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Coordinated Reset Deep Brain Stimulation of Subthalamic Nucleus Produces Long-Lasting, Dose-Dependent Motor Improvements in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Non-Human Primate Model of Parkinsonism

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ABSTRACT

Background: Novel deep brain stimulation (DBS) paradigms are being explored in an effort to further optimize therapeutic outcome for patients with Parkinson's disease (PD). One approach, termed 'Coordinated Reset' (CR) DBS, was developed to target pathological oscillatory network activity. with desynchronizing effects and associated therapeutic benefit hypothesized to endure beyond cessation of stimulus delivery.
Objective: To characterize the acute and carry-over effects of low-intensity CR DBS versus traditional DBS (tDBS) in the region of the subthalamic nucleus (STN).
Methods: A within-subject, block treatment design involving the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) non-human primate model of parkinsonism was used. Each treatment block consisted of five days of daily DBS delivery followed by a one week minimum post-treatment observation window. Motor behavior was quantified using a modified rating scale for both animals combined with an objective, upper-extremity reach task in one animal.
Results: Both animals demonstrated significant motor improvements during acute tDBS; however, within-session and post-treatment carry-over was limited. Acute motor improvements were also observed in response to low-intensity CR DBS; however, both within- and between-session therapeutic carry-over enhanced progressively following each daily treatment. Moreover, in contrast to tDBS, five consecutive days of CR DBS treatment yielded carry-over benefits that persisted for up to two weeks without additional intervention. Notably, the magnitude and time-course of CR DBS' effects on each animal varied with daily dose-duration, pointing to possible interaction effects involving baseline parkinsonian severity.
Conclusion: Our results support the therapeutic promise of CR DBS for PD, including its potential to induce carryover while reducing both side effect risk and hardware power consumption.

Introduction

Deep brain stimulation (DBS) has transformed the treatment of advanced-stage Parkinson's disease (PD), with significant motor benefits attainable when high-frequency, isochronal electrical pulses are delivered chronically to key regions within the basal ganglia thalamocortical (BGTC) 'motor' circuit [1,2]. Three decades later, however, the therapy remains largely unchanged despite advances in our knowledge of the neurophysiological changes that accompany parkinsonian motor signs as well as persistent clinical limitations, including stimulation-induced, therapy-limiting side effects that can be associated with traditional DBS (tDBS) [3–7]. Such considerations have contributed to interest in novel stimulus delivery paradigms that either target directly the putative pathophysiological processes associated with PD or reduce the overall amount of electrical charge delivered to the brain, or both [8–13].

Abbreviations: mUPDRS, modified Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; CR, coordinated reset; DBS, deep brain stimulation; tDBS, traditional deep brain stimulation; STN, subthalamic nucleus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; BGTC, basal ganglia thalamocortical; SA, subacute; IPG, implantable pulse generator.

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One such approach, termed coordinated reset (CR) DBS, involves the intermittent, pseudo-randomized delivery of brief, low-intensity, spatially-distributed pulse trains for the purpose of desynchronizing 'pathological' neural oscillations [9]. A key advantage of CR relative to tDBS is that its effects are achieved using lower individual pulse amplitudes [9,14,15], thereby reducing the risk of provoking side-effects attributable either to the spread of electrical current outside of the target region or to chronic, continuous stimulation of the target itself [7,16–18]. Furthermore, its desynchronizing effects are hypothesized to endure beyond treatment delivery, such that intermittent therapy may yield benefits that outlast cessation of stimulation by days or weeks [9,14]. Although the effects of CR DBS currently are well-supported by theoretical models [13,19–22], in vivo, preclinical or clinical data are limited [14,15].

Here we used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) non-human primate model of parkinsonism to examine the acute, sub-acute and long-term efficacy profile of CR relative to tDBS. In contrast to the stable, stimulation-dependent motor improvement observed in response to tDBS, the therapeutic profile of low-intensity CR DBS was marked by progressive, dose-dependent acute and sub-acute changes in motor behavior followed by carry-over effects that endured days after treatment cessation. The overall response profile of CR DBS across individual parkinsonian motor signs was similar to that observed during acute tDBS, further supporting a potential role for CR in PD DBS therapy.

Materials and methods

Animals and behavioral metrics

Two adult female rhesus monkeys (*Macaca mulatta*; Animal *P*, 6 kg; Animal *F*, 8 kg) were used. Animal care complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and all procedures were performed under a protocol approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

Animals were acclimated to the laboratory environment and to passive manipulation of the limbs using positive reinforcement techniques. The severity of the parkinsonian state was indexed using a motor rating scale adapted for use with the parkinsonian non-human primate (mUPDRS) [23]. The mUPDRS is used to rate five key parkinsonian features (rigidity, bradykinesia, akinesia, tremor, and food retrieval [upper-limb only]) on a 4-point scale (0–3; 0 = unimpaired), with ratings derived for both the upper and lower limbs (Maximum = 27 points). Scoring was performed during observation of spontaneous behavior and investigator interaction, including passive limb manipulation. Additional objective quantification of upper-limb motor performance was achieved using a cued-reach task in animal *P*, which involved the animal reaching between a start-pad and a computer-generated target displayed on a touch-sensitive screen [24]. A trial was initiated when the animal placed its unrestricted hand on a start-pad placed at a fixed, midline location immediately in front of it. After a variable hold period (1.0–1.5 sec), the presentation of a circle (8-cm diameter) provided both the target and the go-cue. Successful release of the start pad followed by a touch inside the circular target within specified reaction and reach (3.0 sec) limits triggered a liquid reward. No time limits were imposed for the initiation of consecutive trials.

MPTP administration

The MPTP neurotoxin was used to induce a parkinsonian state following standard techniques [25]. For animal *P*, two separate unilateral intracarotid injections (0.6 mg/kg [0.18 mg/ml solution], then 0.4 mg/kg [0.12 mg/ml solution]; 15-minute infusion) induced a stable, moderate hemiparkinsonian state, with the last injection administered three months prior to the start of treatment. Animal *F* underwent two intracarotid injections of MPTP (0.4 mg/kg; 0.16 mg/ml solution; 15-minute infusion) followed by serial intramuscular injections (0.3–0.4 mg/kg, 10 mg/ml solution), resulting in a stable, asymmetric parkinsonian state. The final injection occurred two months prior to the first treatment block. Post-operative management for intracarotid procedures included prophylactic antibiotics and opioid analgesics.

DBS chamber placement

Pre-operative cranial CT and 7-Tesla MRI were acquired in the anesthetized animal. The merged images were used to plan the placement of cephalic chambers using Cicerone software [26], with the central axis of the chamber positioned and aligned to target the MRI-determined dorsolateral region of the STN. All cephalic hardware, including the chamber and head restraint post, was implanted during an aseptic surgical procedure as detailed previously [25,27]. Post-surgically, animals were provided ad libitum food and water for a minimum of two weeks with prophylactic pain and infection management provided under veterinary guidance. For animal *P*, the chamber was oriented 10 degrees lateral to the parasagittal plane and 35 degrees anterior, while for animal *F* the chamber was oriented along the parasagittal plane at an anterior angle of 35 degrees.

STN mapping and DBS lead implantation

The sensorimotor region of the STN and its borders were mapped using microelectrode recording and stimulation techniques similar to those applied during human functional neurosurgery [28,29]. A hydraulic microdrive (Narishige Scientific Instruments) was attached to the chamber and used to advance a tungsten microelectrode (impedance 0.5–1.0 MΩ at 1 kHz) into the brain. The acoustically transduced neuronal activity was monitored and qualitative correlations between spontaneous movements or passive manipulation of the limbs was used to determine the receptive field characteristics of each isolated neuron. Once the boundaries of sensorimotor STN were determined, a final recording track was performed to establish the target depth for lead placement. Leaving the insertion cannula in place, the microelectrode was removed and replaced with a scaled-down, quadripolar DBS lead consisting of four concentric-ring platinum–iridium contacts [27]. For animal *F*, each ring was 0.63 mm in diameter, 0.50 mm long and separated from one another by 0.50 mm (NuMed Inc., Hopkinton, NY). For animal *P*, each ring was 0.86 mm in diameter and 0.50 mm long with an inter-contact spacing of 0.50 mm (St. Jude Medical, Plano, TX). Approximately one week later, a post-implant CT was acquired in anesthetized animal and merged with the pre-operative MRI to verify lead location.

The implanted lead was connected to a programmable, implantable pulse generator (IPG) (Brio™, St. Jude Medical, Plano, TX), which was placed in a subcutaneous pocket at the level of the chest in animal *P* during a separate surgical procedure [25,27]. For animal *F*, the IPG was not implanted as the proximal end of the STN DBS lead implanted in that animal was not compatible with the implantable extension cable used with Brio™ IPG. Thus, for this animal the proximal end of the implanted lead was routed to a secondary dry chamber placed on the cephalic implant and connected to the same model IPG acutely, during each daily stimulation session. In either case, however, the constant-current stimulation was delivered with the animal in the laboratory setting, seated in a standard primate chair with impedance values checked to confirm the integrity of all connections.