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Motor cortex stimulation: mild transient benefit in a primate model of Parkinson disease

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Object. The authors sought to examine the therapeutic efficacy of motor cortex stimulation (MCS) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated macaques and to characterize therapeutic differences with varying modes, frequencies, and durations of stimulation.

Methods. Motor cortex stimulation was delivered at currents below motor threshold and at frequencies between 5 and 150 Hz through epidural electrodes over the primary motor cortex. The animals were studied during and without MCS using video analysis, activity logging, and food retrieval tasks. Animals were examined using two different stimulation protocols. The first protocol consisted of 1 hour of MCS therapy daily. The second protocol exposed the animal to continuous MCS for more than 24 hours with at least 2 weeks between MCS treatments.

Conclusions. Daily MCS yielded no consistent change in symptoms, but MCS at 2-week intervals resulted in significant increases in activity. Effects of biweekly MCS disappeared, however, within 24 hours of the onset of continuous MCS. In this study, MCS only temporarily reduced the severity of MPTP-induced parkinsonism.

Key Words • Parkinson disease • primary motor cortex • MPTP • motor cortex stimulation • *Macaca fascicularis*

Long-term medical management of PD is limited by reductions in drug efficacy over time and by increased incidence of side effects such as dyskinesias.[25] Although surgical treatments such as pallidotomy and deep brain stimulation have proven therapeutic efficacy,[14,15] these treatments are not recommended for all patients because of their complex and invasive natures.[12]

The primary motor cortex has received recent attention as a potential therapeutic target for PD. In some studies of rTMS of the primary motor cortex, symptomatic improvement in patients with PD has been reported,[21] although this effect has not been substantiated uniformly.[9] Authors of some case reports in which patients have undergone low-frequency MCS have also provided descriptions of clinical improvement.[3,19,20] Short bouts of high-frequency MCS at 2-week intervals have been reported to yield substantial reductions of symptoms in MPTP-treated baboons.[7] Together, these observations raise the novel possibility that a global amelioration of parkinsonian symptoms can be produced by unilateral stimulation of a small portion of the primary motor cortex at intensities subthreshold to those required to evoke movement. Unfortunately, previous animal studies lack details on the long-term effects of MCS and the effects of variations in stimulation polarity and frequency. We sought to clarify the effects of MCS in MPTP-treated primates blinded to treatment, particularly with respect to the mode and duration of MCS.

Abbreviations used in this paper: GP = globus pallidus; MCS = motor cortex stimulation; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD = Parkinson disease; rTMS = repetitive transcranial magnetic stimulation; SEM = standard error of the mean; TH = tyrosine hydroxylase.

Materials and Methods

Animal Model and Implantation Surgery

Three juvenile monkeys *(Macaca fascicularis)* were used. The monkeys weighed 2.8, 3.6, and 4.5 kg. All procedures involving the animals were approved by the Institutional Animal Care and Use Committee.

The overlesioned hemiparkinsonian model[2,18] was followed to induce bilateral lesions of the dopaminergic system without completely disabling the animals. In brief, animals received initial unilateral intracarotid artery infusions of MPTP (right hemisphere, 0.55 mg/

kg), followed by a course of escalating intramuscular doses. All animals received six intramuscular doses administered evenly over 2 weeks (three doses at 0.35 mg/kg, followed by three at 0.55 mg/kg). In two animals that continued to show relatively mild symptoms, additional doses were administered during the 3rd week (one and two doses each at 0.75 mg/kg). In the months following the course of MPTP administration, the animals displayed stable symptoms of severe parkinsonism including flexed posture, a general paucity of spontaneous movement and frequent freezing (akinesia), bradykinesia, and increased limb rigidity. Due to the unilateral intracarotid artery infusions, these symptoms were more severe in the left limbs. All animals tended to turn in the clockwise direction and all showed evidence of a mild left hemineglect consistent with previous reports.[1] Symptom severity was rated regularly using a scale developed by Schneider and colleagues,[24] which includes numerical scores for limb and full body movement, manual dexterity, tremor, and other behaviors associated with parkinsonism in monkeys. All three animals had scores indicative of severe parkinsonism throughout the period of testing described here. The mean Schneider scores were 37, 38, and 45, on a scale that ranged from 0 ($<$ 10 considered asymptomatic) to 53 (maximal severity). In a further indication of classic parkinsonism, all three animals responded to replacement therapy (5 mg/kg levodopa methyl ester with 10 mg/kg benserazide) with a transient but marked increase in mobility, increased limb use, reduced rigidity, and a tendency to turn in the counterclockwise direction.

Implantation surgeries were performed after induction of isoflurane anesthesia, using aseptic technique. A craniotomy was performed over the arm region of the primary motor cortex of the right hemisphere at the following Horsley–Clark coordinates: anterior 10, lateral 20, depth 20.[30] A two-contact paddle electrode (Northstar Neuroscience; 2.5 $\times$ 1 cm, 0.8 cm between contacts, 2Ω at 1 kHz) was implanted on the dura mater overlying the primary motor cortex with the two electrode contacts approximately 1 cm anterior to and parallel with the central sulcus. The bone flap was replaced and secured with bone screws and acrylic cement. A reference electrode was placed under the temporalis muscle contralateral to the site of stimulation.

Following the behavioral assessment experiments in two animals, recording chambers were implanted to allow neuronal recording in GP. A cylindrical titanium chamber (18-mm internal diameter) was implanted using stereotactic guidance over the bur hole created previously. By necessity, the previously implanted extradural stimulating electrode was removed during this surgery. The chamber was oriented parallel to the coronal plane at an angle approximately 35° from vertical. The chamber was fixed to the skull with bone screws and dental acrylic. Bolts were embedded in the acrylic to allow fixation of the head during recording sessions.

Motor Cortex Stimulation Procedures

Motor cortex stimulation was administered using a telemetry-controlled, constant-current pulse generator (Northstar Neuroscience) placed in a backpack on the animal's back. Stimulus pulses consisted of an initial square wave (width 130 μsec) followed by an exponentially decaying opposing deflection to balance the charges. The polarity of the MCS was defined as anodal (positive square wave at both cortical electrodes), cathodal (negative at both cortical electrodes), or bipolar (two cortical electrodes used as positive and negative contacts). Pulse frequencies ranged from 5 to 150 Hz.

The MCS was administered at 70% of motor threshold, which was established separately for each frequency, polarity, and animal immediately prior to each MCS session. Motor threshold was defined as the lowest current capable of reliably evoking visible muscle contraction in response to 2 seconds of stimulation. The muscles most commonly activated at motor threshold were those of the thenar eminence. Motor thresholds ranged from 1.2 to 3.2 mA, with the lowest motor thresholds obtained by stimulation at high frequencies. Individual motor thresholds for a given animal, frequency, current, and polarity combination remained nearly constant over the course of 6 to 12 months of testing. Currents applied above motor threshold consistently evoked arm and leg movement when delivered through medial contacts, and arm and orofacial movement when delivered through lateral contacts. The precentral location of implanted electrodes was confirmed by postmortem examination in one animal and during the subsequent chamber implantation surgery in the other two.

Behavioral Assessments

Effects of MCS were evaluated during multiple 1-hour observation periods (Fig. 1A) while the animal was in a soundproof cage under videotape observation. An Actitrac (IM Systems) activity logger fixed to the animal's backpack recorded the total number of whole-body movements ($>$ 0.613 cm/second^2) per minute. Manual dexterity was assessed four times (every 15 minutes) per 1-hour session, using a Klüver task in which the animal retrieved food from a board with 12 wells (1 in diameter, 0.25 in deep, each holding a grape slice), accessible only to the left arm. Stimulation conditions were randomized between sessions so as to avoid confounds that might bias an animal's response to MCS. The sensitivity of these methods was confirmed by performing identical 1-hour observation periods following intramuscular administration of 5 mg/kg levodopa methyl ester with 10 mg/kg benserazide. Differences in average activity were assessed for significance using the t-test.

One researcher, blinded to therapeutic conditions, reviewed each videotaped observation period and rated the animal's level of parkinsonism using both the Schneider scale and a quantitative analysis of the prevalence of nine different behaviors. We found the Schneider scale to be insensitive to small or transient changes in symptoms. Moreover, the video-based assessments prevented inclusion of the following Schneider scale subscores: defense reaction, blinking, appetite, and climbing. Quantitative analysis of the videos was adapted from a similar method used by Grabli and coworkers.[11] This method reports, as a percentage of each 1-hour observation session, the prevalence of nine behaviors: food retrieval in the Klüver task, exploring, touching/licking cage bars, chewing, climbing, licking/biting fingers, visually tracking, grooming, and not moving.

All three animals were studied for the effects of daily 1-hour MCS at different frequencies and polarities (Fig. 1A). One animal was also studied using biweekly (once every 2 weeks) long-term MCS at 30 Hz bipolar. For each biweekly stimulation trial, 12 1-hour observation sessions were distributed over 2 weeks (Fig. 2A). Following 1 week of control observations, MCS was delivered continuously for approximately 25 hours, after which the animal's behavior continued to be measured after MCS discontinuation. For both treatment schemes, measures obtained during on-MCS and off-MCS conditions were compared using t-tests, similar to the approach used by Drouot et al.[7] and Pagni and coworkers.[19,20]

Electrophysiology and Histology

The parkinsonian status of animals was confirmed by single unit recording in the GP (two animals) or by TH immunohistochemistry (one animal). The spontaneous activity of multiple single pallidal neurons was sampled from awake animals at rest using a four-electrode microdrive, 1-MΩ glass tungsten electrodes (Alpha Omega) and an acquisition system (Tucker Davis Technologies) sampling at 24 kHz. Single-unit action potentials were discriminated using Offline Sorter software (Plexon Inc.) and analyzed using custom routines in the Matlab environment. The L-burst statistic was used to determine the prevalence of pathological neuronal activity within the GP.[13,27] Unfortunately, neuronal activity could not be measured during MCS due to significant electrical artifacts from the MCS.

At the completion of the study, one animal underwent transcardial perfusion using phosphate buffered saline with 10% formalin. The tissue was blocked and cut into 40-μM sections in the coronal plane and stained using TH immunohistochemistry. Specifically, a mouse anti–tyrosine monoclonal antibody was incubated with the tissue for 24 hours, followed by 1 hour of incubation with a biotinylated horse anti–mouse antibody (Chemicon International). Sections were then incubated with streptavidin for 1 hour and then revealed using 3′3-diaminobenzidine-vector SK-4100 (Vector Laboratories). Histological study of the other two animals was unavailable because one died unexpectedly and the other is engaged in an ongoing study.

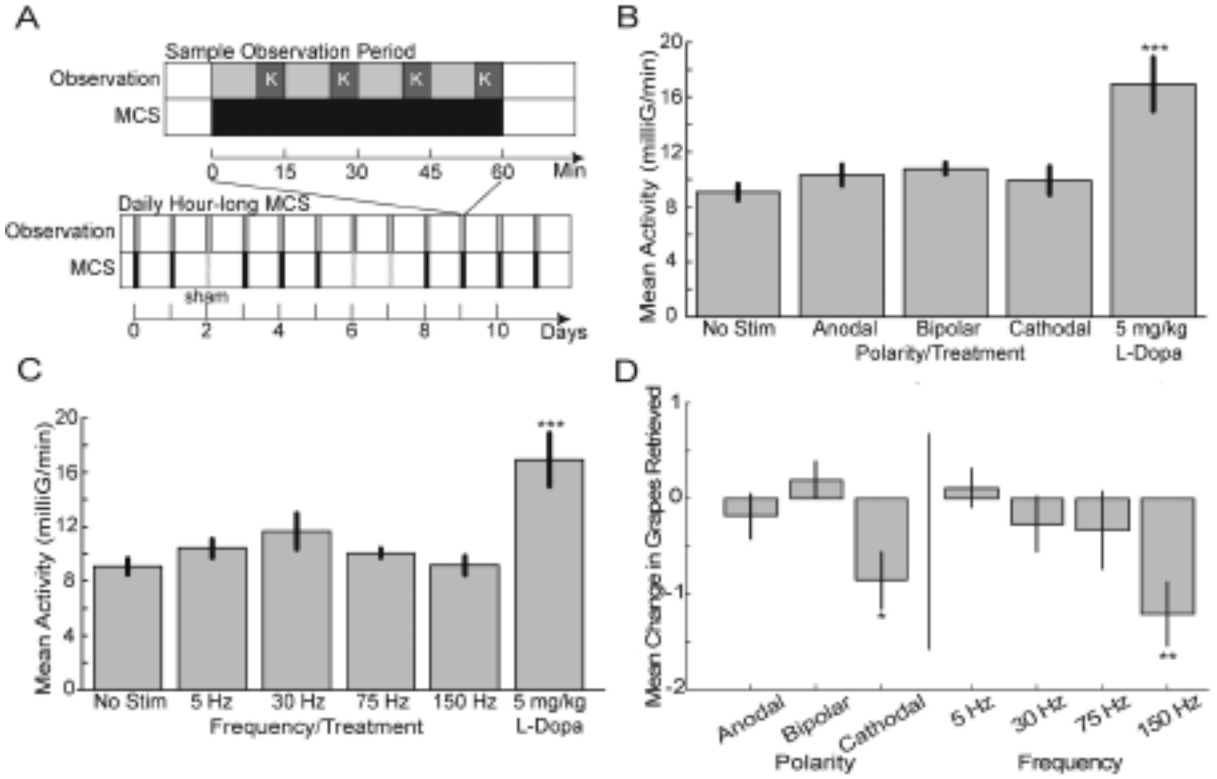

FIG. 1. Graphs representing the schedule for daily 1-hour MCS testing (A) and showing that daily MCS failed to improve general akinesia or Klüver task performance (B–D). A: Upper timeline illustrates the course of a typical 1-hour observation period during which MCS *(black bar)* was delivered continuously and the Klüver task (K) was administered four times. Lower timeline illustrates how these observation sessions were administered at the same time every day with active MCS at different frequencies and polarities, and sham stimulation (Stim) sessions *(hatched vertical bars)* delivered in random order. B: Mean whole-body activity levels for different MCS polarities (data collapsed across frequencies; 33, eight, and 19 sessions for anodal, bipolar, and cathodal MCS, respectively), and for off-MCS (No Stim, 21 sessions) and levodopa (L-dopa, five sessions) control conditions. C: Mean whole-body activity levels for different MCS frequencies (data collapsed across polarities; 23, 13, seven, and 17 sessions for 5-, 30-, 75-, and 150-Hz MCS, respectively), and for off-MCS (21 sessions) and levodopa (five sessions) control conditions. D: Effects of MCS on Klüver task performance for different MCS polarities and frequencies. *Error bars* = SEMs. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (relative to the off-MCS control condition).

Results

Treatment Model with MPTP

Throughout the period of MCS testing, parkinsonism was apparent in all animals bilaterally as evidenced by marked akinesia, bradykinesia, limb rigidity, action tremor, and stooped posture. The left side was more severely affected due to the initial unilateral intracarotid artery infusion of MPTP. Nonmotor effects, such as decreased appetite, were also apparent. A mean Schneider score of 40 was recorded during the period of MCS testing (means were 37, 38, and 45 for individual animals) compared with a mean score of 8 prior to systemic MPTP treatment.

Electrophysiological recording in two animals (in 80 neurons) confirmed the presence of pathological neuronal activity within the GP characteristic of parkinsonism. Recordings were obtained from animals that were awake and sitting quietly. The firing of GP neurons was characterized by an abnormally high number of bursts, as determined by a comparison of the L-burst statistic for these neurons (6.9 ± 0.25 SEM) compared with a large population of pallidal neurons (157) sampled from three healthy macaques ($p < 0.0001$; 5.41 ± 0.09 SEM, t-test).[27] We have observed a similar high number of discharge bursts in the GP of patients with PD who undergo surgical therapy.[27] Of 20 cell pairs recorded simultaneously, 35% showed synchronized activity (significant peaks in cross-correlograms), similar to the numbers reported previously for parkinsonian monkeys and well in excess of the 6.8% incidence reported for the pallidum in healthy primates.[16] Other aspects of the neurophysiological studies in these animals will be reported elsewhere. The postmortem histology available from one animal indicated a widespread dopamine depletion throughout the striatum and lateral substantia nigra compacta as measured by TH immunohistochemistry.

Daily 1-Hour MCS

Motor cortex stimulation applied at varying frequencies (23, 13, seven, and 17 sessions for 5-, 30-, 75-, and 150-Hz MCS, respectively) and polarities (33, eight, and 19 sessions for anodal, bipolar, and cathodal MCS, respectively) did not produce significant differences in the rate of whole-

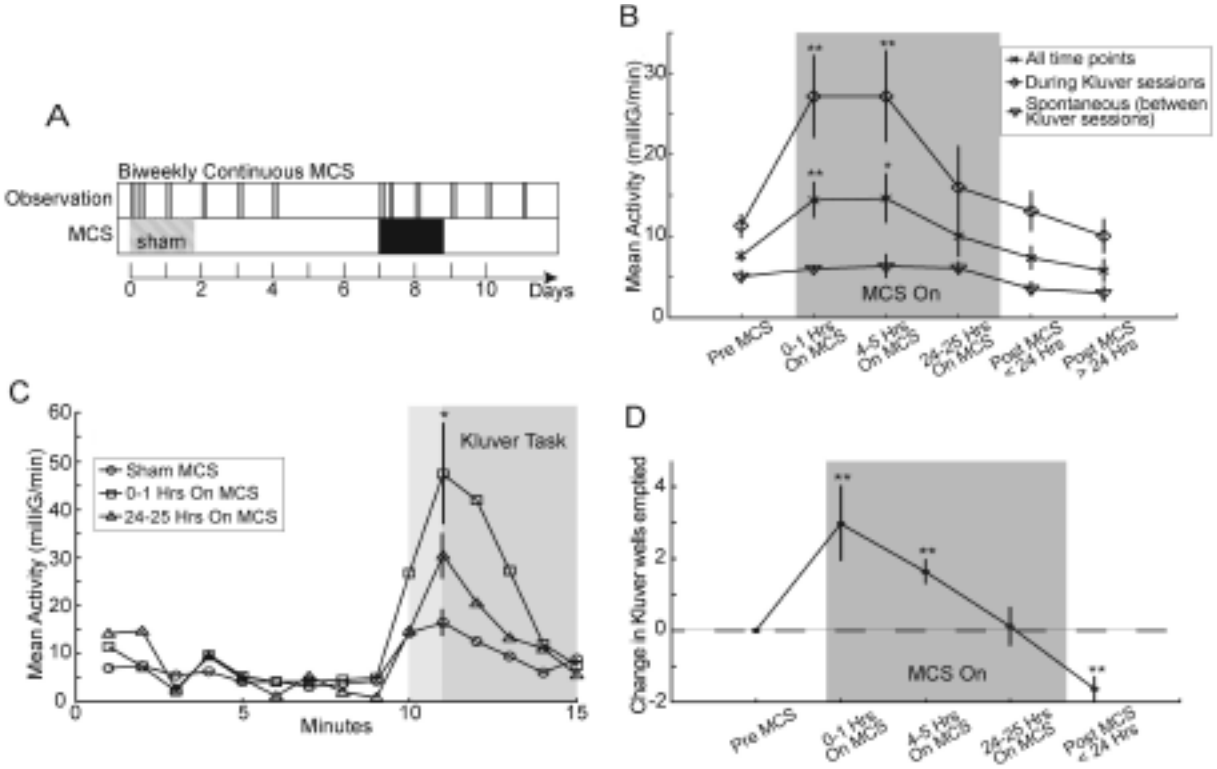

FIG. 2. Graphs showing organization of biweekly continuous MCS schedule (A) and that MCS yielded a transient context-dependent improvement in akinesia and Klüver task performance (B–D). A: After 1 week of observations during and following sham stimulation, MCS was delivered continuously for approximately 25 hours. One-hour observation periods were performed twice on the 1st day of sham/MCS and then daily for 4 days. B: Effects of continuous MCS on mean activity levels as a function of time since the onset of stimulation. Activity averaged across whole 1-hour observation periods *(center line)* showed a significant increase during the 1st day of MCS. That effect returned almost to baseline by the 24th hour of testing, which was almost completely accounted for by increased activity during the 5-minute epochs around presentations of the Klüver task *(top line)*. The MCS did not affect spontaneous activity during the 10-minute epochs between Klüver task presentations *(bottom line)*. C: Minute-by-minute averages of activity level aligned on presentations of the Klüver task illustrate the strong enhancement of activity restricted to the period during the Klüver task *(shaded region)*. The MCS-induced enhancement was large during the 1st hour of MCS but attenuated by the 24th hour of MCS. D: Klüver task performance as a function of MCS duration. Each plotted point is an average of three sessions. *Error bars* = SEMs. *$p < 0.005$, **$p < 0.001$ (relative to the matching pre-MCS conditions).

body accelerations as measured by the Actitrac, relative to off-MCS (21 sessions) (Fig. 1B and C). Manual dexterity of the left arm as assessed by the Klüver task also did not improve significantly during MCS compared with off-MCS (Fig. 1D). Of the frequencies and polarities tested, 30-Hz MCS and bipolar polarity, respectively, showed the greatest increases in activity. Even at these settings, however, the increase in activity did not reach significance ($p = 0.173$). In contrast, low dosages (5 mg/kg) of levodopa resulted in an 89.3% average increase in activity ($p < 0.001$, five sessions). There was no improvement in Klüver task performance with daily MCS at any frequency or polarity. Klüver task performance deteriorated during cathodal MCS at 150 Hz ($p < 0.01$, Fig. 1D).

Videotaped records of each observation session were evaluated by an investigator who was blinded to therapeutic conditions. Evaluations based on the Schneider rating scale provided no evidence that MCS ameliorated parkinsonian symptoms (data not shown). The quantitative behavioral analysis revealed similar results for daily MCS (representative results for 30 Hz bipolar shown in Fig. 3). Eight of the nine behaviors did not differ in prevalence between off-MCS and active 30-Hz MCS ($p > 0.05$). The one significant effect of 30-Hz MCS was that animals spent slightly less time attempting the Klüver task ($p < 0.05$).

Biweekly Continuous MCS

Biweekly continuous MCS (30 Hz bipolar) resulted in transiently increased activity levels and improved Klüver task performance (Fig. 2B and D). These increases in activity and Klüver task performance were present for the first 5 hours of continuous MCS, but diminished by the 24th hour. In the 24-hour period immediately following the end of continuous MCS, the activity of the animal was not different from pre-MCS levels, but Klüver task performance declined to below pre-MCS levels ($p < 0.001$).

The activating effects of MCS were greatest during presentation of the Klüver task. Across all observation sessions, minute-by-minute measures of activity were typically low when the Klüver board was not visible (that is, when external stimuli were minimized), whereas the gen-

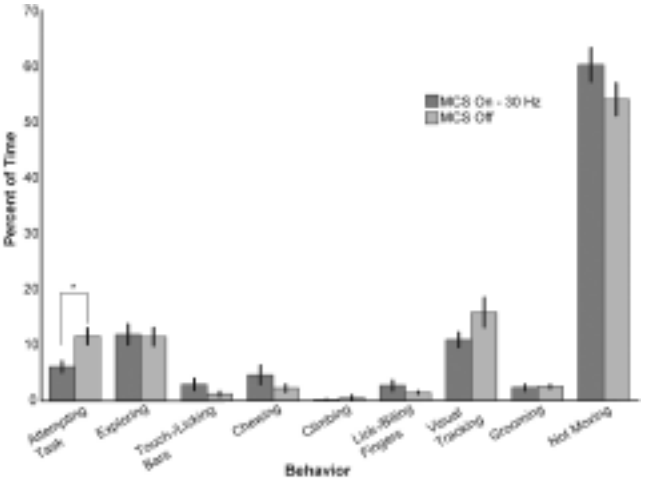

FIG. 3. Bar graph demonstrating the minimal effects of daily MCS on clinically relevant behavioral measures. An observer blinded to the stimulation condition quantified the prevalence of nine different behaviors during each hour-long observation session by using videotapes. Representative results are presented comparing sessions off MCS (five sessions) and 30-Hz MCS (four sessions). *Error bars* = SEMs. *$p < 0.05$.

eral level of activity of each animal was elevated during the 5-minute period when the Klüver board was accessible. Offline video analysis indicated that much of this activity during the Klüver task was attributable to whole-body movement and postural adjustment related to positioning for Klüver task performance. Although increases in activity during the Klüver task were evident even when MCS was off, 30 Hz bipolar MCS accentuated those increases in activity ($p < 0.005$, Fig. 2C). The increase in activity during the Klüver task accounted for nearly all of the effects of MCS.

Discussion

Three important results can be derived from this study: 1) We were unable to demonstrate a reliable reduction in parkinsonian symptoms when MCS was delivered daily for 1 hour. 2) Increased activity and improved Klüver performance were observed during the first 24 hours of continuous biweekly MCS. 3) Increases in activity were context-specific.

We failed to demonstrate reliable symptom amelioration when MCS was delivered for 1 hour every day, despite the fact that our battery of behavioral tests was sensitive to small changes in the core symptoms of parkinsonism and that we explored a wide range of stimulation modes and frequencies. One might ask why unilateral subthreshold stimulation restricted to a small portion of the primary motor cortex would be expected to ameliorate parkinsonian symptoms globally, but authors of a number of clinical reports[3,19,20] and one primate study[7] have suggested that this general mode of therapy has value. Using a broad range of stimulation parameters and sensitive quantitative analysis, we were unable to demonstrate significant improvements in response to daily MCS therapy.

It is noteworthy that the optimal frequency found by Drouot et al.[7] was 130 Hz, whereas our group and Pagni and colleagues[19,20] found that MCS frequencies between 25 and 30 Hz had the greatest effect (although in our study the effects were not statistically significant). The reason for this discrepancy is a matter of speculation.

Biweekly MCS produced a significant but transient amelioration of symptoms. Drouot and coworkers[7] also reported a significant increase in activity during 30 minutes of MCS when at least 1 week passed between MCS administrations. The mechanism underlying this transitory effect is also open to conjecture. Drouot and coworkers implicate a mechanism by which MCS disrupts the pathological firing patterns of basal ganglia output neurons, presumably via cortical inputs to the basal ganglia.[7] Motor cortex stimulation could also work directly at the cortical level to block the abnormal oscillatory and synchronized activity that has been described for the motor cortices in PD and animal models of parkinsonism.[10,26] Neither of these potential mechanisms, however, explains the apparent transitory nature of the effect. Recent evidence presented in an abstract by Chen et al.[4] noted that the intensity of primary MCS necessary to evoke an H-reflex of a fixed size increases continuously over the course of 20 days. These findings may help to explain the reduced efficacy of MCS over the course of 24 hours of continuous stimulation. These results, however, do not explain why daily MCS was relatively ineffective as motor thresholds were reestablished prior to each MCS session.

It is also possible that the positive effects of MCS (or rTMS) are mediated by stimulation-evoked release of dopamine in the striatum. Strafella and colleagues[28,29] have shown in healthy volunteers that rTMS of the primary motor cortex increases dopamine in the ipsilateral putamen. Ohnishi and coworkers[17] showed that rTMS over the primary motor cortex also increases dopamine release in macaques, restricted in this study to the mesolimbic ventral striatum. These effects may be mediated by direct corticostriatal excitation of striatal dopamine terminals or through multisynaptic pathways.[6] Such an effect would depend on the presence of residual stores of striatal dopamine, which have been documented for the mesolimbic striatum of the MPTP-treated primate.[8,22,23] Daily application of MCS may be so frequent as to leave dopamine terminals in a perpetually depleted state, and consequently provide no therapeutic benefit. Consistent with this possibility, the only significant effect of daily MCS was a reduction in Klüver task–associated behaviors.

The increased activity associated with biweekly MCS was largely dependent on the presence of the Klüver task. This context sensitivity may be seen as further evidence of a mechanism involving dopamine. The motivating effects of MCS-induced dopamine release may account for the animals' increased effort in the Klüver task[5] in the absence of an effect on spontaneous activity.

Conclusions

Authors of previously published studies have reported impressive effects of MCS in both parkinsonian baboons and humans with PD. In contrast, our results show that the positive effects of continuous MCS on mobility do not last beyond 1 day, and daily MCS, even when delivered in short 1-hour sessions, fails to reduce symptoms reliably. These

data suggest that MCS, though promising, should be pursued with caution. Motor cortex stimulation may eventually prove to be a clinically significant therapy for PD, but it must first overcome the limitations described here.

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