Behavioral modulation with central thalamic deep brain stimulation in non-human primates

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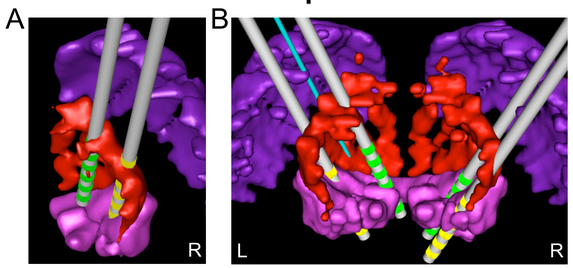
INTRODUCTION

Central thalamic deep brain stimulation (CTDBS) has been proposed as a therapeutic strategy to remediate impaired consciousness following severe brain injury (Schiff et. al., 2000; Schiff and Purpura, 2002). Disruptions within the frontal-striatal-thalamic network, specifically involving the central thalamus, lead to marked disturbances in normal cognitive function, which can be partially ameliorated through pharmacological interventions (Williams et al, 2009) and deep brain stimulation within the central thalamus (Schiff et al., 2007). However, the specific physiological mechanism(s) enabling CTDBS to provide therapeutic value are unknown. Therefore, the goal of this study was two-fold, to explore the vast CTDBS parameter space (frequency, amplitude and electrode contact geometry) within the intact non-human primate and to characterize large-scale neuronal activity recorded simultaneously within key regions of the frontal-striatal-thalamic network while the animals performed a series of goal-directed behavioral tasks.

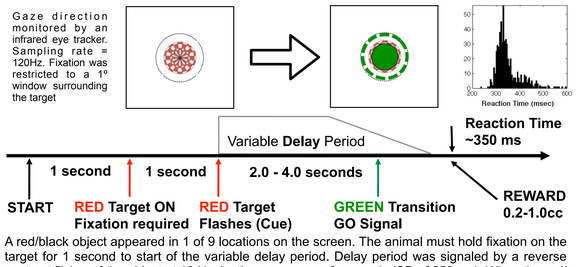
GENERAL METHODS

Central Thalamic Deep Brain Stimulation



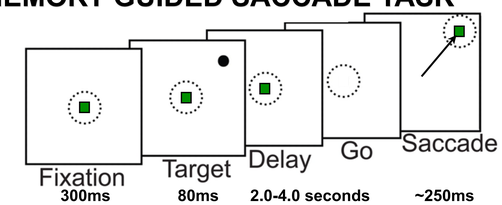
Model reconstruction of the DBS electrode positions within **(A)** the right central thalamus of the first animal and **(B)** bilaterally in the second animal. The central thalamic nuclei (CL/Pc are shown in **red**, CM/Pf in **magenta**) and reticular nuclei **(purple)** are shown in relation to the DBS electrodes. Multiple 6-contact DBS electrodes coated with BT DOT (Biotectix, LLC, Ann Arbor, MI) were implanted within the central thalami of two animals. Each animal was implanted with multiple Gray Matter Research, LLC recording chambers and devices and a custom EEG array in order to investigate interactions among large cellular populations within the central thalamus, dorsal striatum, prefrontal cortex and broadly across the cerebral hemispheres using EEG. A current-controlled charge-balanced asymmetrical biphasic waveform, varying in amplitude and frequency was delivered continuously during blocks of trials while the animals performed a series of visual-motor behavioral tasks.

VIGILANCE TASK

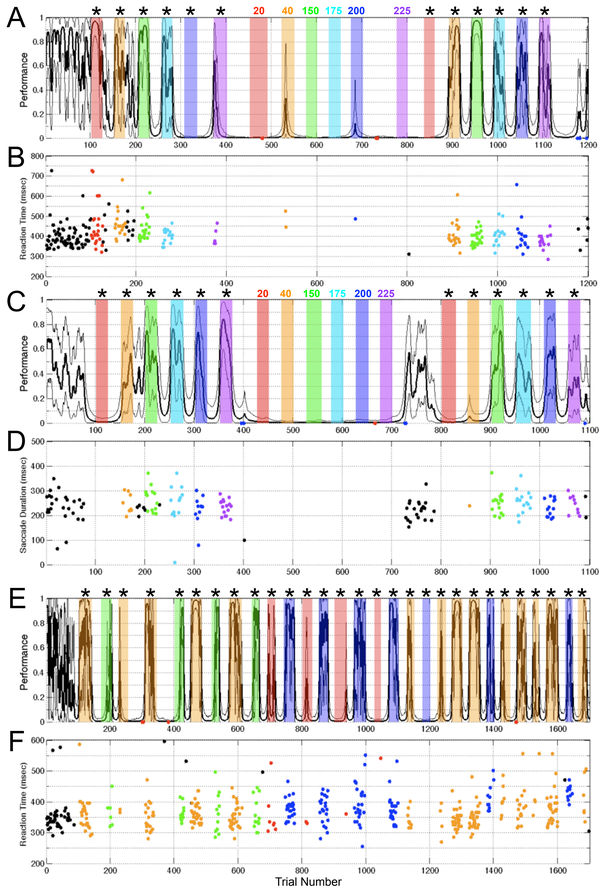


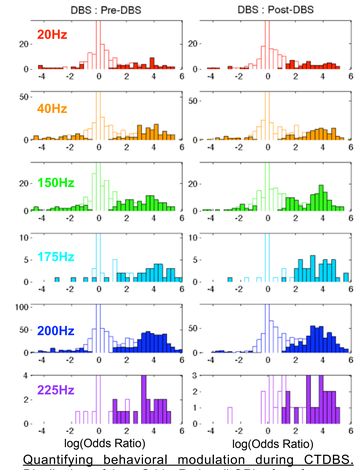
A red/black object appeared in 1 of 9 locations on the screen. The animal must hold fixation on the target for 1 second to start of the variable delay period. Delay period was signaled by a reverse contrast flicker of the object at 10 Hz, lasting on average 3 seconds (SD of 250 ms). When the red/black object changed to green/black (GO signal), the animal had to touch a bar or IR switch within 250-800 ms following the GO signal. Performance varied greatly across the experimental session(s) and average peak performance ranged between 70-90% correct.

MEMORY GUIDED SACCADE TASK

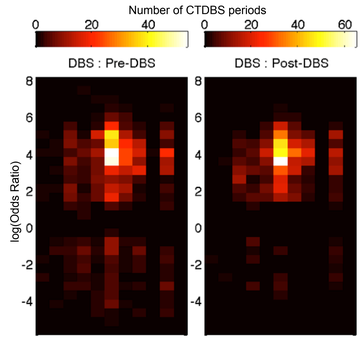


BEHAVIORAL FACILITATION DURING CTDBS



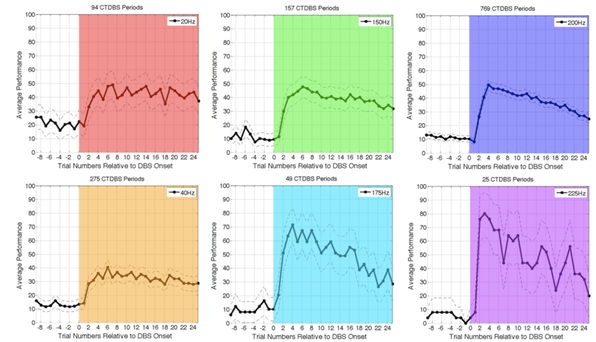


Quantifying behavioral modulation during CTDBS. Distribution of Log Odds Ratios (LOR) of performance (correct vs. incorrect) comparing performance during CTDBS / performance prior to CTDBS (LEFT column) performance during CTDBS / performance following CTDBS (RIGHT column). All amplitudes, frequencies and electrode configurations are included (N=2007) from a total of 212 CTDBS sessions.

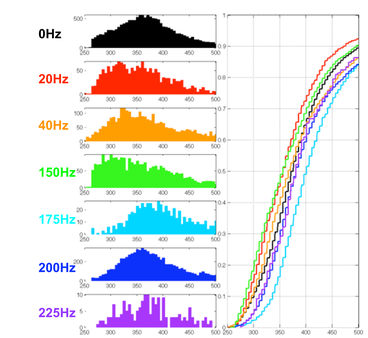


Histogram of ***significant*** LOR versus CTDBS amplitude. (LEFT) LOR of performance during CTDBS / performance prior to CTDBS (N=883) versus CTDBS amplitude. (RIGHT) LOR of performance during CTDBS / performance following CTDBS (N=864) versus stimulation amplitude. All amplitudes, frequencies and electrode configurations are included.

Performance during three behavioral sessions. **(A)** The first animal's performance during the Vigilance task. The thick black line and 95% CI represents the performance profile derived from the State-Space Model (Smith et al., 2009), which highlights the causal linkage between periods of continuous CTDBS and performance fluctuations during a session containing 1200 continuous trials. The colored bars represent blocks of current-controlled **20Hz**, **40Hz**, **150Hz**, **175Hz**, **200Hz and 225Hz** CTDBS. "Effective" cathode/anode configurations are highlighted with an asterisk. **(B)** Reaction times are plotted as a function of trial number. **Black** points represent reactions times during CTDBS OFF periods and colored points represent CTDBS ON periods. **(C and D)** The animal's performance and reaction times during a session of the Memory Guided Saccade task. **(E and F)** The first animal's performance and reaction times during a Vigilance task session where CTDBS amplitude and electrode geometry were fixed during the 1700 trials.

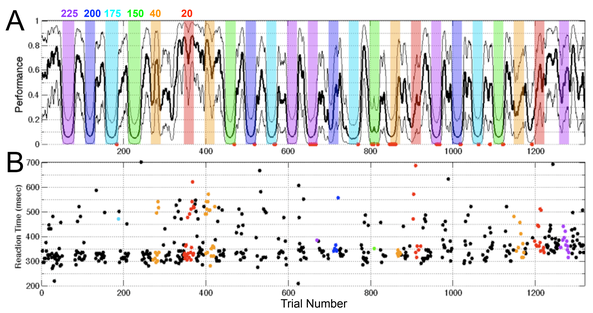


Average correct performance before and during ***'Effective'*** CTDBS. All plots illustrate the first animal's average performance 10 trials prior to CTDBS onset and average performance during stimulation at **20Hz**, **40Hz**, **150Hz**, **175Hz**, **200Hz and 225Hz** for all tasks combined. Trials with stimulation amplitudes of 1.0 to 2.5 mA are combined in this analysis. Total number of CTDBS periods are noted above each plot.

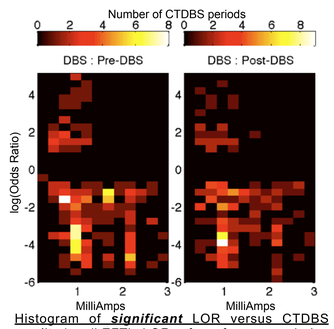


Reaction time distributions during the Vigilance task. (LEFT column) Distributions of reaction times during 165 CTDBS sessions (34,502 correct trials). (RIGHT) CDF of the reaction time distributions shown on the LEFT.

BEHAVIORAL SUPPRESSION DURING CTDBS

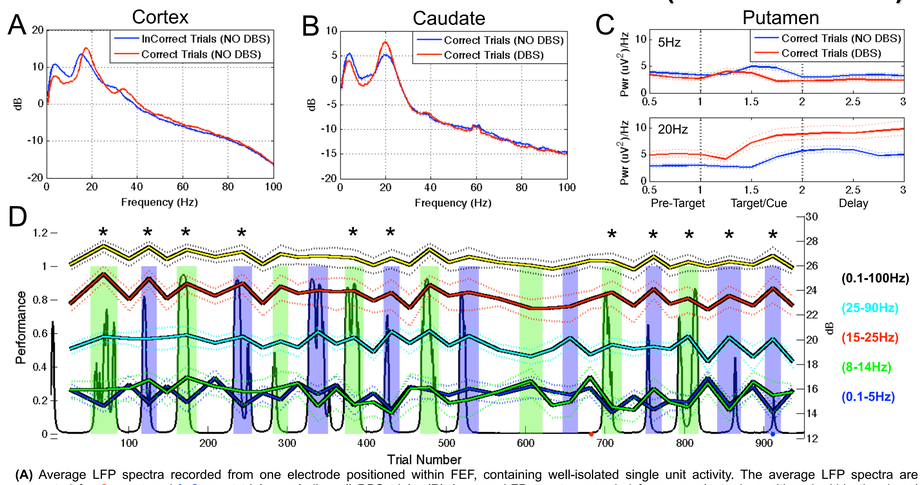


Second animal's performance during the Vigilance task **(A)** The performance profile derived from the State-Space Model (Smith et al., 2009) highlights the causal linkage between periods of continuous **20Hz**, **40Hz**, **150Hz**, **175Hz**, **200Hz and 225Hz** CTDBS and fluctuations in the animals performance during 1320 contiguous trials. **Red** markings along the zero axis of the performance plot indicate periods of eye closure and somnolence. **(B)** Reaction times are plotted as a function of trial number. **Black** points represent reactions times during CTDBS OFF periods and colored points represent reaction times during **20Hz**, **40Hz**, **150Hz**, **175Hz**, **200Hz and 225Hz** CTDBS ON periods.



Histogram of ***significant*** LOR versus CTDBS amplitude. (LEFT) LOR of performance during CTDBS / performance prior to CTDBS (N=214) versus CTDBS amplitude. (RIGHT) LOR of performance during CTDBS / performance following CTDBS (N=177) versus stimulation amplitude. All amplitudes, frequencies and electrode configurations are included (N=492) from a total of 33 CTDBS sessions.

NEUROPHYSIOLOGY DURING CTDBS (see 811.26/FFF9)



(A) Average LFP spectra recorded from one electrode positioned within FEF, containing well-isolated single unit activity. The average LFP spectra are separated for **Correct** and **InCorrect** trials, excluding all DBS trials. **(B)** Average LFP spectra recorded from one electrode positioned within the dorsal caudate. Only 1.5 seconds of delay period activity in the Correct trials was included and then separated for trials with DBS and without DBS. (C) Peak LFP power centered at 5 and 20 Hz (+/- 2Hz) for a single electrode positioned within the dorsal putamen during correct performance. The **red** curves represent LFP power during 200Hz DBS ON periods (188 correct trials) and the **blue** curves represent LFP power during DBS OFF periods (137 correct trials). The Pre-Target, Target/Cue and Delay periods are noted and marked by vertical hashed lines (*see Vigilance Task for details*). **(D)** The first animal's performance profile during periods of continuous **150** and **200Hz** CTDBS. "Effective" cathode/anode configurations are highlighted with an asterisk. The five superimposed colored lines represent integrated power within select frequency bands: Yellow = total power across the entire frequency range (0.1 – 100 Hz); **Blue** = power in the delta range (0.1 – 5 Hz); **Green** = power in the alpha range (8 – 14 Hz); **Red** = power in the beta range (15 – 25 Hz); **Cyan** = power in the gamma range (25 – 90 Hz). Jackknife estimates of the 95% confidence intervals for each measure of integrated power are indicated by the dotted lines.

SUMMARY AND CONCLUSIONS

- **Robust and reproducible modulation of behavioral performance was observed in two animals during central thalamic deep brain stimulation (CTDBS). Behavioral modulation was observed in several visuomotor tasks, requiring vigilance and memory guided saccades. Both animal's reaction times and percentage of correct trials were sensitive to a unique subset of DBS parameters.**
- **A significant enhancement within the beta frequency band (15-25Hz) of the LFP spectra recorded from prefrontal cortex, dorsal striatum and central thalamus is consistently observed during correct performance in all tasks. The peak frequency and amplitude within the beta band is significantly influenced by performance enhancing CTDBS.**

REFERENCES:

Schiff, N.D. and Plum F. (2000) The role of arousal and "gating" systems in the neurology of impaired consciousness. J Clinical Neurophysiology 17(5): 438-52.

Schiff, N.D and Purpura, K.P. (2002) Towards a neurophysiological foundation for cognitive neuromodulation through deep brain stimulation. Thalamus and RS 2, 55-69.

Schiff, N.D. et al. (2007) Behavioral improvements with thalamic stimulation after severe traumatic brain injury. Nature 448, 600–603.

Smith A.C. et al. (2009) A bayesian statistical analysis of behavioral facilitation associated with deep brain stimulation, J Neuroscience Methods, 183(2):267-76.

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