Deep Brain Stimulation of the Rodent Nucleus Accumbens Recruits Subcortical Limbic Networks

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Introduction: Although deep brain stimulation (DBS) was initially recognized for its efficacy in treating motor disorders, it has recently gained traction as a therapeutic option for many neuropsychiatric disorders [1]. In particular, the nucleus accumbens (NAc; ventral striatum) has emerged as a promising DBS target for the treatment of eating disorders, addictions, depression, and obsessive-compulsive disorder. Several studies in humans and animal models have been undertaken to decipher the circuit-level effects of NAc-DBS [2,3]. Perhaps the most reliable finding has been DBS-induced modulation of the medial prefrontal cortex (mPFC), which may be an important therapeutic node for obsessive-compulsive disorder. However, we reasoned that given the diverse array of disorders effectively treated by NAc-DBS, additional therapeutic circuit mechanisms might be at play. To this end, we employed a rodent model of NAc-DBS, undertaken with simultaneous fMRI to examine the circuit-level effects of NAc DBS in a widely used preclinical model. In addition to replicating the well-characterized modulation of prefrontal cortex, we report that NAc-DBS robustly activates several key subcortical limbic structures. Importantly, several of these structures (e.g., hypothalamus and amygdala) are known to be dysregulated in patients suffering from eating disorders and treatment-refractory depression [3-5]. Given that DBS disrupts pathological patterns of neural activity [1,6], we postulate that these may represent therapeutic circuit elements downstream of NAc stimulation.

Methods: Homemade MRI-compatible two-channel tungsten microelectrodes [7] were stereotactically implanted into the dorsal edge of the nucleus accumbens shell region (2.28mm anterior to bregma, 1.2mm right of midline, and 6.6mm ventral to cortical surface) in 4 adult male Sprague Dawley rats (300-450 g) under deep anesthesia with 2% isoflurane. The electrode was fixed with dental cement and the rats were allowed to recover for at least 24 hours before imaging studies (**fig.a-b**). For fMRI, rats were anesthetized, intubated, paralyzed, and ventilated with medical air. The ventilation volume and rate were adjusted to maintain $EtCO_2$ of 2.6-3.2% and SpO_2 above 96%. Rectal temperature was maintained at 37 ± 0.5 ^{o}C. Dexmedetomidine (0.1 mg/ml) and pancuronium bromide (1.0 mg/ml) were infused intravenously for the scan duration, supplemented with 0.5% isoflurane. For CBV-weighted MRI, a tail-vein catheter was used to deliver monocrystalline iron oxide contrast agent at a dose of 30 mg Fe/kg. Single shot, single sampled GE-EPI sequences (BW= 300 kHz, TR= 1000 ms, TE= 8.107 ms, 80x80 matrix, FOV= 2.56 x 2.56 cm2, slice thickness= 1 mm) were acquired using a Bruker 9.4T MR scanner and home-made surface coil. DBS was delivered simultaneously with GE-EPI scanning, under the following stimulation parameters (Amplitude: 500uA; Pulse Width: 90us, Frequencies: 10, 40, 70, 130, 200, 400Hz), and stimulation paradigm of (in seconds): 20OFF, 10ON, 40OFF. Stimulation was bipolar, delivered as square-wave pulses. At least one minute rest periods were given between scans. Automatic co-registration using SPM codes were applied to realign time-series data within subjects and then again across subjects. Data were then averaged across subjects in order to provide group-averaged fMRI maps using general linear model (GLM) analysis with reference to the DBS paradigm. Bonferroni correction was applied to adjust for the multiple comparisons of fMRI maps by dividing the significance level ($p<0.05$) by the number of brain voxels.

Results: NAc-DBS resulted in robust CBV increases in several discrete anatomical locations, spanning in length over 10mm of the rat brain **(Fig.c)**. Interestingly, with the exception of prefrontal cortex (which showed the largest DBS-evoked CBV increases), all of the modulated regions resided in the subcortical territory. Identified areas of modulation include: nucleus accumbens, septum, lateral hypothalamus, and amygdala. No regions with significant CBV decreases were detected. CBV increases by NAc-DBS were frequency-dependent for all targets, generally peaking at 40Hz (**Fig.d-e**). An exception was the lateral hypothalamus, which showed a consistent response amplitude from 40-400Hz.

Discussion: Here, we report on the circuit-level, frequency-dependent effects of NAc-DBS in the rat. Given the widespread application of the rat as a model of NAc-DBS effects [7-9], our findings should be of broad interest to both the clinical and basic neuroscience communities. Several subcortical areas were strongly modulated by NAc-DBS, and each of these is limbic in nature. We postulate that this widespread downstream response profile may relate to the ability of NAc-DBS to treat a diverse group of neuropsychiatric disorders [1]. Of further interest, our work suggest that high frequency DBS at the NAc induces local activation. This is quite noteworthy, as a longstanding question in the DBS field is whether high frequency stimulation activates or silences the target structure, with data existing to support both hypotheses [10-11]. Our uncovering of local activation to high frequency DBS is consistent with other fMRI studies conducted with simultaneous DBS at motor structures, both in humans and rodents [12-13].

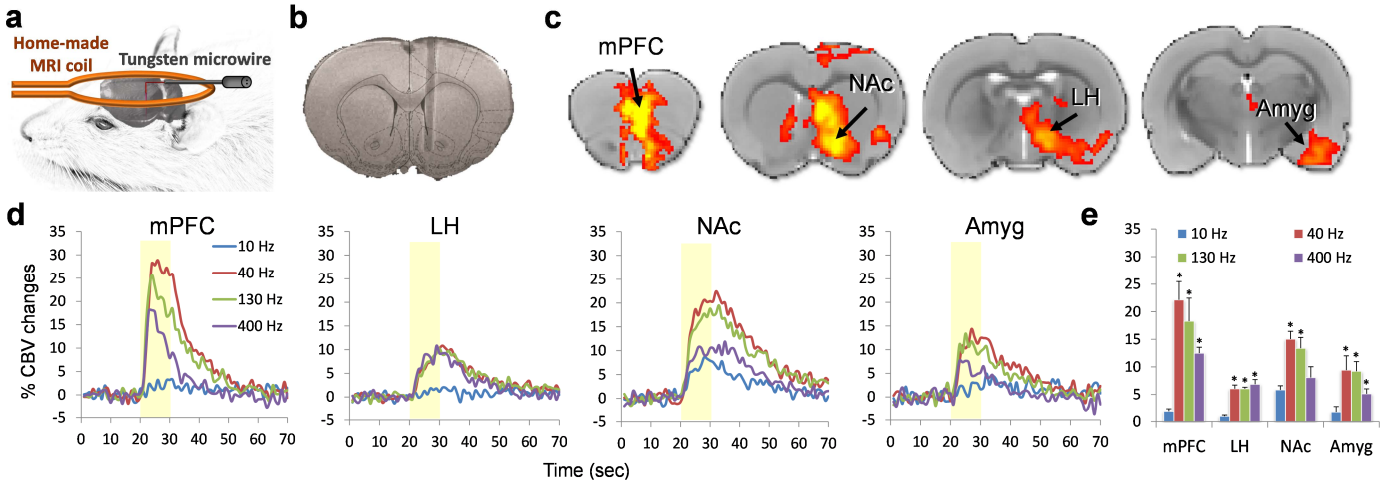

Figure (a) Schematic characterization of setup for simultaneous DBS-fMRI. **(b)** Representative T2-weighted anatomical image confirming electrode placement within the nucleus accumbens (core-shell boundary). **(c)** Representative functional activation maps of NAc-DBS at 130Hz (color range represents t-score from 0-10). **(d)** Percent CBV time-courses of multiple stimulation frequencies, at the medial prefrontal cortex (mPFC), lateral hypothalamus (LH), NAc, and amygdala (Amyg). Yellow bar denotes stimulation period. **(e)** Percent CBV changes to Nac-DBS (n=4). * denotes significant difference from 10Hz.

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