Rapidly reversible behavioral arrest during fasciculus retroflexus deep brain stimulation in a healthy non-human primate

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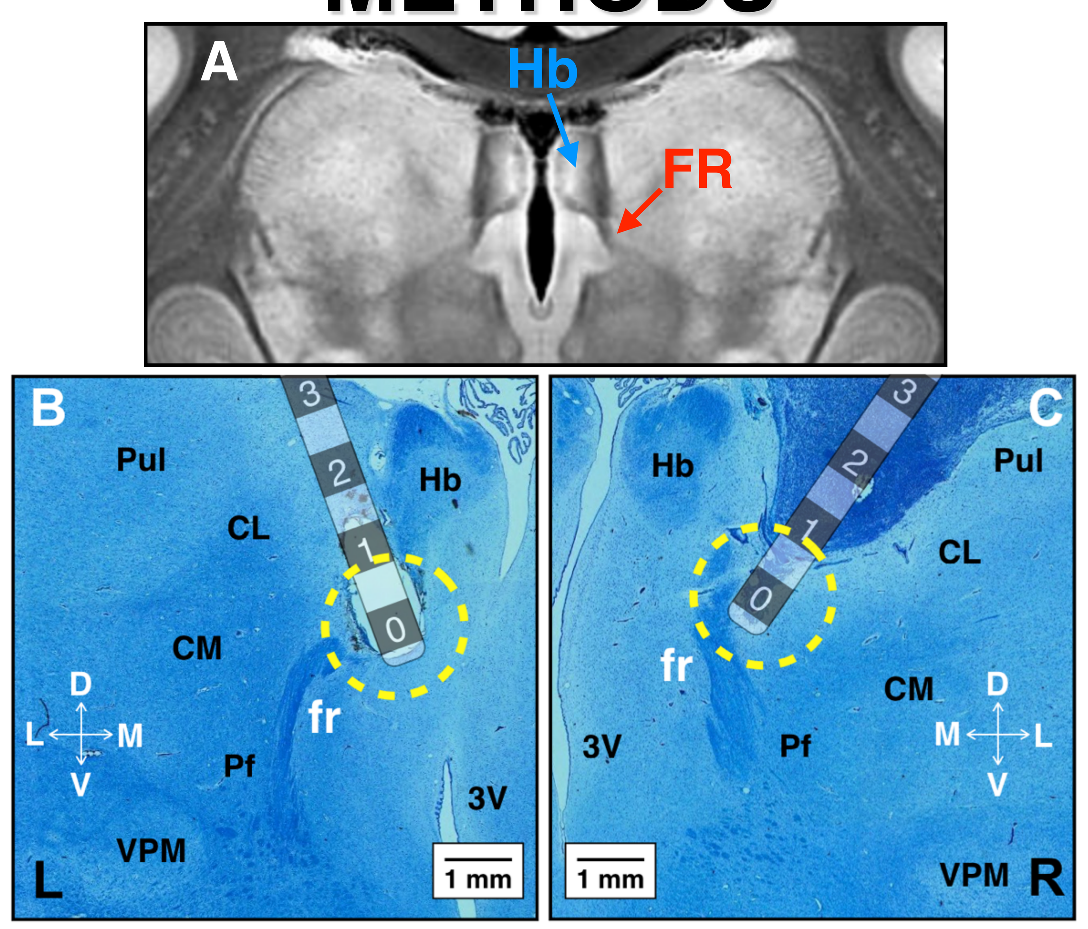
INTRODUCTION

Rapid cessation of purposeful movement is frequently observed when a stimulus-response pair is associated with an aversive outcome, for example a lower than expected reward, or a painful or threating stimulus. Behavioral arrest of ongoing movement is a general strategy for survival in all vertebrates and has been proposed as a primary function of the lateral habenula (Hikosaka 2010), an evolutionarily conserved epithalamic structure that gathers broad cortical and subcortical inputs and modulates monaminergic midbrain structures that regulate motor outflow. The primary descending output of the habenula, the fasciculus retroflexus, both directly and indirectly innervates dopaminergic and serotonergic regions in the vertebrate midbrain and dysfunction of the habenula has been linked to specific symptoms of psychiatric conditions, including depression, schizophrenia and addiction.

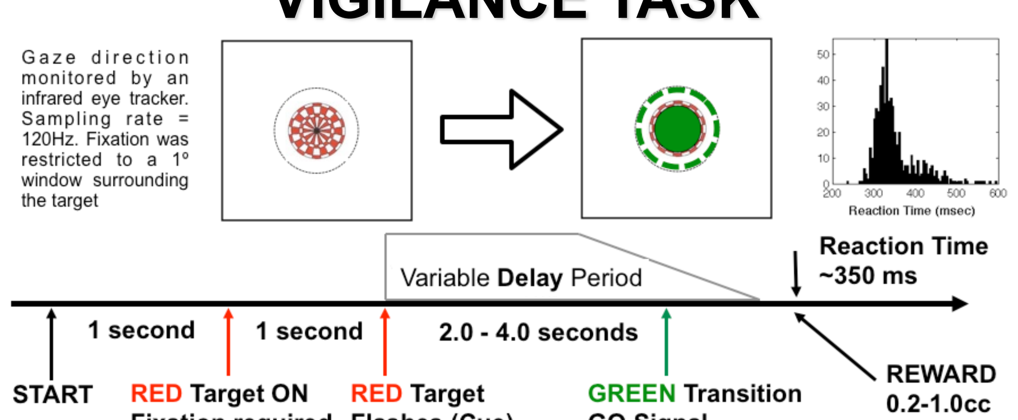
Here we show that deep brain stimulation of the fasciculus retroflexus (FR-DBS) induces a rapidly reversible behavioral syndrome consisting of global akinesia, conjugate slow drifting eye movements, periodic facial and upper skeletal atonia, a lack of normal response to aversive stimuli and 'sleep-like' episodes in a healthy non-human primate. During FR-DBS, a consistent temporal order of the above behavioral effects were correlated with pathologically enhanced cortical theta and beta oscillations. Following FR-DBS offset, consistent stereotypical dyskinesias in the upper and lower limbs and rapid conjugate 'non-purposeful' eye movements were observed prior to the animal's resumption of goal-directed behaviors. These results support the hypothesis that the primary output of the habenula, via the fasciculus retroflexus, regulates purposeful movements and sleep/wake activity in the vertebrate brain and potentially provide insight into the proposed dysfunction of the habenula in the symptomology of several human psychiatric disorders.

METHODS



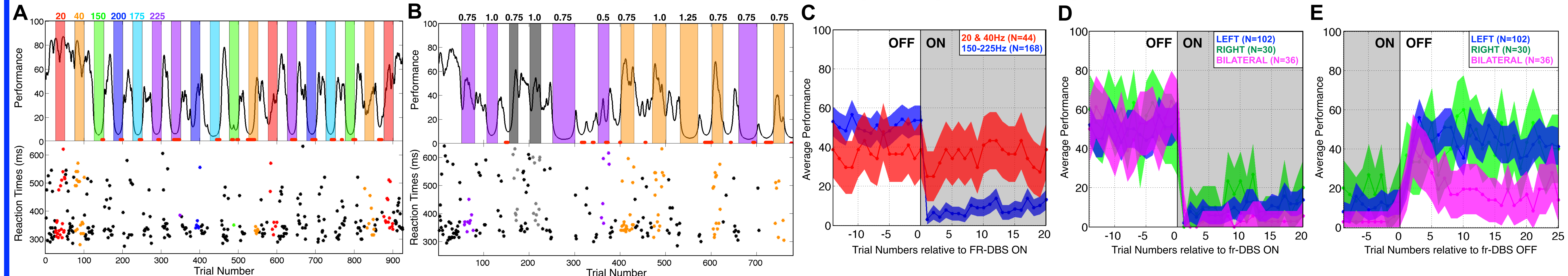
(A) Coronal gradient echo image from the rhesus macaque template (Calabrese et al., 2015, http://www.civm.duhs.duke.edu/rhesusatlas/). Blue arrow indicates the habenula (Hb) and the red arrow indicates the fasciculus retroflexus (FR). **(B)** Coronal photomicrograph of myelin and Nissl staining of the animal's left thalamus identifying the position of the left DBS lead, adjacent to the lateral habenula and within the fasciculus retroflexus. The yellow dotted circle surrounding contact 0 of a schematic DBS lead indicates the approximate volume of tissue influenced during 0.75mAmp cathodal stimulation. Note the location of the fasciculus retroflexus (fr) relative to contact 0. *Nuclei:* CL - Central Lateral; CM - Central Medial; Pf - Parafascicularis; Hb - Habenula; Pul - Pulvinar; VPM - Ventral Posterior Medial. **(C)** Right thalamus.

VIGILANCE TASK



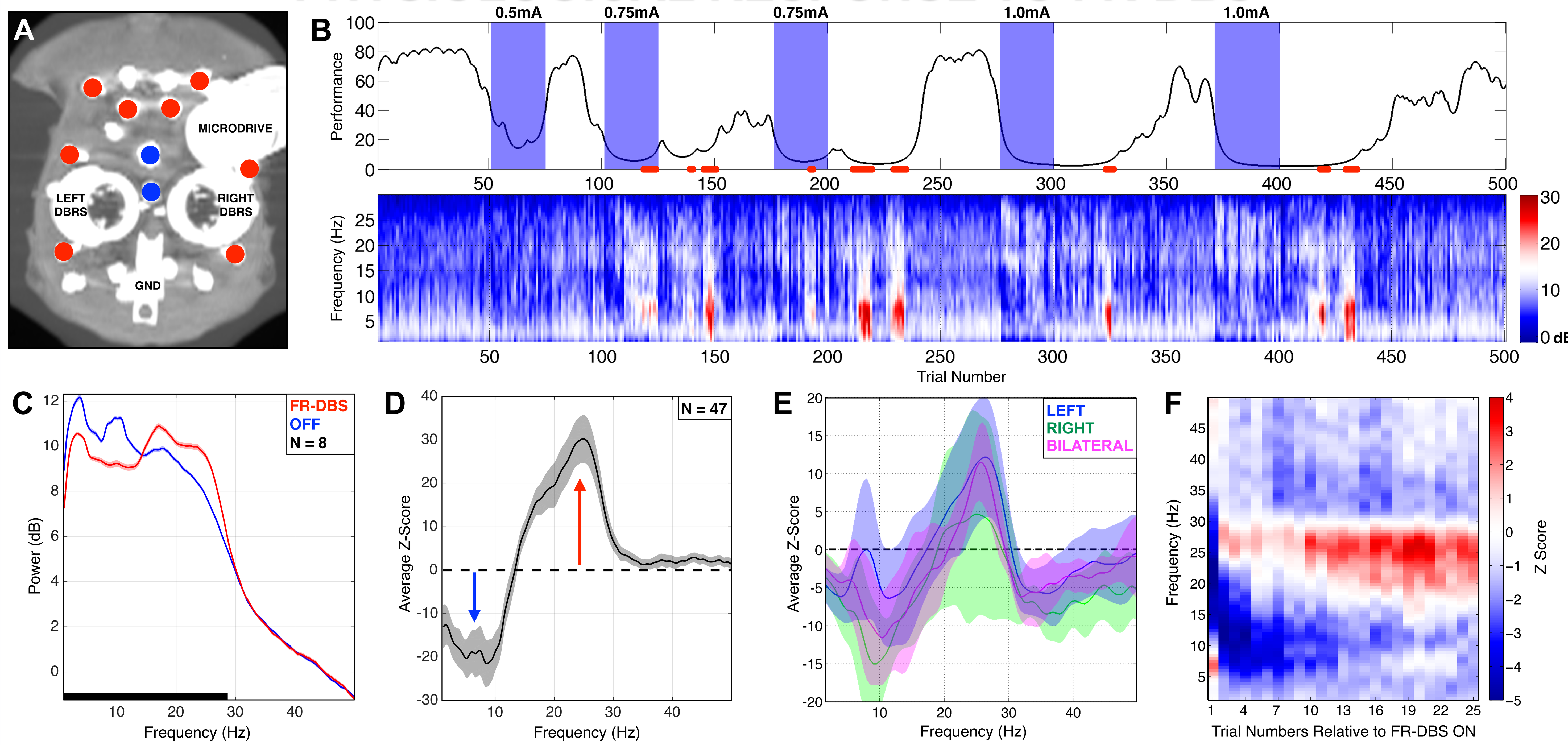
A red/black object appeared in 1 of 9 locations on the screen. The animal was required to fixate the red/black object until it changed to green/black (GO signal). Then the animal had to touch an IR switch located within the chair and within 250-800 ms following the GO signal for juice rewards.

BEHAVIORAL RESPONSE TO FR-DBS



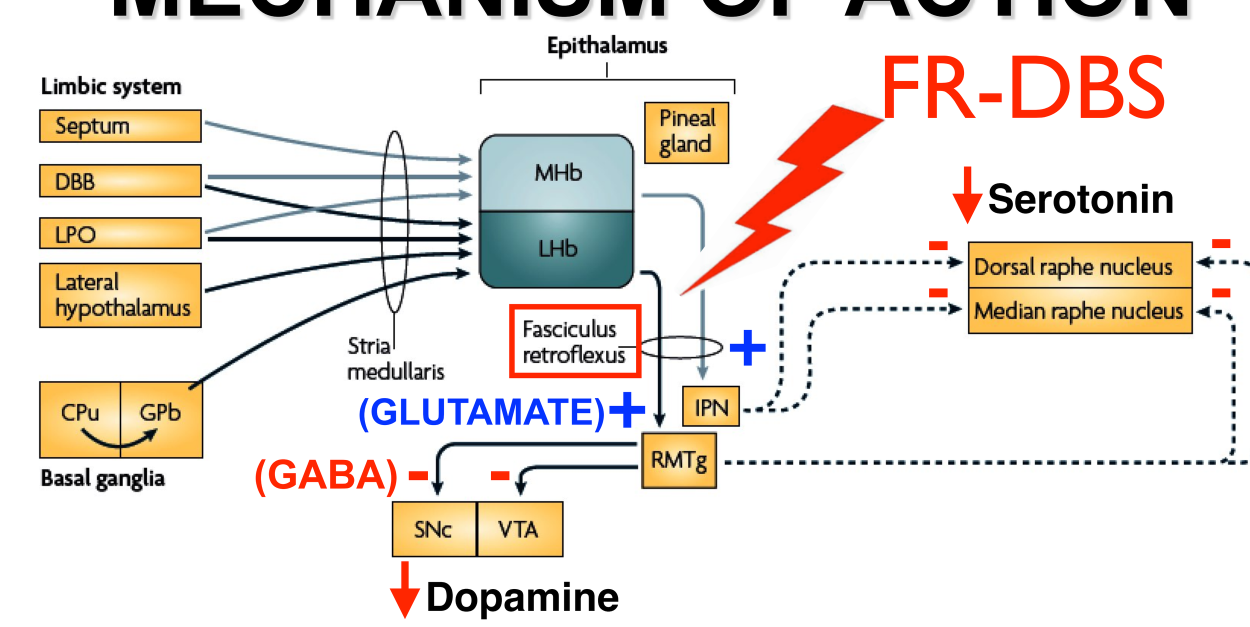
The frequency dependence of FR-DBS on the animal's performance of the vigilance task. **(A)** *Upper Panel:* The animals performance estimate during ON periods of 20, 40, 150, 175, 200 and 225Hz 0.75mAmp FR-DBS, color-coded respectively. In this session, the same anode-cathode configuration, left DBS lead, cathode contact 0 was used throughout. Red points along the zero performance level indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. *Lower Panel:* Reaction times for correctly performed trials are color-coded as above. Black points represent reaction times during OFF FR-DBS periods. **(B)** *Upper Panel:* The animals performance estimate during ON periods of 40 (**Orange**) and 225Hz (**Purple**) FR-DBS at various amplitudes ranging from 0.5 to 1.25mAmps. *Lower Panel:* Same as in A. **(C)** Average behavioral performance during low frequency FR-DBS (20 and 40Hz, **red curve**) and high frequency (150, 175, 200 and 225Hz, **blue curve**) FR-DBS with stimulation amplitudes ranging from 0.25 to 1.5mAmps. The gray shaded region from trial 0 to 20 represents the FR-DBS ON period. Each average performance profile includes 15 trials prior to FR-DBS onset and 20 trials during FR-DBS. **(D)** Average behavioral performance during left, right and bilateral high frequency (150, 175, 200 and 225Hz) FR-DBS with stimulation amplitudes ranging from 0.25 to 1.5mAmps. **(E)** Same as in D, but average behavioral performance profiles are shown following FR-DBS offset. Note the rapid arrest and resumption of behavior during and following high frequency FR-DBS, respectively.

PHYSIOLOGICAL RESPONSE TO FR-DBS



High frequency (150, 175, 200 & 225Hz) FR-DBS markedly shifts local prefrontal cortical and global physiology during behavioral arrest. **(A)** CT scan of the animal's cephalic implant with the location of the 10 ECoG electrodes marked with **red** and **blue** circles. The **blue electrodes** approximate Fz and Cz electrodes. The bilateral deep brain recording and stimulation (DBRS) devices and the right prefrontal microelectrode microdrive and common ground connection over the occipital pole are marked. **(B)** *Upper Panel:* An estimate of the animal's performance during periods of bilateral 200Hz FR-DBS from 0.5 to 1.0mAmps, each highlighted in blue. Red points along the zero performance level indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. *Lower Panel:* The average spectrogram of local field potentials (LFP) recorded simultaneously from *eight* microelectrodes located in various regions of the prefrontal cortex (area 8 and 46). **(C)** Average power spectra of the *eight* prefrontal LFPs recorded during 200Hz FR-DBS (shown in **red**) when the animal was akinetic and *not* performing the task, compared to delay period activity recorded when the animal was performing the task correctly, but not moving (shown in **blue**). Black points along the bottom of the frequency axis indicate significant difference between the two average power spectra (two-group test, $p<0.05$ and false discovery rate, $p<0.05$). **(D)** Average Z score of LFP power spectra from 47 microelectrode recordings located in the frontal cortex (areas 8 & 46) during 89 high frequency FR-DBS periods ranging from 0.5 to 1.5mAmps, collected across 13 experimental sessions. **(E)** Average Z score of bipolar FzCz (**blue electrodes**) ECoG power spectra recorded during 107 high frequency FR-DBS periods ranging from 0.5 to 1.5mAmps, collected across 18 experimental sessions and segregated based on Left, Right and Bilateral high-frequency FR-DBS. **(F)** Same as in E, but for 25 trials relative to the onset of high frequency FR-DBS. Note the marked suppression of low frequency power (0-12Hz) and the enhancement of 'beta' band (15-30Hz) spectral power during high frequency FR-DBS.

MECHANISM OF ACTION



Proposed mechanism of action during high frequency FR-DBS. Afferent and efferent connections of the habenula (*figure and text modified from Figure 1b in Hikosaka, 2010*). The medial habenula (MHb), lateral habenula (LHb) and pineal gland constitute the epithalamus in vertebrates. The MHb receives inputs mainly from limbic areas and sends glutamatergic outputs to the interpeduncular nucleus (IPN), which projects to the serotonergic raphe nuclei. The LHb receives inputs primarily from the basal ganglia and sends glutamatergic outputs to the deep brain structure, the rostromedial tegmental nucleus (RMTg), which sends GABAergic inputs to areas containing dopaminergic neurons (SNc and VTA) and serotonergic neurons of the raphe nuclei. In this study, high frequency FR-DBS drove the glutamatergic output of the habenula via the fasciculus retroflexus to inhibit activity within the SNc, VTA and dorsal and medial raphe, resulting in rapid behavioral and physiological changes in the healthy non-human primate studied.

SUMMARY & CONCLUSIONS

- **Robust and reproducible behavioral arrest of a healthy non-human primate was established with high frequency FR-DBS.**
- **High frequency FR-DBS resulted in significant enhancement of 'beta-band' (15-30Hz) spectral power in local field potentials recorded in the prefrontal cortex and in the global coherence (not shown) of brain-wide ECoG signals.**
- **The behavioral and physiological effects during high frequency FR-DBS may provide mechanistic insights into several psychiatric and movement disorders involving dysfunction of the habenula in humans.**