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Modulation of cortical motor evoked potential after stroke during electrical stimulation of the lateral cerebellar nucleus

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Abstract

Background—Deep brain stimulation (DBS) targeting the dentato-thalamo-cortical (DTC) pathway at its origin in the lateral cerebellar nucleus (LCN) has been shown to enhance motor recovery in a rodent model of cortical ischemia. LCN DBS also yielded frequency specific changes in motor cortex excitability in the normal brain, indexed by motor evoked potential (MEP) amplitude.

Objective—To investigate the effect of cortical stroke on cortical motor excitability in a rodent ischemia model and to measure the effects of LCN DBS on post-ischemia excitability as a function of stimulation parameters.

Methods—Adult Sprague-Dawley rats were divided into two groups: naïve and stroke, with cortical ischemia induced through multiple, unilateral endothelin-1 injections. All animals were implanted with a bipolar electrode in the LCN opposite the affected hemisphere. MEPs were elicited from the affected hemisphere using intracortical microstimulation (ICMS) techniques. Multiple LCN DBS parameters were examined, including isochronal stimulation at 20, 30, 50, and 100 Hz as well as a novel burst stimulation pattern.

Results—ICMS-evoked MEPs were reduced in stroke (n=10) relative to naïve (n=12) animals. However, both groups showed frequency-dependent augmentation of cortical excitability in response to LCN DBS. In the naïve group, LCN DBS increased MEPs by 22–58%, while in the stroke group, MEPs were enhanced by 9–41% compared to OFF DBS conditions.

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DISCLOSURES Drs. Machado and Baker have potential financial conflict of interest with the research related to intellectual property and ownership rights in IntElect Medical, ATI and Cardionomics. The Cleveland Clinic Conflict of Interest committee has approved a plan for managing the conflict of interest in the conduct of this research. The authors have adhered to the management plan in the conduct and reporting of research findings.

Conclusions—Activation of the DTC pathway increases cortical excitability in both naïve and post-stroke animals. These effects may underlie, at least partially, functional reorganization and therapeutic benefits associated with chronic LCN DBS in post-stroke animals.

Keywords

deep brain stimulation; stroke; motor evoked potential; dentato-thalamo-cortical pathway; lateral cerebellar nucleus

INTRODUCTION

Stroke is a debilitating neurological disorder affecting millions of people in the United States alone [1]. Several strategies have been explored to facilitate motor recovery after stroke, including invasive and noninvasive neuromodulation techniques. To date, however, both noninvasive transcranial magnetic stimulation (TMS) of the ipsi- and contra-lesional hemispheres [2,3] and invasive techniques, including chronic epidural electrical stimulation of the perilesional sensorimotor cortex have demonstrated limited clinical efficacy. Although epidural electrical stimulation of the cerebral cortex showed initially promising results in preclinical animal studies [4] and in clinical trials with a small number of patients [5,6], long-term benefits were not confirmed in a large-scale clinical trial [7].

Electrical stimulation can affect neural tissue excitability and it has been proposed that changes in perilesional excitability can modulate functional reorganization after cortical ischemia or injury [8–10]. While direct stimulation of perilesional cortex with epidural electrodes would be a simple way to achieve greater perilesional excitability, it is possible that this approach failed in a larger study due to significant variability in preservation and excitability of descending corticospinal pathway across patients and difficulties in consistently placing the electrodes relative to the perilesional cortex [6,7,11]. In addition, there are significant differences in cortical anatomy between the animal models and humans, which may have jeopardized clinical translation [12,13].

New strategies for enhancing post-stroke motor recovery are needed given the high incidence and prevalence in both industrialized and developing nations. We have proposed a deep brain stimulation (DBS)-based approach for promoting motor recovery after ischemia, targeting the lateral cerebellar nucleus (LCN), which is the output nucleus of the cerebellum in the ascending dentato-thalamo-cortical (DTC) pathway. By way of the excitatory DTC pathway, stimulation of the LCN can activate broad cerebral cortical areas, including perilesional regions that may carry potential for functional re-mapping in post-stroke recovery. We have shown that chronic DBS of the DTC pathway reproducibly facilitates motor recovery after small or large cerebral infarcts [14–16]. These effects are associated with increased perilesional synaptic density, increased perilesional representation of the affected forepaw and greater expression of markers of long-term potentiation [16]. One of the possible mechanisms underlying the effects of DTC pathway stimulation on motor recovery and perilesional plasticity is via modulation of cortical excitability and reversal of crossed cerebellar diaschisis [10]. We have recently shown that chronic stimulation of the LCN increases cortical excitability over sustained periods of time in naïve animals, in a

frequency-specific fashion [17]. Further, we have shown previously that despite phase-specific interactions with anesthetic agents, the enhanced cortical excitability by LCN stimulation is robust and reproducible in naïve animals [18]. Cortical excitability enhancement by LCN stimulation is mediated by activation of the ascending, di-synaptic glutamatergic excitatory DTC pathway. Specifically, activation of the LCN and its projections to the ventrolateral-ventral intermediate nuclei of the thalamus increases excitatory thalamic output to the cerebral cortex. Nevertheless, the effects of DTC pathway stimulation on perilesional cortical excitability after stroke still remain unknown. It is possible that stroke would alter thalamocortical interactions, which could hamper or alter the effects of ascending stimuli via the DTC pathway either completely or partially. In addition, stroke could alter the frequency-dependent relationship between LCN stimulation and cortical excitability [17]. Here, we present the results of a series of experiments designed to assess how electrical stimulation of the DTC pathway affects cortical excitability in the post-ischemia rodent model, compared to naïve controls. Cortical excitability was assessed by motor evoked potentials [19,20], and changes in cortical excitability related to the stroke, as well as frequency of stimulation, are reported.

MATERIALS & METHODS

Animals

Experiments were performed on male Sprague-Dawley rats weighing 250–350 g (Harlan®, Indianapolis, IN). All surgical and experimental procedures complied with United States Public Health Service policy and were performed under a protocol approved by the Institutional Animal Care and Use Committee (IACUC) of the Cleveland Clinic.

Ischemia and Electrode Implantation

Electrode placement in the LCN and induction of focal ischemia were conducted as previously described [15]. Briefly, animals were anesthetized with ketamine (50 mg/kg) and medetomidine (0.5 mg/kg) and fixed in a standard stereotaxic frame (David Kopf Instruments, Tujunga, CA). For animals assigned to the cortical ischemia group, the calvaria was exposed and burr holes were drilled at three locations for intracortical injection of 800 pmol endothelin-1 (ET-1, EMD Millipore, Billerica, MA) diluted to 2 μl per site. The coordinates of the three burr holes in relation to bregma were: 1) AP= −1.0 mm, ML= 2.5 mm, DV= −2.3 mm, 2) AP= +1.0 mm, ML= 2.5 mm, DV= −2.3 mm and 3) AP= +3.0 mm, ML= 2.5 mm, DV= −2.3 mm. After all burr holes were drilled, a primed 28G needle was inserted into the brain such that the center of the tip was at the target depth. Following a one-minute pause, ET-1 was injected at 0.5 μl/min. After injection of the first microliter, injection was paused for an additional minute before injection of the second microliter. Once the infusion was complete, the needle was left in place for three additional minutes prior to withdrawal in order to minimize potential backflow [21].

Under the same anesthesia as for ischemia induction (or as the single procedure for animals assigned to the naïve group), a bipolar macro-electrode (Model MS306, Plastics One Inc., Roanoke, VA) was implanted in the LCN (Figure 1A) contralateral to the ET-1 injections as described previously [15]. Briefly, a burr hole was drilled at AP= −11.0 mm and ML = −3.6

mm and the tip of the electrode inserted to DV= −6.3 mm in relation to bregma [22]. The electrode was fixed to the skull using dental acrylic, with small stainless steel screws (MX-0090-2; Small part Inc., Miami Lakes, FL) placed across the exposed skull for reinforcement. The burr holes created for the ET-1 injections were covered with cellulose paper (Data Sciences International, St. Paul, MN) and sealed with Vetbond™ tissue adhesive (3M, St. Paul, MN). Upon completion of the surgical procedure, medetomidine anesthesia was reversed with atipamezole (1mg/kg), and buprenorphine (0.05 mg/kg) was administered for prophylactic pain management. A post-operative recovery period of one week with food and water provided *ad-libitum* ensued in order to minimize potential confounding effects of electrode placement (e.g., microlesional effect).

Experimental setup

The general procedures and experimental set-up for intracortical microstimulation (ICMS)-elicited motor evoked potentials (MEPs) have been described previously by our group [17,18]. Following a loading dose of ketamine (75 mg/kg, i.m.), each animal received an intravenous line in the tail vein through which ketamine was infused at a constant rate (125 μg/kg/min, i.v.) throughout the remainder of the experimental procedure. Once anesthetized, animals were placed in a stereotactic head frame and the calvaria re-exposed. A 4 mm×5 mm craniectomy was created over the motor cortex contralateral to the LCN DBS electrode, which corresponded to the cerebral hemisphere previously injected with ET-1 in the cortical ischemia group. Mapping of the motor cortex was performed with ICMS using 50–75 kΩ tungsten microelectrodes (FHC Inc., Bowdoin, ME) until the area corresponding to the contralateral forelimb was identified (typically AP: 1.0 mm, ML: 2.0 mm, DV: −1.5 mm) [23], corresponding to the perilesional border. Surface electromyogram (EMG) recording electrodes (Model F-E5GH, Grass Technologies, Warwick, RI) were placed bilaterally over the forelimb muscle, with the corresponding muscle on the ipsilateral hemibody serving as the reference (Figure 1B). EMG recordings were bandpass filtered (1 Hz – 1 kHz) and amplified with an isolated differential amplifier (Octal Bio Amp, ADInstruments, Colorado Springs, CO). Thereafter, the raw EMG signal was digitized (10 kHz) and saved to a PC computer for off-line analysis (PowerLab 16/35 with LabChart Pro, ADInstruments).

Motor evoked potentials and deep brain stimulation

Motor thresholds for ICMS and LCN DBS were determined in the anesthetized animal, restrained in a stereotactic head frame. Stimulation amplitude was adjusted stepwise until a motor response was noted. During the experiments, LCN DBS stimulus amplitude was set to 80% of the LCN DBS motor threshold and delivered using one of five different parameters alternating with OFF-DBS washout periods: isochronal stimulation at 20, 30, 50, and 100 pulses per second as well as BURST mode. The BURST parameter set was designed to mimic a Hebbian paradigm and involved the delivery of periodic, high frequency pulse trains superimposed on a chronic, isochronal 30 Hz background. The inter-burst interval was 900 ms and the burst duration was 100 ms, with 10 pulses within each burst (100 Hz intra-burst frequency).

Motor evoked potentials were elicited serially throughout the experiment, with ICMS delivered approximately every 15 seconds, with a random interval (± 500 ms) added to the

inter-ICMS interval to minimize potential concurrence of the ICMS and the LCN DBS pulses. Each ICMS delivery consisted of three charge-balanced biphasic pulses with an intra-burst frequency of 330 pulses per second and an individual pulse width of 400 μs. The ICMS pulse amplitude was set at 125% of motor threshold for forelimb activation as determined immediately prior to experimental data collection.

Motor evoked potentials for a given DBS condition (i.e., ON-DBS, OFF-DBS) were recorded in 10-minute blocks, yielding a total of 40 trials per block (i.e., 4 trials/minute). Each experiment began with an initial pre-stimulation 10-minute baseline (OFF-DBS) block. Thereafter, the order of the ON-DBS parameter sets was pseudo-randomized for each animal such that all five frequencies were tested once in random order, and then stimulation parameters were repeated in another random order. Each ON-DBS condition was separated from the next by an intervening 10-minute OFF-DBS block in order to identify and characterize any persistence of effect from the preceding ON DBS parameter set (Figure 1C).

Data analysis

Individual MEP responses were analyzed using LabChart macros (ADInstruments, Colorado Springs, CO). For each trial, the raw EMG signal between 8 ms and 17 ms after the first pulse of the ICMS burst was rectified and averaged. To compensate for muscle tone variation across animals and time lapse, the signal was normalized by subtracting the rectified and averaged EMG signal in the 10 ms window immediately prior to the first pulse of the same ICMS burst. Physiological outliers in the MEP data were identified within each animal and condition using the inter-quartile range method (> 1.5×IQR) [24] and excluded from further analysis. Statistical analysis was performed using a mixed model approach to account for multiple measurements taken from a single animal over time, with DBS conditions (six levels, including OFF), trial, and their interaction used as independent, fixed variables. Trial was identified as the repeated measurement and animal within DBS condition as the subject identifier. Significance level was initially set to 5% (i.e. $\alpha = 0.05$), with post-hoc comparisons performed using Dunnett's test. All analyses were conducted using JMP® Pro (v11.0.0) and R (v3.0.3).

RESULTS

ICMS-evoked MEPs were recorded from a total of 12 naïve and 10 stroke animals, with all DBS parameter sets evaluated at least once per animal. Typical stroke volume and topography induced by the ET-1 injection are shown in Figure 1D. Baseline differences in cortical excitability between the two groups were examined directly by comparing data from the initial OFF-DBS block. As depicted in figure 2A, baseline MEP amplitudes were, on average, 70% higher in the naïve (M = 59.9 μV, SEM = 5.1 μV) relative to the stroke (M = 33.1 μV, SEM = 5.9 μV) group ($t_{20} = 3.19$, p = 0.004) during this pre-treatment condition.

OFF-DBS MEPs increased over time in both naïve and stroke animals

For both groups, motor cortical excitability, as measured across serial OFF-DBS epochs, increased over the course of the experimental period (Figure 2B). This progression,

expressed as the percent change in mean MEP amplitude relative to the initial, OFF-DBS block, was best fit by a linear regression for both the naïve ($R^2 = 0.96$, $F_{1,8} = 172$, $p < 0.00001$) and stroke ($R^2 = 0.96$, $F_{1,8} = 173$, $p < 0.00001$) groups (Figure 2C). Overall, the rate (i.e. slope) of increase across the experimental period was similar as revealed (Figure 2D) by the ratio of the median amplitude per block between the naïve and stroke groups ($R^2 = 0.18$, $F_{1,8} = 1.77$, $p = 0.22$).

Despite the overall increase in MEP amplitude across the experimental period in the OFF-DBS condition, responses remained relatively stable across the individual 10-minute, OFF-DBS blocks for the naïve ($R^2 = 0.065$, $F_{1,38} = 2.64$, $p = 0.112$) and the stroke ($R^2 = 0.097$, $F_{1,38} = 4.07$, $p = 0.051$) groups (Figure 2E). In order to account for any drift over time in the ON-DBS condition data analysis, ON-DBS MEP amplitudes were divided by the time effect ratio determined from the OFF-DBS block data. The time effect ratio was calculated as the ratio of the median of the last five minute MEP amplitudes in the OFF-DBS block preceding the ON-DBS block to the median MEP amplitude of the baseline OFF-DBS block. Analysis of the data revealed no difference in the compensated response pattern for blocks of the same stimulus frequency within a given animal. The time drift compensated data from repeated DBS parameter blocks were combined for statistical analysis to determine the effects of the stimulation parameters.

LCN DBS changes in cortical excitability are parameter-dependent

Both groups demonstrated changes in cortical excitability that varied based upon the parameters of LCN DBS applied; however, the distribution of the effect across parameter sets varied between the two groups (Figure 3). In the naïve group, cortical excitability tended to increase regardless of the LCN DBS parameters applied, with the magnitude of the effect ranging from 22% – 58% relative to baseline, and the maximal effect observed during BURST stimulation. A mixed-model ANOVA revealed a significant main effect of DBS condition on MEP amplitude ($F_{5,54} = 4.20$; $p = 0.0027$), with Dunnett's post-hoc test identifying the increases at 30 Hz, 50 Hz, 100 Hz and BURST conditions as significant relative to baseline. For the stroke group, all LCN DBS parameter showed augmentation of the MEP response, with the absolute increase ranging from 9% – 41% of baseline. Here, however, the effect was maximal when LCN DBS was delivered at an isochronal frequency of 50 Hz. The mixed ANOVA model revealed a main effect of DBS condition ($F_{5,40} = 3.03$; $p = 0.0206$), with Dunnett's post-hoc test signifying the changes at 50 Hz and 100 Hz as significantly different from baseline.

DISCUSSION

In this study, we evaluated for the first time the effects of LCN DBS on contralateral cortical excitability in a rodent model of focal ischemia. The cortical ischemia model adopted in this study has been previously shown to yield functional deficits in skilled reaching tasks using a pasta matrix, which can be reversed with chronic LCN DBS [15,16]. Cortical ischemia also drastically reduces cortical representation of the affected forelimb and increases the motor threshold of residual forelimb cortical representation [16].

MEP data in the current study show an overall reduction in cortical excitability in stroke-affected animals relative to naïve controls. However, both groups showed a frequency-dependent enhancement in cortical excitability in response to LCN DBS. The findings are in general consistent with our central hypothesis that LCN DBS can modulate cortical function in both naïve and post-ischemia states. In our previous studies, we found that continuous electrical stimulation of the LCN can modulate motor cortex excitability of naïve rodents, also in a frequency-specific fashion [17]. In that study, which was performed with animals under propofol anesthetic, high frequency stimulation at 100 Hz had a net inhibitory effect while lower frequencies, between 30 Hz and 50 Hz, yielded a net excitatory effect. Subsequent experiments by our group showed, however, that cortical excitability was not modulated solely by LCN DBS, with significant confounding effects introduced by choice of anesthetic agent and dose [18]. Of the agents evaluated, ketamine anesthesia was associated with the least amount of phase-dependent interactions between DBS and ICMS compared to standard dose of propofol anesthesia, and was thus selected for the experimental procedures reported here. Low or moderate doses of ketamine may enhance cortical excitability by selectively inhibiting NMDA-mediated glutamatergic inputs to GABAergic inhibitory interneurons [25,26]. These mechanisms may have contributed to the observed MEP amplitude increase in OFF-DBS block over time in our current study. In addition, rapid increase in synaptogenesis by ketamine [27], which can be facilitated by LCN DBS [16] might also have contributed to the MEP amplitude increase over time. In the future, studies examining the effects of continuous OFF-DBS MEP over long periods of time may be conducted to delineate the effects of repetitive ICMS as well as time and anesthesia on MEP amplitude.

The findings reported herein represent an important step in evaluating the translational potential of LCN DBS, as they represent the electrophysiological effects of this emerging therapy in the disease state [10]. We found that the magnitude of MEPs induced by ICMS of the perilesional post-stroke area was significantly reduced in the OFF-DBS state compared to naïve animals. These results are consistent with studies evaluating ipsilesional cortical excitability in the subacute post-stroke phase in humans, indexed by the magnitude of transcranial magnetic stimulation motor evoked potentials [28]. Such changes can be consequent to the direct effects of the lesion on the cortex, as well as due to changes in local circuitry dynamics. Furthermore, cortical lesions can reduce excitability due to reduced cerebellar output associated with crossed-cerebellar diaschisis [10].

Our translational model targets DBS at the LCN, the origin of the ascending cerebellar output in the DTC pathway. To date, we have shown that chronic LCN DBS promotes recovery from post-stroke motor impairment and is associated with significant perilesional plasticity [16]. We have postulated that a possible mechanism underlying these rehabilitative effects is via enhancement of cortical excitability and reversal of the effects of crossed cerebellar diaschisis [10]. In the present experiments, we evaluated how sustained LCN stimulation at different stimulus frequencies (20, 30, 50, 100 Hz and BURST) modulated cortical excitability compared to the OFF-DBS condition in post-ischemia as well as naïve animals. In agreement with our central hypothesis, LCN DBS increased cortical excitability not only in naïve animals, but also in stroke-affected animals. Furthermore, we note that frequency-dependent effects of LCN DBS on MEPs amplitudes are different in stroke

animals compared to naïve animals. While a broad band of stimulation frequencies enhanced MEP amplitudes in naïve animals, a similar effect was seen only with stimulation at 50 and 100 Hz in stroke-affected animals. The mechanisms underlying this filter-like effect of stroke on stimulation-mediated modulation of cortical excitability are not fully understood. In the case of epidural cortical stimulation of an animal model of cortical ischemia, high frequency stimulation (≥ 50 Hz) enhanced synaptic potentiation, which was shown to be related to the improvement in the skilled motor task after stroke [29]. In addition to frequency-specific modulation of synaptic potentiation after stroke, we speculate that stroke also induces significant changes in thalamocortical rhythms resulting from cortico-thalamic deafferentation. In addition, strokes affecting the motor cortex have been shown to cause crossed-cerebellar diaschisis due to informational deafferentation [30–33], resulting in cerebellar hypometabolism. Loss of cortical modulation may result in a narrowing of the dynamic range of cerebellothalamic or thalamocortical synapses, thus reducing the responsiveness range of the DTC to exogenous stimulation.

The present results are interesting if compared to our prior data, which showed that stimulation at lower frequencies (20 Hz and 30 Hz) were associated with the robust rehabilitative results [14,15]. They are an indication that while cortical facilitation indexed by MEP amplitude can be a valuable method to assess the effects of electrical stimulation on cerebral cortex function [7,11], it cannot fully predict the effects of specific chronic stimulation paradigms on post-injury recovery and plasticity. Therefore, in addition to MEPs, local field potential (LFP) recordings of the perilesional area in the future may also be useful to further characterize the effects of LCN stimulation on cortical excitability and its spatial modulation.

In summary, our findings indicate a) cerebral ischemia significantly reduces cortical excitability indexed by intracortical motor evoked potentials in the rodent model and b) LCN DBS can significantly reverse the negative effects of focal ischemia on cortical excitability in a frequency-specific fashion.

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ABRIBIATIONS

DTC	dentato-thalamo-cortical
ICMS	intracortical microstimulation
LCN	lateral cerebellar nucleus
MEP	motor evoked potential

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- Cortical ischemia reduced MEPs elicited by intracortical microstimulation.
- Lateral cerebellar nucleus DBS enhanced MEPs compared to OFF DBS.
- The enhancement of MEPs depends on the DBS frequency.

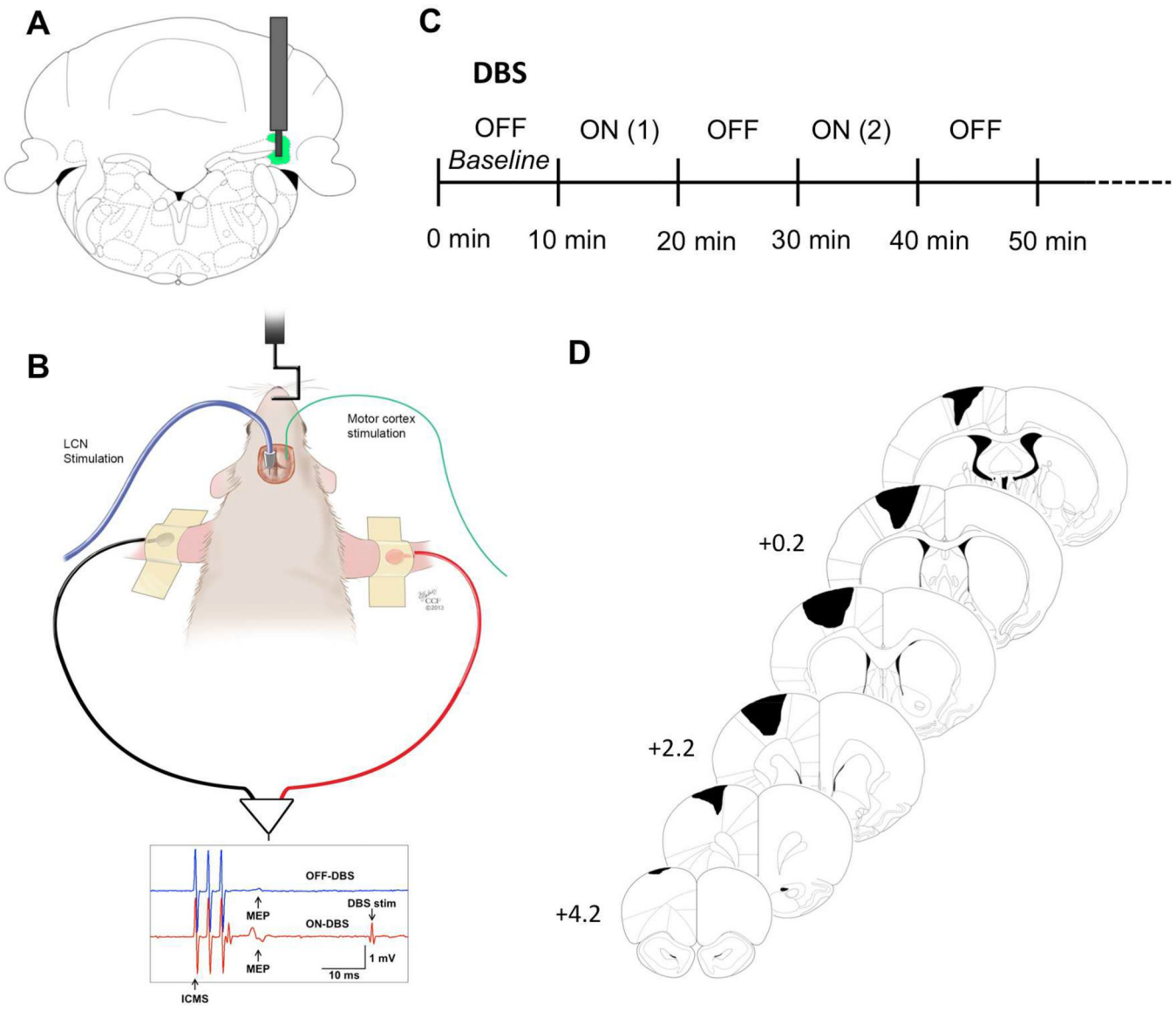

Figure 1. Experimental setup

(A) The LCN, represented in green, is the target of DBS. The bipolar electrode is shown superimposed on a coronal view of the rat atlas (AP= −11 mm). (B) LCN and ICMS stimulation and MEP recording set-up. MEPs recorded from the biceps brachii muscle in response to ICMS of the contralateral motor cortex during OFF-DBS (first row) and during ON-DBS (second row) of the LCN. Both ICMS artifacts and LCN DBS artifacts are noticeable. (C) Diagrammatic representation of the time course of the experiments. Each ON-DBS stimulation condition was tested in a 10 min block. The order of ON-DBS settings was tested pseudo-randomly but there was always an OFF-DBS condition block in between ON-DBS blocks. (D) A typical lesion volume induced by endothelin-1 intracortical injections in relation to bregma [22].

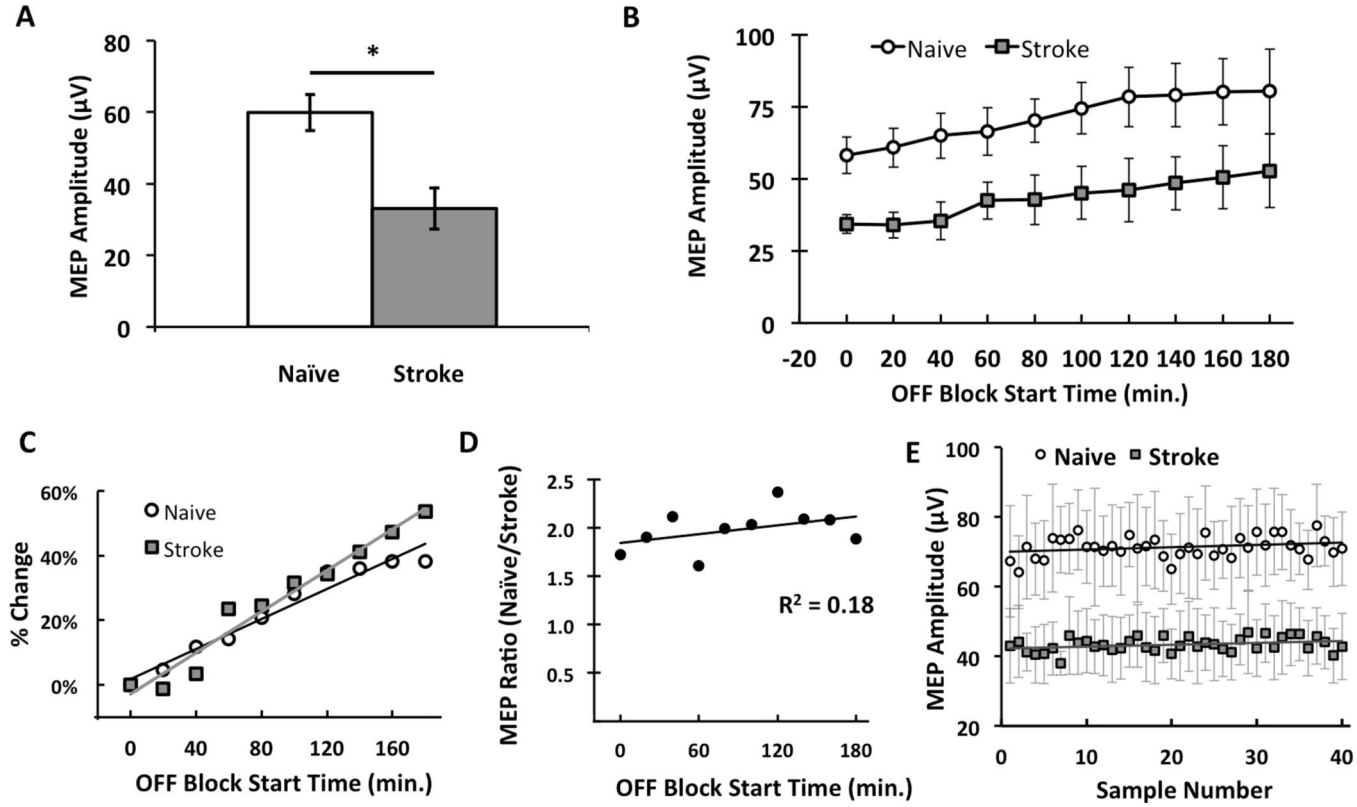

Figure 2. OFF-DBS MEPs

Motor evoked potential characteristics in the naïve and stroke group in the absence of LCN DBS. (A) The mean (± SEM) amplitude of the MEP response differed significantly between the naïve and stroke groups during the initial baseline (time 0), OFF DBS block. (B) The mean (± SEM) response during sequential OFF-DBS blocks increased as a function of experimental duration for both the naïve and stroke group animals. (C) The percent change in mean MEP response relative to the baseline epoch increased linearly for both groups, however (D) this increase, expressed as the ratio of the median response of each group per epoch, did not differ significantly between groups. (E) Despite the overall increase in mean MEP amplitude across sequential OFF blocks, changes in MEP amplitude (mean ± SD of the average MEPs over the animals per each trial) across the 40 ICMS trials within each of the ten OFF-DBS blocks were limited and not significant.

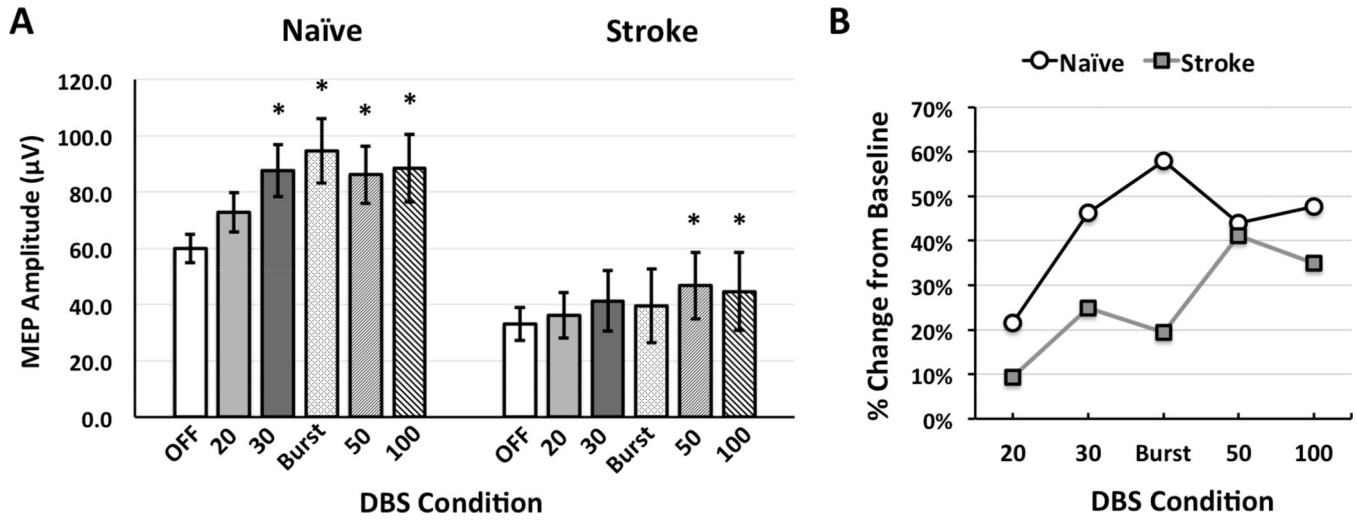

Figure 3. The effects of LCN DBS on MEPs

(A) Time drift compensated MEP amplitudes under different LCN stimulation conditions including OFF DBS for both naïve and stroke group animals. LCN DBS tended to increase MEP amplitude regardless of stimulus parameters; however, the magnitude of the effect varied both between the two groups and across the parameter sets. * $p < 0.05$ relative to baseline (i.e., OFF DBS) MEP values. (B) Percent changes in the mean MEP amplitudes in (A) from the mean baseline MEP amplitude during LCN DBS for each of the five DBS parameter sets evaluated in naïve and stroke animals.