Central thalamic deep brain stimulation modulates local field potential rhythms in the anterior forebrain during a sustained attention task

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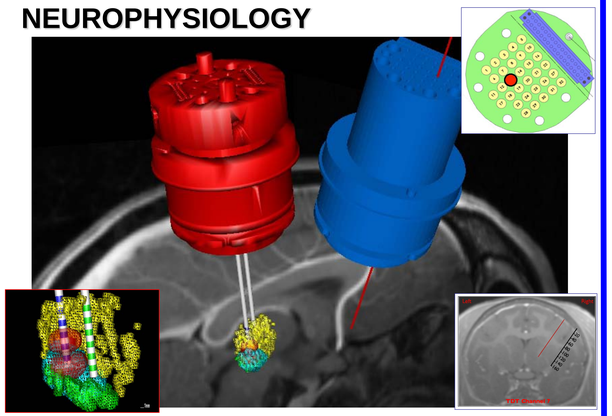
INTRODUCTION

The formation of stable patterns of rhythmic activity in local neural populations in the frontal cortex and striatum plays an important role in the control of arousal, holding attention, task learning and the execution of behavior. Shifts between dominant frequencies in these rhythms may be a signature of transitions between functional brain states, and understanding how this activity can be modulated in the anterior forebrain has implications for the treatment of brain disorders.

To investigate the role and control of rhythmic activity in striatum and cortex we perturbed the anterior forebrain network by delivering high-frequency (150 and 200 Hz) biphasic electrical stimulation to the central thalamus in a rhesus monkey trained to perform a sustained attention task. The central thalamus provides robust afferent drive to the striatum and to widespread regions of the cerebral cortex. We exploited this pathway to provide additional afferent drive to the anterior forebrain. Neural activity in the caudate, putamen, and frontal cortex was recorded as local field potentials (LFPs) by chronically implanted microelectrodes. Central thalamic deep brain stimulation (CTDBS) was provided over contiguous runs of trials with periods of ON DBS alternating with OFF DBS segments. The task required that the monkey acquire a visual target, hold fixation, wait for a cue that signaled the start of a variable delay period, and wait for the target to change color before contacting a touch switch.

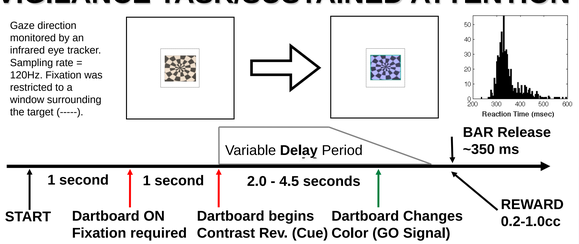
GENERAL METHODS

NEUROPHYSIOLOGY



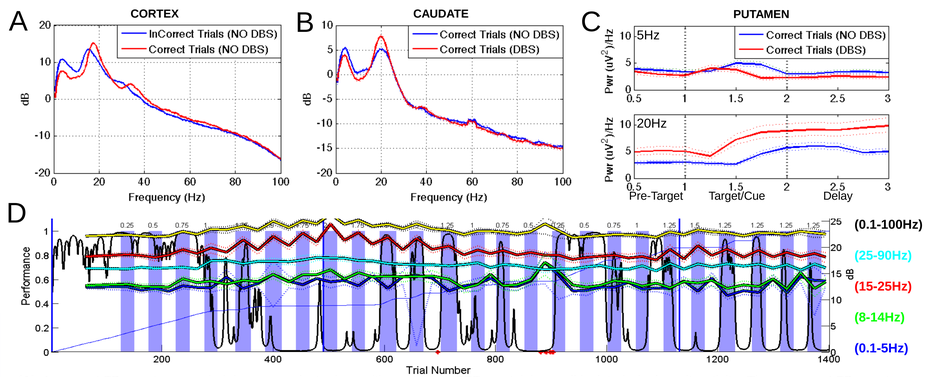
One adult macaque monkey was implanted with multiple Gray Matter Research, LLC (GMR) recording chambers, custom recording and stimulation devices, and a fixed set of 10 EEG electrodes, in order to investigate interactions among large cellular populations within the central thalamus, dorsal striatum, prefrontal cortex and broadly across the cerebral hemispheres using EEG. Multiple 6-contact DBS electrodes coated with BT DOT (Biotectix, LLC, Ann Arbor, MI) were chronically implanted into the right central thalamus. Current-controlled CTDBS was delivered over contiguous during blocks of trials while the animal performed a visual-motor behavioral task requiring vigilance and sustained attention. The **red** chamber in the above figure represents the Deep Brain Recording and Stimulation (DBRS) system with two chronic indwelling DBS electrodes, and the **blue** chamber represents the semi-chronic 32-microelectrode GMR microdrive, centered over the spur of the arcuate sulcus, targeting the frontal eye fields (FEF), dorsal premotor (area 6), dorsal lateral prefrontal cortex (DLPF) and anterior dorsal portions of the striatum, including both the caudate and putamen.

VIGILANCE TASK/SUSTAINED ATTENTION

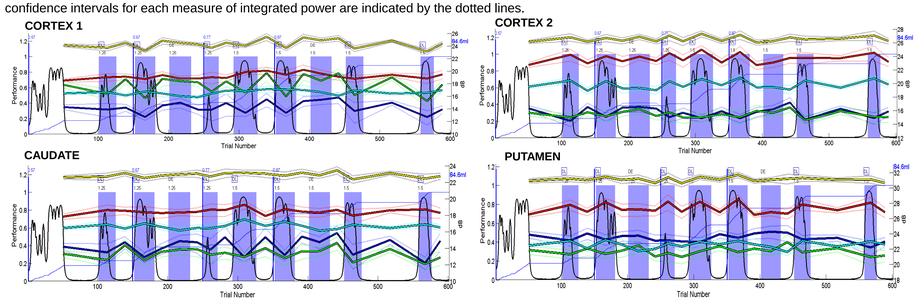


A red/black dartboard (5º x 5º) appeared in 1 of 9 locations on the screen. The animal was required to hold fixation on the target for 1 second to start the variable delay period. Delay period was signaled by a reverse contrast flicker of the dartboard at 10 Hz. The mean duration of the delay period was 3 seconds (std dev 250 ms). When the red/black dartboard 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 peak performance ranged between 70-90% correct.

EFFECTS OF CTDBS ON NEURAL ACTIVITY ACROSS A SESSION

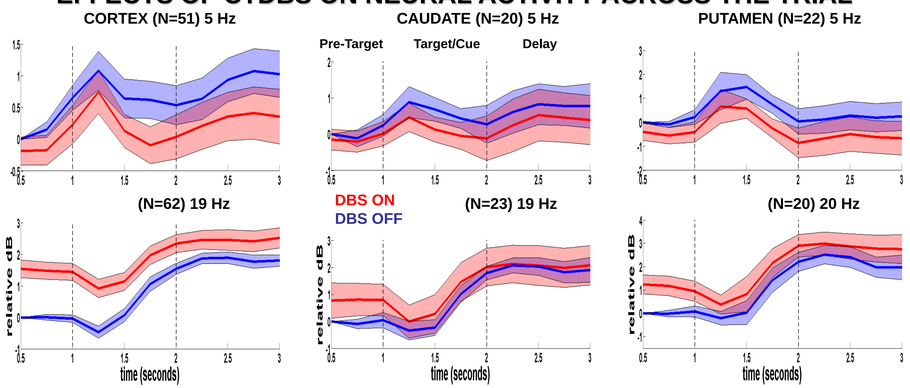


(A) Average LFP spectra recorded from one electrode positioned within FEF, containing well-isolated single unit activity. The average LFP spectra are separated for **Correct** and **InCorrect** trials, excluding all DBS trials. **(B)** Average LFP spectra recorded from one electrode positioned within 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 animal's performance profile during periods of continuous **200Hz** CTDBS ranging from 0.25 to 2.0 milliamps of current. 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.



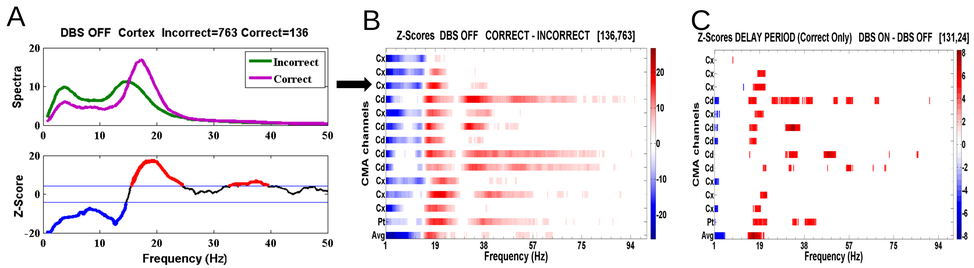
The animal's performance profile during periods of continuous **200Hz** CTDBS is shown in each of the four figures. The five superimposed colored lines represent integrated power within select frequency bands: Yellow = total power across the entire frequency range (0.1 – 100 Hz); **Blue** = power in 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. (UPPER ROW) Spectral profiles for two cortical electrodes containing well isolated single unit activity. (LOWER ROW) Spectral profiles for two electrodes positioned within the striatum and containing well isolated single unit activity. All LFP activity shown in the four panels was recorded simultaneously.

EFFECTS OF CTDBS ON NEURAL ACTIVITY ACROSS THE TRIAL

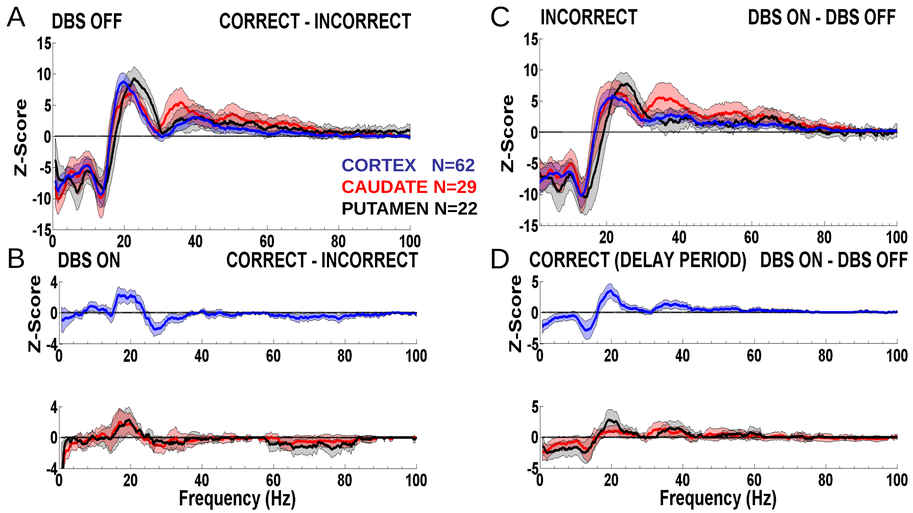


POPULATION SUMMARIES OF AVERAGE POWER FROM SELECTED FREQUENCY BANDS OF

EFFECT OF CTDBS ON POPULATIONS IN THE ANTERIOR FOREBRAIN



METHOD FOR EXTRACTING SAMPLE EFFECTS ON SPECTRA: To compare LFP power spectra recorded under different experimental conditions, we employed the two-sample spectral test (Bokil et al., 2007, available in the CHRONUX software toolbox). The two-sample test calculates a sample size-bias corrected z-score (ratio of mean power difference to total power fluctuation at each frequency) and provides a measure of significance of the statistic at each frequency. **A.** TOP PANEL: average power spectra calculated from a cortical LFP recording during 136 correct trials and 763 incorrect trials. BOTTOM PANEL: correct-incorrect z-score for the two spectra . Horizontal lines indicate the 99% confidence interval for accepting the hypothesis that the two samples produced spectra drawn from the same ensemble. The blue and red colored regions indicate those z-score values that survive a multiple-comparisons test across the frequencies in the spectrum (FDR). **B.** Multi-microelectrode plots of the significant z-scores obtained for a DBS OFF/correct-incorrect conditional comparison , and **C.**, for a Delay period (correct trials only)/DBS ON (200 Hz) – DBS OFF conditional comparison.



POPULATION SUMMARIES OF Z-SCORES: Averages of significant Z-scores are calculated from various subsets of the LFPs recorded across the microelectrode array during eighteen behavioral/recording sessions. Averages (thick lines), and 95% confidence limits calculated by jackknife (shaded areas), are shown for **CORTEX** (N=62 recordings from 57 different sites), **CAUDATE** (N=29 recordings from 24 sites), and **PUTAMEN** (N=22 from 17 sites). **A.** In the absence of CTDBS, task performance alone is seen to have a dramatic impact on the distribution of spectral power. Incorrect trials are associated with greater power in the lower frequencies (delta to alpha) whereas correct trial performance is associated with greater power in the beta and gamma range. **B.** With DBS ON (a range of DBS frequencies from 150 – 200 Hz and a range of amplitudes 0.75 – 3 mA are included) significant betaband activity is produced during correct trials and gamma activity appears during the incorrect trials. **C.** The presence or absence of DBS has a significant impact on the activity produced during incorrect trials. **D.** The impact of DBS on correct trial LFP activity is also to suppress low frequency power and enhance the power at higher frequencies. For **A**, **B** and **C**, LFP activity during the Pre-Cue, Cue/Target and beginning of delay period are analyzed. For **D**, only the first 1.5 seconds of delay period activity are included.

SUMMARY AND CONCLUSIONS

- **Task performance, trial epoch and CTDBS all influence LFP rhythms in the anterior forebrain (FEF, PFc and striatum).**
- **For correct trials, delta power displays a transient peak in the cue period while beta power dips during the same epoch before ramping up as the trials enter the delay period. CTDBS shifts power in the LFP power spectrum from lower (delta-alpha) to higher frequencies (beta-low gamma) for both correct and incorrect trials. CTDBS adds a small but significant contribution to the modulation of power produced by changes in task performance alone in the absence of CTDBS.**
- **Recordings within the cortex and striatum demonstrate similar changes in LFP spectral power in response to CTDBS supporting the view of the anterior forebrain as a cluster of anatomically distinct but integrated functional units that together generate stable patterns of rhythmic activity that can be modulated by CTDBS.**

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