Central thalamic deep brain stimulation (CT/DBS) has been proposed and is being developed as a therapy for the treatment of disorders of consciousness following traumatic brain injury. CT/DBS aims to exploit the multiregional mechanisms in the brain that control levels of global activity that regulates the integration of sensory information and the execution of goal-directed behaviors. Proper integration and execution of behavior is associated with dynamic patterns of rhythmic neural activity generated by the concurrent activation of brain wide cortical-striatal-thalamic networks. In order for CT/DBS to be become a viable therapy it is necessary to determine with greater precision the sites and temporal patterns and anode/cathode configurations of stimulation that are most effective at modulating behavior and neural activity. To achieve these goals we carried out a series of experiments in two intact and behaving rhesus monkeys to 1) explore the vast CT/DBS parameter space (frequency, amplitude, electrode contact geometry and temporal pattern of stimulation), and 2) 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 under the influence of CT/DBS. In addition, [$F^{18}$] fludeoxyglucose measurements were conducted in one monkey to measure global glucose uptake prior to and during CT/DBS.

Targeting of the central thalamus was guided by a 3-D model of both the thalamus and stimulating electrodes translated into stereotaxic space by fusing the models with high-resolution volumetric CT/MRI data. Multiple 6-contact DBS electrodes were chronically implanted into the thalami of both animals. In addition, the animals were chronically instrumented with a 10 electrode EEG montage, a multi-contact recording probe placed within the thalamus and a high density 32-microelectrode microdrive placed over the arcuate and principle sulci. The monkeys were trained to perform cued, delayed reaction-time tasks and behavioral performance and electrophysiological recordings were evaluated against parameters of CT/DBS.

Unambiguous evidence of behavioral facilitation and suppression was observed during current controlled CT/DBS, using asymmetrical biphasic pulses in conventional and novel bipolar configurations delivered at various frequencies (20Hz, 40Hz, 150Hz, 175Hz, 200Hz, and 225Hz), amplitudes (0.1-3.0mA) and temporal patterns that included truncated Gaussian and Poisson noise stimulation. Model reconstruction of the cathode/anode contact geometries producing behavioral facilitation identify stimulation within the centrolateral (CL) and lateral portion of the medial dorsal (MD) nucleus and the dorsal portion of the centromedian (Cm) nucleus. Behavioral modulation was observed and quantified across 234 experimental sessions in the first animal and 72 in the second. A subset of frequencies (>100Hz), amplitudes (>0.5mAmps) and electrode configurations elicited robust and reproducible behavioral effects, including increased correct or incorrect performance and increased and decreased reaction times in both animals.

In addition to behavioral modulation in the first animal, we also observed significant enhancement of power in the beta/gamma range within the EEG and LFP signals recorded in the frontal cortex and striatum, along with significant decreases in alpha/theta/delta power. Interestingly, shifts in the power of similar frequency ranges over frontal cortical regions have been observed in the EEG of patients in association with spontaneous and drug induced recovery of consciousness. Global glucose consumption was measured in the first animal when the facilitatory CT/DBS parameters were used. ROIs in the MRI data were used to define volumes for comparing the uptake of FDG and we found that, compared to baseline, CT/DBS increased glucose consumption in the ipsilateral thalamus, striatum and anterior cingulate.

In addition to behavioral facilitation in the second animal, we report a novel behavioral syndrome, ‘mindlock’, induced by DBS near the boundary of the central thalamus and upper brainstem. This DBS induced syndrome is characterized by periods of both global akinesia and bradykinesia of the upper limbs, conjugate horizontal drifting eye movements, an absence of vertical eye movements and minimal eye blink. Upon DBS offset, hyperkinetic stereotyped movements of the upper limbs and ‘tic-like’ behaviors were observed for several seconds prior to the animal’s resumption of baseline behavioral performance. Model reconstruction of the cathode/anode contact geometries producing ‘mindlock’ identify stimulation ventral to the centromedian (Cm) and parafascicular (Pf) nuclei, in both the right and left thalami. In addition to the pronounced behavioral suppression, we observed significant enhancement in beta frequency (15-25Hz) power across a subset of EEG channels located along the midline and parietal cortices. Interestingly, these observations are strikingly similar to the symptoms and EEG signal abnormalities observed in human subjects suffering from basilar migraine with profound alterations of consciousness.

In summary, CT/DBS in the intact non-human primate results in both facilitation and suppression of behavior. Dynamic shifts in amplitude and frequency of brain rhythms are normally associated with changes in behavioral state and arousal, however in this study we show that CT/DBS can influence these shifts, and concomitantly influence behavior. Large-scale recordings of activity within distributed and functionally linked regions of the non-human primate brain will ultimately lead to a better understanding of the circuits involved in executive functions and help focus the clinical CT/DBS parameter space.