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Regular Article

Chronic deep brain stimulation of the rat ventral medial prefrontal cortex disrupts hippocampal–prefrontal coherence☆

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ABSTRACT

Deep brain stimulation (DBS) of the subgenual cingulate gyrus (SCG) has been used to treat patients with treatment-resistant depression. As in humans, DBS applied to the ventromedial prefrontal cortex of rats induces antidepressant-like responses. Physiological interactions between structures that play a role in depression and antidepressant treatment are still unknown. The present study examined the effect of DBS on inter-region communication by measuring the coherence of local field potentials in the rat infralimbic cortex (IL; homologue of the SCG) and one of its major afferents, the ventral hippocampus (VH). Rats received daily IL DBS treatment (100 μA, 90 μs, 130 Hz; 8 h/day). Recordings were conducted in unrestrained, behaving animals on the day before treatment, after 1 and 10 days of treatment, and 10 days stimulation offset. VH-IL coherence in the 2–4 Hz range was reduced in DBS-treated animals compared with shams after 10 days, but not after only 1 day of treatment. No effect of DBS was observed in the 6–10 Hz (theta) range, where coherence was generally high and could be further evoked with a loud auditory stimulus. Finally, coherence was not affected by fluoxetine (10 mg/kg), suggesting that the effects of DBS were not likely mediated by increased serotonin levels. While these data support the hypothesis that DBS disrupts communication between regions important for expectation-based control of emotion, they also suggest that lasting physiological effects require many days of treatment and, furthermore, may be specific to lower-frequency patterns, the nature and scope of which await further investigation.
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Introduction

Deep brain stimulation (DBS) of the subgenual cingulate gyrus (SCG) can be effective at alleviating depression symptoms in patients who are otherwise treatment-resistant (Mayberg et al., 2005; Lozano et al., 2008). Previous experiments from our lab have found that DBS applied to the rodent ventral medial prefrontal cortex (vmPFC) can also induce antidepressant-like effects (Hamani et al., 2010, 2012, 2014). This treatment model has provided a tool to directly probe how the nervous system is affected by stimulation and how physiological consequences are linked to depression. For example, recent work found that patterns of immediate early gene (IEG) expression across regions become less correlated between animals who have received vmPFC stimulation compared with correlations between non-stimulated animals (Hamani et al., 2014; Wheeler et al., 2013). This observation can be considered alongside demonstrations that brains of depressed patients exhibit abnormally high activity correlations ("functional connectivity") between the SCG and connected regions (Greicius et al., 2007; Berman et al., 2011; Zeng et al., 2012; Sambataro et al., 2013; Davey et al., 2012), raising the question of whether DBS may disrupt communication between brain networks that become pathologically hyperactive in depression. Precisely how DBS affects neural signaling between brain regions, and which physiological processes might underlie depression-related changes in inter-region activity correlations, remains unclear.

In the present set of experiments we test the hypothesis that chronic stimulation of the vmPFC disrupts communication with a major afferent, the ventral hippocampus (VH). We specifically target the infralimbic cortex (IL), because this region in particular may be part of the rodent homologue of the SCG, and because it shows the highest density of projections from VH (Swanson, 1981). We record local field potentials (LFPs) from

Abbreviations: SCG, subgenual cingulate gyrus; IL, infralimbic cortex; VH, ventral hippocampus; LFP, local field potential.

☆ NI, MP and CH designed the experiments; NI and MP performed the experiments; NI analyzed the data; NI, JN, WDH, KT, and CH wrote the paper.

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both regions in freely-moving rats before as well as after multiple days of high-frequency electrical stimulation.

Methods

Experimental subjects, surgeries, and histology

All procedures were approved by the University of Toronto Animal Care Committee and the Animal Care Committee of the Centre for Addiction and Mental Health. Experimental subjects were 15 male, Sprague–Dawley rats between 2 1/2 to 4 months old (Charles River). Following habituation to our animal facility, the animals were randomly assigned to those receiving DBS (n = 8) or sham stimulation (n = 7; electrodes implanted with no stimulation being delivered).

Surgeries were performed under isoflurane anesthesia. In each rat, monopolar stimulating electrodes (250 μm diameter with approximately 100 μm of insulation removed at tips) were placed bilaterally into the IL (3.0 mm anterior and 0.8 mm to the left and right of bregma lowered 4.4 mm ventral from the brain surface). One stainless steel (76 μm diameter bare, 140 μm coated) electrode was twisted around the right-side stimulating electrode to record local field potentials (LFPs), with tips of the two electrodes estimated to be 50 to 200 μm from one-another. Using different electrodes for stimulation and recording ensured that observed physiological changes could not be explained by stimulation effects on the tissue immediately adjacent to the electrode tip. A second LFP recording electrode was placed in the CA1 subfield of the ventral hippocampus (6 mm posterior and 5.7 mm to the right of bregma, lowered 6.2 mm from the brain surface). Approximate target locations are illustrated in Fig. 1A. A third stainless steel electrode was implanted into the cerebellum to be used as reference. A ground screw placed above the parietal cortex was wired to the ground of the recording equipment and used as an alternative reference channel. Rats were given at least two days of recovery from implantation surgery before recordings and treatment began.

Following the experiment, the rats were administered an overdose of sodium pentobarbital and perfused with 4% paraformaldehyde. Electrode location was confirmed in Nissl-stained sections (Fig. 1B).

Schedule of recording sessions and treatments

Fig. 1C shows the timeline of the experiments. Each recording session took place in a 50 × 50 cm square box where rats were allowed to move freely and involved three recording epochs. The first fifteen minutes of the session together constituted the "spontaneous behavior" epoch. This was followed by the "auditory stimulation" epoch, during which a brief auditory tone (100 ms, 2.5 kHz, 95 DB) was presented from speakers placed 50 cm above the rat. The tone was repeated 80 times over 33 min, each pulse presented between 20–30 s following the previous. The purpose of the auditory stimulation was to evoke attentional responses that provided a temporal reference for the analysis of neural activity. Following auditory stimulation, recording sessions continued for another 45 min, the "rest" epoch, to allow further investigation of physiological patterns across animals' activity states.

Data were collected in 5 or 6 recording sessions for each rat. The first recording session took place one day prior to the first day of DBS or sham treatment (Day 0). Other recording sessions took place in the evening or night (near the transition of rats' dark-to-light cycles) after 1 day of treatment, after 10 days of treatment, and 10 days following the termination of treatment (Day Post-10). An additional recording session took place (Day Post-1 or Post-11) while rats were injected with the selective serotonin reuptake inhibitor (SSRI) fluoxetine (10 mg/kg). As a control for the effects of injections, a subset of animals (4 DBS, 3 sham) was also recorded from after a single saline injection (Day Post-1). During injection days, protocols included pre- (15 min) and post-injection (30 min) baseline recording periods. These epochs

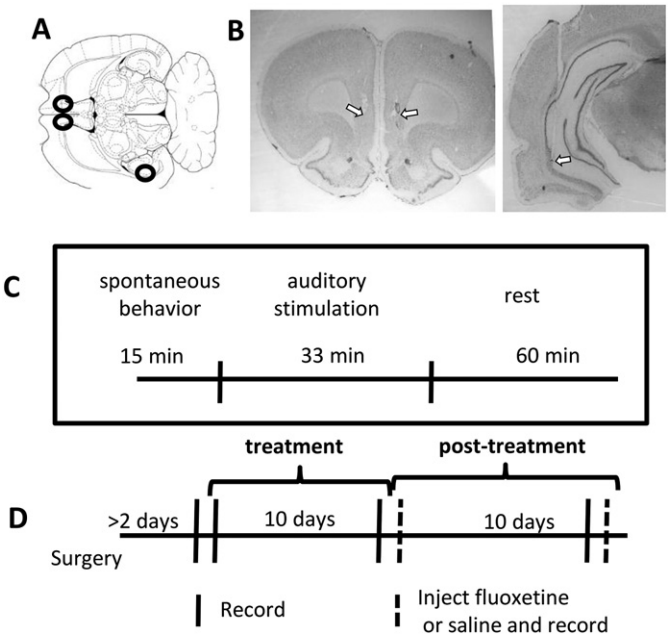

Fig. 1. Experimental design. A) Illustration of a rat brain horizontal section roughly 5.3 mm ventral from bregma (Paxinos and Watson, 1998). Black circles show approximate target locations for the bilateral IL stimulating/recording electrodes and the VH stimulating electrode. B) Nissl-stained coronal sections showing example electrode tracks and estimated tip location in one rat brain for both the IL (left) and hippocampal (right) electrodes. Arrows point to estimated electrode tip locations. C) Timeline of epochs within a session, for all non-injection sessions. D) Timeline of treatment and recording sessions. Recordings were performed on the day before treatment, following 1 and 10 days of treatment, and 1, 10, and 11 days after treatment ended; on Post-Day 1 and 11 rats were treated with either fluoxetine or saline (dashed lines).

were followed by a 33 min auditory stimulation epoch and a shortened (approximately 20 min) rest epoch.

DBS treatments consisted of 8 continuous hours of unipolar stimulation (90 μs pulses of 100 μA at 130 Hz) delivered bilaterally to the IL. Treatments were administered in each rat's homecage by a handheld medical stimulator (St. Jude Medical model 6510; Plano, Texas), interfaced by a headcap and cable (Plastics One, Roanoke, VA) and commutator to ensure freedom of movement. Rats receiving sham stimulation were connected on the same days that DBS rats were connected but stimulators were not turned on.

Data collection

Behavioral and neural data were acquired during each recording session. Movements were monitored by an overhead camera (14 Hz frame rate) tracking red LEDs attached to the headcap. Movement data was synchronized with neural data using a custom-built program in Python (https://www.python.org/) implementing the OpenCV library (http://opencv.org/). Position information was computed from video using a custom-written program in MATLAB (MathWorks; Natick, MA). Neural data was collected using a Tucker Davis Technologies (Alachua, FL) RZ5D system and consisted of LFPs sampled at 2034 Hz and filtered between 0.1 and 400 Hz, collected from the right infralimbic cortex and the right ventral hippocampus. All were referenced against the cerebellar electrode. The cerebellar reference electrode was recorded against the ground screw to allow for re-referencing.

Data analysis

Coherence during spontaneous behavior

All analyses were implemented in MATLAB. Coherence measures relied on a multitaper technique provided within the Chronux toolbox (http://www.chronux.org/). LFP signals during the first 15 min of

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