset shown in Fig. 2 there are 1493 total trials (all with task SA) of which 503 were performed correctly. The red bars on the horizontal axis in the top panel represent the trials where monopolar, 130 Hz square wave (60 microseconds per phase pulse width) stimulation was applied. In this experiment, the animal's initial moving average performance was approximately 60% correct trials (trial 1 was the first recorded trial).

In the top panel of Fig. 2, we plot the median estimated probability (black line) and the 95% credible intervals (--grey line) of a correct response computed using the state-space formulation. This calculation is independent of the stimulation ON/OFF periods.

The bottom panel shows a surface plot [12] that allows for trial by trial comparison of performance. Dark (light) indicates when the performance on the x-axis is higher (lower) than the performance at the trials on the y-axis. When dark (light) regions extend beyond 95% intervals, they are highlighted in red (blue).

In this experimental session, the animal's performance follows a declining curve (typical) but responses to the CT/DBS can be seen during certain ON periods. There is no modulation in performance to 3mA, a slight modulation to 4mA and a mixed effect with 5mA. However, the performance increases with 6mA and 7mA despite the baseline dropping to ~5% correct. The increase demonstrates a dose dependence that is reproduced when the current is dropped back again to 6mA and finally increased back to 7mA. This dataset provides two lines of evidence of the causal influence of CT/DBS on behavior (statistical linkage of increased performance with stimulation ON periods and dose dependence) as well as insight into the complex dynamic nature of behavioral modulation due to CT/DBS.

The preliminary summary results from 32 stimulation experiments are as follows: consistent increase in behavioral performance was seen in 3/32 experiments, consistent decrease in 1/32 and mixed (increase and decrease) in 14/32. The remaining 14 datasets showed no modulation to DBS. Two of the mixed datasets also showed dose dependence to the applied current.

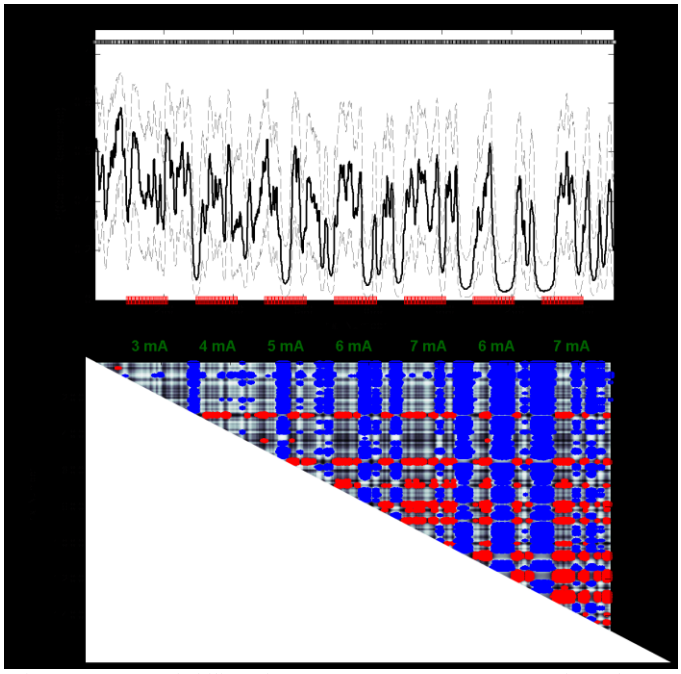

Fig. 2: Top – Probability of correct response; Bottom – Surface plot comparison trial by trial.

V. DISCUSSION

A. Possible mechanisms

The proposed primary expected effect of CT/DBS is depolarization of target neurons in the cortex (particularly regions of frontal and prefrontal cortex) and striatum through activation of the excitatory glutamatergic connections issuing from the central thalamus. It is proposed that providing a severely damaged brain with a broad, albeit partial and abnormally patterned, amplification of excitatory drive to cortical and striatal neurons from the CT may promote marked changes in the firing patterns and hence of network behavior. The challenge then becomes one of finding how to control activity within the CT thalamocortical projections to replace the normal afferent drive lost through brain injury.

The effects of CT/DBS in the injured brain may have particular importance in the striatum which depends on strong synaptic background activity likely reduced in the setting of multi-focal brain injuries [4]. Anterior intralaminar projections from the central lateral nucleus of CT make contact with dendritic spines of Medium Spiny Neurons (MSNs) suggesting that they may provide a dominant excitatory drive to the striatum [13]. Thus, CT/DBS could be an effective way to directly restore activity in the MSNs through thalamostriatal activation (and indirectly through strong efferent projections to frontal systems providing corticostriatal outflow and hence disynaptic facilitation of striatum).

Another potentially important mechanism of action for CT/DBS is facilitation of long-range corticocortical

interactions that is proposed as one of the functional roles for the central thalamus [5]. The wide point-to-point connections of the afferents from the central thalamus would allow co-activation across large cerebral territories in a damaged brain through CT/DBS and may enable increased integration of synaptic activity linking cortical regions.

In the aggregate, through broad depolarization of cortico-cortical and striatal targets of the projecting thalamic neurons, CT/DBS might be expected to similarly influence both patterns of large-scale circuit function and the detailed response properties of individual neurons across many neuronal populations.

B. Future work

Although DBS induced modulation of behavior was observed, the wide variance in results (in part due to day-to-day fluctuations in the animal's behavior even without DBS, and the nature of the setup – day-to-day insertion of electrode to a previously measured site) make overall interpretation of our results difficult. As a next step, we are planning a semi-chronic implantation of a custom designed Deep Brain Recording Stimulating (DBRS) system.

The DBRS system will contain stimulating electrodes (up to 2) and a recording microelectrode (8-channel Linear Micro Array, Micro Probe Inc). This system will be implanted bilaterally, allowing us to rigorously test the efficacy of unilateral vs bilateral stimulation, and increase the reliability of DBS related effects on behavior. The DBRS system has a grid of 52 positions with a grid spacing of 1.3mm for guide tube holes that are 1mm in diameter. The guide tubes will be inserted during a surgical procedure, to a position 2-4 mm outside the central thalamus. The DBS electrodes are scaled-down versions of the electrodes used in human DBS procedures and can be used in either monopolar or bipolar modes (4 total elements). In order to record and characterize the effects of CT/DBS on global cortical activity and within the frontal cortex, a 10-channel grid of electroencephalographic (EEG) electrodes and a 32-channel Grey Matter Research microdrive will be mounted over the frontal cortex. The combination of EEG recordings over both hemispheres and dense recordings within the frontal cortex will improve our understanding of the spatial and temporal extent and impact of the CT/DBS.

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CONFLICT OF INTEREST

The paper describes work that was, in part, funded by a company, IntElect Medical, Inc., in which Cornell University has part ownership; through the licensing of technology, K.P.Purpura and N.D.Schiff are listed Cornell inventors and may benefit in the future from commercialization of intellectual property owned by Cornell. N.D.Schiff acts as a consultant to IntElect Medical, Inc.

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