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 threatening stimulus. Behavioral arrest of purposeful movement has been proposed as a primary function of the habenula (Hikosaka 2010), an evolutionarily conserved hypothalamic structure that gathers subcortical and subcortical inputs and modulates mesencephalic midbrain structures that regulate motor output. The primary descending output of the habenula, the fasciculus retroflexus, both directly and indirectly regulates dopaminergic and serotonergic regions in the vertebrate midbrain and hypothalamus. Behavioral arrest of purposeful movement 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 behavioral arrest which is akinetic and akinetic. Fast-scan cyclic voltammetry (FSCV) of DA and NA revealed that the rapid behavioral and physiological arrest during high frequency FR-DBS is due to a significant increase of DA in the striatum. The behavioral and physiological effects during high frequency FR-DBS result in significant enhancement of ‘beta-band’ (15-30Hz) spectral power in local field potentials recorded in the prefrontal cortex and in the global electrocorticogram (ECoG). The L-DOPA (100 mg/kg) reversed the behavioral and physiological impairments induced by high frequency FR-DBS. In this study, high frequency FR-DBS drove the glutamatergic output containing dopaminergic neurons (SNc and VTA) and serotonergic neurons of the raphe nuclei. The habenula contains a population of GABAAergic interneurons that project to the prefrontal cortex (area 8 and 46). In this study, 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 electrocorticogram (ECoG).

METHODS

VIGILANCE TASK

A red light object appeared in 1 of 9 locations on the screen. The animal was required to fixate the object and within 500 ms following the GO signal and within the trial. The trial ended when the animal fixated the object for 1 second. The intertrial interval was 500 ms. The task was repeated 100 times. A red light object appeared in 1 of 9 locations on the screen. The animal was required to fixate the object and within 500 ms following the GO signal and within the trial. The trial ended when the animal fixated the object for 1 second. The intertrial interval was 500 ms. The task was repeated 100 times.

PHYSIOLOGICAL RESPONSE TO FR-DBS

High frequency (100, 150, 200 & 250Hz) FR-DBS markedly shifts local prefrontal cortical and global physiology during behavioral arrest. (A) AT scan of the animal's cephalic midline with the location of the 10 EEG electrodes marked with red and blue circles. The blue electrodes approximate Fpz and Fz electrodes. The lateral prefrontal brain recording and stimulation electrodes are shown. The gray box denotes the right prefrontal cortex. (B) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (C) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (D) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (E) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (F) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (G) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (H) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (I) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (J) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (K) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz. (L) Average performance of the animals during trials of bilateral 100Hz to FR-DBS from 0.5 to 1.5mAmps, each highlighted in blue. Points along the animal's cephalic midline indicate periods of eye closure and marked increase in the Fz-Cz ECoG power spectra 4-12Hz.