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Original Article

Exploring Magnetic and Electrical Brain Stimulation in Parkinsonian Dyskinetic Monkeys

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ABSTRACT: ***Background:*** Parkinson's disease (PD) chronic L-Dopa treatment often triggers motor complications, such as L-Dopa-induced dyskinesias (LID). LID are reported to be associated with abnormal glutamatergic activity between the striatum and primary motor cortex (M1), resulting in M1 hyperactivation. Beneficial noninvasive brain stimulation (NIBS) paradigms were reported to normalize glutamatergic activity. The objective of the present study was thus to set up a NIBS paradigm in parkinsonian monkeys to investigate motor behavior under basal conditions and with L-Dopa treatment-inducing dyskinesias. ***Methods:*** Motor behavior was investigated in five 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) dyskinetic female *Macaca fascicularis* monkey models of PD, allowing us to monitor the administration of NIBS and drugs. NIBS used were inhibitory protocols, that is, cathodal transcranial direct current stimulation (c-tDCS) and continuous theta-burst stimulation (cTBS). A procedure of three weeks was developed to progressively acclimate animals to the experimental conditions, equipment and noise of c-tDCS and cTBS before stimulating them with either vehicle or L-Dopa. ***Results:*** One session of c-tDCS with L-Dopa yielded no effect, whereas five sessions briefly reduced LID but decreased the duration of L-Dopa anti-PD effects. cTBS alone improved (decreased) parkinsonian scores as compared to sham stimulation or vehicle alone. Two sessions of cTBS with L-Dopa decreased LID without affecting L-Dopa anti-PD effects. ***Conclusion:*** This is the first study testing c-tDCS and cTBS on the motor behavior of MPTP dyskinetic monkeys. As compared to medicated patients, MPTP monkeys offer the opportunity to evaluate NIBS after-effects in drug-free and LID conditions, which are critical in the search for new PD treatment.

RÉSUMÉ : ***Objectif :*** Le traitement chronique de la maladie de Parkinson (MP) avec la L-Dopa déclenche souvent des complications motrices, telles que les dyskinésies induites par la L-Dopa (LID). Les LID ont été rapportées être associées à une activité glutamatergique anormale entre le striatum et le cortex moteur primaire (M1), entraînant une hyperactivation du M1. Certains paradigmes de stimulation cérébrale non invasive (SCNI) peuvent normaliser cette activité glutamatergique. L'objectif de la présente étude était donc de mettre en place un paradigme SCNI chez le singe parkinsonien et d'en étudier l'influence sur le comportement moteur de base et les dyskinésies induites par la L-Dopa. ***Méthodes :*** Le modèle simiesque de la MP permet en effet de contrôler l'administration de SCNI et de médicaments. Donc cinq singes femelles Macaca Fascicularis rendues "parkinsoniennes" avec le 1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine (MPTP) et dyskinétiques par administration de L-Dopa ont été testées avec des protocoles SCNI inhibiteurs: stimulation cathodique transcrânienne à courant continu (c-tDCS) et stimulation thêta-burst en mode continu (cTBS). Le conditionnement progressif des animaux s'est organisé sur trois semaines pour la contention, l'équipement et le bruit des deux types de SCNI, avant de débuter la stimulation combinée avec le véhicule ou la L-Dopa. ***Résultats :*** Une séance de c-tDCS avec L-Dopa n'a produit aucun effet alors que cinq séances ont brièvement réduit les LID mais ont diminué la durée des effets anti-parkinsonien de la L-Dopa. La cTBS seule a amélioré (diminué) les scores parkinsoniens par rapport à la stimulation placebo ou au véhicule seul. Deux séances de cTBS avec la L-Dopa ont diminué les LID sans affecter les effets anti-parkinsoniens de la L-Dopa. ***Conclusions :*** Il s'agit de la première étude testant la c-tDCS et la cTBS sur le comportement moteur de singes MPTP dyskinétiques. Comparativement aux patients médicamentés, les singes MPTP offrent la possibilité d'évaluer les répercussions de la SCNI dans des conditions sans médicament ou avec LID, ce qui répond aux exigences de la recherche d'un nouveau traitement en MP.

Keywords: Theta-burst stimulation; transcranial direct current stimulation; Parkinson's disease; non-pharmacological treatment; motor symptoms; nonhuman primates

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease affecting nearly 1.3% of the world's population.[1] PD results from a loss of dopamine (DA) neurons in the substantia nigra *pars compacta* (SNc),[2] which impairs the basal ganglia loop with the thalamus and cerebral cortex and leads to motor and non-motor symptoms.[3] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin, originally discovered in a synthetic heroin, which caused parkinsonian symptoms in young people.[4] MPTP intoxication in nonhuman primates induces SNc DA neuronal degeneration,[5] leading to parkinsonian symptoms close to those observed in humans, thus providing an excellent model of PD.[4,6,7]

The DA precursor, L-Dopa, is the most effective pharmacotherapy for PD.[8] But as the disease progresses, a majority of patients develop motor complications associated with L-Dopa treatment such as motor fluctuations (e.g., wearing-off) and L-Dopa-induced dyskinesias (LID, involuntary movements), which interfere with quality of life and are very challenging to manage.[9–11] Like humans, the MPTP monkey treated chronically with L-Dopa develops LID.[7]

Amantadine and its extended-release formulation ADS-5102 are the most prescribed anti-LID drugs.[12–14] However, the efficacy of this nonspecific antagonist of glutamate N-methyl-D-aspartate receptors (NMDA-R) is limited in time and presents with debilitating side effects.[13,14] According to a meta-analysis of amantadine trials in PD patients with LID, the most frequent adverse events are visual hallucinations, confusion, blurred vision, leg edema, dry mouth and constipation: their occurrence increases with higher doses.[15] In clinical practice, two types of adverse events can lead to amantadine discontinuation: mental state changes (confusion, visual hallucinations) and agitation states (review[16]). Research is thus mandatory to test more efficient anti-LID treatments with fewer or no side effects or adjuvant treatment allowing the decrease of anti-LID drug intake.[17,18]

LID develops upon the hyperactivation of the primary motor cortex (M1) and corticostriatal routes[19] together with an increase of corticostriatal glutamate neurotransmission and dysfunction of striatal post-synaptic NMDA-R.[20] We showed that LID were associated with an increase of striatal NMDA-R (containing NR2B subunits) in postmortem brains of PD patients[21] and MPTP monkeys.[22–24]

A possibility to counter bilateral M1 overactivation is the use of noninvasive brain stimulation (NIBS) over M1, including transcranial direct current stimulation (tDCS)[25] and repetitive transcranial magnetic stimulation (rTMS).[26] Transcranial direct current stimulation (tDCS) with the cathode over M1 and the anode over the contralateral supraorbital area is referred to as cathodal tDCS (c-tDCS) that hyperpolarizes the resting membrane potential and inhibits M1 cells.[27] Theta-burst stimulation applied in a continuous mode (cTBS, a patterned paradigm of rTMS)[28,29] is known to decrease M1 and corticospinal excitability.[28,29] The effects of both c-tDCS and cTBS were shown to depend on NMDA receptors[30] and are inhibited by NMDA receptor antagonists.[31] Their use to counter the expression of LID (which depends on NMDA-R) is thus of great interest in PD.

To date, the NIBS procedures have shown minimal side effects (e.g., transient migraine in a few people), leading most studies to directly test their therapeutic influence in patients with PD. However, the MPTP monkey with LID promises to be a useful model to investigate NIBS after-effects in off and on periods with L-Dopa without the interference of amantadine intake.

The objective of the present study was thus to investigate if the administration of c-tDCS or cTBS, alone or with L-Dopa, was feasible in MPTP monkeys with LID and was successful to decrease LID without altering the L-Dopa anti-PD effects, as compared to sham stimulation. Our promising results encourage the development of larger controlled studies.

Materials and Methods

MPTP monkeys and study design of experiments

Five female ovariectomized cynomolgus monkeys (*Macaca fascicularis*) (Charles River Lab, Reno, Nevada, USA; Primus Bio Resources) weighing between 3.75 and 4.9 kg and aged between 7 and 17 years were tested with c-tDCS or cTBS. Handling of these primates was performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. All procedures, including the means to minimize discomfort, were closely reviewed and approved by the Institutional Animal Care Committee of Université Laval (# 2020-420). The monkeys were rendered parkinsonian by continuous infusion of MPTP (Sigma-Aldrich, Oakville, ON, Canada) using subcutaneous Alzet osmotic minipumps (Durect Corporation, Cupertino, CA 95014-4166, USA, 0.5 mg/24 h) until they developed a stable parkinsonian syndrome. Reproducible dyskinesias were induced with the daily oral administration (p.o.) of L-Dopa 100/25 capsules (Prolopa, Hoffmann-La Roche; a mixture of 100 mg of L-Dopa and 25 mg benserazide) for about one month or until dyskinesias stabilized. Before the present study, these monkeys had participated in various pharmacological experiments over several years, except monkey 4 of experiment 2 that received only dopaminergic drugs for comfort and to induce dyskinesias. Monkeys 1, 2 and 3 had stable parkinsonian symptoms for up to eight years at the time of the present experiments. Monkey 4 had stable parkinsonian symptoms for one year and monkey 5 for five years at the time of the experiment. Thus, the number of monkeys used in each experiment and the duration of each experiment depended on the monkey's availability. At least one month was left between the previous experiments and ours to allow a washout period and provide the monkeys with time to rest. During this period, they received L-Dopa at a dose and frequency appropriate to treat their parkinsonian disability.

The c-tDCS and cTBS effects on motor behavior and LID were compared with sham stimulation alone or in combination with drugs in three experiments (Figure 1), as follows: Experiment 1 tested a single session of c-tDCS administered with L-Dopa in three monkeys; Experiment 2 tested three sessions of c-tDCS administered with L-Dopa and two sessions of c-tDCS administered with vehicle in one monkey; Experiment 3 tested two sessions of cTBS administered alone or with vehicle or L-Dopa and compared to drugs alone in one monkey.

For all stimulation sessions, the animals were transported to the experimental room at least 1 h prior to the experiment, and the stimulation session was monitored by video recording of the primate in the observation cage for the total duration of L-Dopa motor effects. Animals live in pairs per cage in the housing rooms and are separated in the observation cages during experimental measurements.

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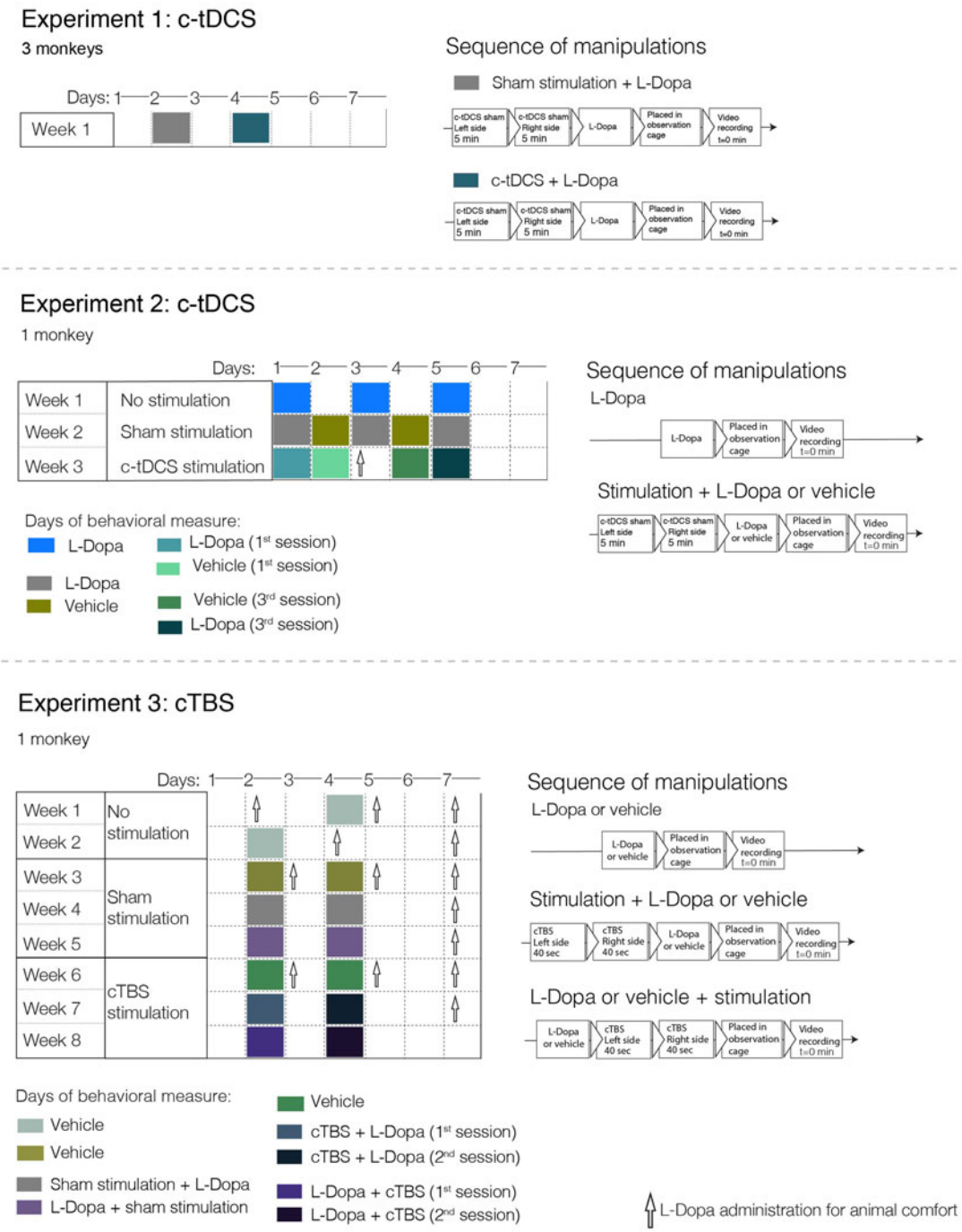

Figure 1. Schematic of experiments. Experiment 1 with continuous theta-burst stimulation (c-tDCS) (5 min left hemisphere then 5 min right hemisphere) in three animals tested the effects of one session of sham stimulation with L-Dopa and one session of c-tDCS with L-Dopa. Experiment 2 with c-tDCS (5 min left hemisphere then 5 min right hemisphere) in one animal included two weeks of five sessions of stimulation each (five days in a row), the first week with sham stimulation and the second with c-tDCS, each combined with L-Dopa (Days 1, 3 and 5) or vehicle (Days 2 and 4). Experiment 3 with continuous theta-burst stimulation (cTBS) (40 sec left hemisphere then 40 sec right hemisphere) in one animal included six weeks of two stimulation sessions each, that is, three weeks of sham stimulation (one week with vehicle and two weeks with L-Dopa) followed by three weeks of cTBS (one week with vehicle and two weeks with L-Dopa). cTBS was tested after and before L-Dopa administration. For each experiment, the weeks of stimulation were preceded by a week of L-Dopa administration without stimulation to adjust the L-Dopa dose.

Drug administration

L-Dopa methyl ester (Sigma-Aldrich, Oakville, ON, Canada) was administered by nasogastric gavage at a fixed dose tailored to each animal (9–17 mg/kg), always in combination with benserazide (50 mg total) (L-Dopa + benserazide is thereafter simply referred to as L-Dopa). The tailored or optimal dose of L-Dopa was the dose that elicited an optimal antiparkinsonian response with limiting side effects, such as stereotypies and hypotension, although it was accompanied by overt LID. Vehicle administration (water) was the control drug of L-Dopa.

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Behavior assessment

Behavioral responses were video-recorded per animal per session before and after vehicle alone or cTBS/c-tDCS combined with vehicle or L-Dopa (see Experimental procedures). A person other than the observer blinded (codified) the video recordings. Thereafter, two observers, blinded to the treatment (NIBS or sham stimulation, L-Dopa or vehicle, combination of NIBS + L-Dopa) assessed the motor responses according to the parkinsonian and dyskinetic scales developed at Université Laval.[32] For parkinsonian score, behaviors were scored every 15 min for the duration of the motor effect (maximal score: 16): (a) Posture: normal = 0, flexed intermittent = 1, flexed constant = 2, crouched = 3; (b) Mobility: normal = 0, mild reduction = 1, moderate reduction = 2, severe reduction = 3; (c) Climbing: present = 0, absent = 1; (d) Gait: normal = 0, slow = 1, very slow = 2, very slow with freezing = 3; (e) Grooming: present = 0, absent = 1; (f) Vocalization: present = 0, absent = 1; (g) Social interaction: present = 0, absent = 1; (h) Tremor: absent = 0, mild action tremor = 1, moderate action tremor = 2, resting tremor = 3. Dyskinesias were also scored every 15 min for the duration of the motor effect. The face, neck, trunk, arms and legs were rated as follows: None = 0; Mild (occasional) = 1; Moderate (intermittent) = 2; Severe (continuous) = 3 for a maximal score of 21. The difference between mild, moderate and severe dyskinesias for a given body segment was based on the assessment of the amplitude of the abnormal movements and the frequency (whether they were occasional, intermittent or constant); each body segment was scored separately. The dyskinetic score obtained was the sum of the scores for all body segments.

In addition, spontaneous locomotor activity was quantified using the Viewpoint electronic monitoring system (VigiePrimates; Viewpoint, Lyon, France).

NIBS of M1

c-tDCS over the hand M1 area of the two hemispheres successively was applied by means of an anode and a cathode (9 cm^2 Rubber electrode, NeuroConn, Ilmenau, Germany), slipped into sponge pads connected to the electrical stimulation system (DC-Stimulator plus, NeuroConn, Ilmenau, Germany). Initially, electrodes commonly used in human research were selected 5 × 7 cm = 35 cm^2), but their size was too large for the cranial surface of the monkeys (see the illustration in Figure 2A). In humans, c-tDCS of 35 cm^2 is usually administered at 1 mA for 20 min. The dimensions of a human brain are approximately 170 mm length and 138 mm width,[33] whereas the brain of a *Macaca fascicularis* primate is approximately 63 mm length and 51 mm width,[34] that is, about 2.7 times smaller. Therefore, 3 × 3 cm = 9 cm^2 electrodes were chosen for the protocol. Given that a different size of stimulated area induces different current flows,[35] different parameters of intensity and duration of c-tDCS had to be calculated for the monkeys. Precisely, $Q = I*t$, where Q is the current charge (in coulomb, C), I is the stimulation intensity (in amperes, A) and t is the stimulation duration (sec). Thus, in humans, $Q_{human} = 0.001$ A * 1200 s = 1.2 C,[36] and for 35 cm^2 electrodes, this corresponds to $Q_{human}/0.0035 = 342.9$ C/m^2. In monkeys, with 9 cm^2 electrodes, Q_{monkey} should be $Q_{human}*$ 0.0009 = 0.309 C. However, Q_{monkey} had to be suitable relative to the brain size ratio of 2.7 and was calculated as 0.309/2.7 = 0.11 C; that is, c-tDCS was given at 0.375 mA for 5 min per hemisphere. c-tDCS was the protocol administered, that is, with the cathode placed over M1 hand area and the anode over the orbitofrontal area of the opposite hemisphere. cTBS was applied over the hand M1 area of the two hemispheres successively by an air film–cooled figure-of-eight coil (7 cm outer diameter each wing) connected to two rapid-rate magnetic stimulators (Rapid2; The Magstim Company Limited, Whitland, UK). cTBS consisted of 5 Hz trains of three 50 Hz TMS pulses over 40 s per hemisphere (total of 600 pulses) applied at an intensity of 80% of the resting movement threshold (rMT).

First, the hand M1 "hotspot" was determined as the location of cTBS eliciting the largest isolated movement of the hand; the rMT at the hotspot was the lowest intensity of single-pulse TMS eliciting a visible hand movement.

All cTBS and c-tDCS sessions began with the successive stimulation of the left, followed by the right hemisphere (Figure 1). For c-tDCS, the left hemisphere was first stimulated for 5 min, followed by the right hemisphere for 5 min in the same session. For cTBS, the left hemisphere was first stimulated for 40 s, followed by the right hemisphere for 40 s in the same session.

Experimental procedures

Monkeys were progressively conditioned to a sling restraint. They were also progressively conditioned to the presence of the device in the experimental room; to the presence of electrodes, soaked sponges and silicone headband to hold the electrodes in place (Experiments 1 and 2); and to the presence of the cTBS coil above their heads as well as to the clicking noise produced by the cTBS (Experiment 3). Conditioning was performed by trained technicians over three weeks. Every day, an additional equipment used in the protocol was brought into the housing room close to the primate under investigation. Over time, the equipment was brought closer to the animal, and electrodes, sponges and headband (Experiments 1 and 2) or the stimulation coil (used in Experiment 3) were placed on the animal's head, first for a few seconds and then longer for up to the duration of the stimulation planned for the protocol. Such conditioning lasted as required for the animal to relax completely relatively to the equipment and for a period with no stress equivalent to the duration of each session of the protocol. We used different primates per protocol following the ethics committee's limitation rules.

Experiment 1: One session of c-tDCS combined with L-Dopa

Experiment 1 tested the effect of one session of c-tDCS + L-Dopa in three monkeys (Monkeys 1, 2 and 3, 16–17 years old, 3.95–4.9 kg, rendered parkinsonian 8 years earlier). After conditioning (previously described), the experiment was organized in one week, first with sham stimulation + L-Dopa, followed by c-tDCS + L-Dopa two days later (see Figure 1). Behavioral responses for parkinsonian and dyskinetic scores were video-recorded immediately after administration of L-Dopa and recorded for the duration of L-Dopa anti-PD effects.

Experiment 2: Three sessions of c-tDCS combined with L-Dopa

Experiment 2 tested the effects of three sessions of c-tDCS + L-Dopa in a monkey (Monkey 4, seven years old, 3.75 kg, rendered parkinsonian one year earlier). After conditioning (previously described), the experiment was organized over three weeks with three to five sessions per week (five days in a row, see Figure 1). The first week tested L-Dopa without stimulation for three sessions. The second week tested sham stimulation combined with L-Dopa or vehicle alternately (beginning with L-Dopa the first day) thus

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with three sessions of sham stimulation + L-Dopa and two sessions of sham stimulation + vehicle. In the third week, c-tDCS was tested using the same procedure as in Week 2, which included three sessions of c-tDCS + L-Dopa and two sessions of c-tDCS + vehicle (see Figure 1). Behavioral responses for parkinsonian and dyskinetic scores were video-recorded starting immediately after the administration of vehicle or L-Dopa and continued throughout the duration of the motor effect.

Experiment 3: Two sessions of cTBS combined with L-Dopa

Experiment 3 tested the effect of two sessions of cTBS + L-Dopa in one monkey (Monkey 5, 15 years old, 4.45 kg, rendered parkinsonian 5 years earlier). After conditioning (previously described), the experiment first tested vehicle administration as control, that is, without stimulation combined (Weeks 1 and 2) (see Figure 1). The stimulation sessions were conducted over six weeks, with two sessions per week, two days apart: Week 3 included two sessions of sham stimulation followed by vehicle (water) administration (sham stimulation + vehicle); Week 4 included two sessions of sham stimulation followed by L-Dopa administration (sham stimulation + L-Dopa); Week 5 tested two sessions of L-Dopa administered before sham stimulation (L-Dopa + sham stimulation). Weeks 6, 7 and 8 followed the exact same patterns as Weeks 3, 4 and 5 but with two sessions of cTBS each, instead of sham stimulation: cTBS + vehicle (Week 6), cTBS + L-Dopa (Week 7) and L-Dopa + cTBS (Week 8). Behavioral responses to collect the parkinsonian, dyskinetic and global motor activity scores were video-recorded directly after the administration of vehicle or L-Dopa for Weeks 1, 2, 3, 4 and 7 and immediately after cTBS for Weeks 5 and 8 and analyzed over 180 min when the vehicle was administered or for the duration of the anti-PD effect after L-Dopa administration.

Statistical analyses

Depending on the pattern of the time courses of parkinsonian and dyskinesias scores, the data were analyzed in time segments by including all 15 min scores obtained for this segment to test the after-effects of cTBS and c-tDCS. One-way analyses of variance on the time points were applied to the data followed by a Holm-Sidak multiple comparison test or by an unpaired or paired *t*-test using GraphPad Prism (version 9.3.1; GraphPad Software, La Jolla, CA, USA). A log transformation of the data was performed when required to homogenize the variance of the groups. Results are presented as means ± SEM. A P value ≤ 0.05 was considered significant.

Results

MPTP monkeys tolerated well magnetic and electrical stimulation

The NIBS protocol with cTBS and c-tDCS proved to be feasible in MPTP dyskinetic monkeys. After three weeks of conditioning, the five animals tolerated well the restraint and the presence of the stimulation equipment, and no intolerance events were noted during the experiments.

Experiment 1

Figure 2A shows the 9 cm^2 electrodes used for the present monkey c-tDCS protocol as compared to the 35 cm^2 electrodes commonly used in human research. Figure 2B presents the different current flows induced by the differences in brain size and electrode surface area between monkeys and humans. c-tDCS parameters were adapted for monkeys with an intensity of 0.375 mA and a duration of 5 min (see Materials and Methods section for details).

A single session of c-tDCS did not alter the anti-PD effect of L-Dopa

Global motor activity measured with the electronic monitoring system and the mean parkinsonian score per animal were left unchanged after c-tDCS + L-Dopa as compared to sham stimulation + L-Dopa for monkey 1 (Figure 2C and D, both $P > 0.05$), monkey 2 (Figure 2G and H, both $P > 0.05$) and monkey 3 (Figure 2K and L, both $P > 0.05$).

A single session of c-tDCS did not reduce dyskinesias

Figure 2F, J and N presents the time courses of dyskinesias per monkey, respectively. The single session of c-tDCS did not yield any effect on LID for monkey 1 ($t = 0.960$, $df = 46$, $p = 0.341$, Figure 2E), monkey 2 ($t = 0.505$, $df = 46$, $p = 0.615$, Figure 2l) and monkey 3 ($t = 0.7910$, $df = 55$, $p = 0.4323$, Figure 2M). In experiment 1 (Figure 2), for two monkeys, the time course of dyskinesias was similar between the sham stimulation + L-Dopa and c-tDCS + L-Dopa. Monkey 1 has dyskinesias in the lower limbs (both sides similarly affected) and the trunk. Monkey 2 had dyskinesias in the upper limbs (the right upper limb slightly more affected than the left side), the trunk and the lower limbs (both sides similarly affected). Dyskinesias sub-scores were similar in amplitude or frequency between the sham stimulation + L-Dopa and c-tDCS + L-Dopa. Monkey 3 had dyskinesias in the upper limbs (the left upper limb slightly more affected than the right side), the lower limbs (both sides similarly affected) and the trunk. This animal presented with slightly more dyskinesias of the trunk after c-tDCS administration.

Overall, LID changes were observed for all limbs affected; hence, we did not include the details per limb and rather reported the global score.

Experiment 2

c-tDCS + vehicle did not change motor activity (no anti-PD effects)

Figure 3A and B shows the time course of global motor activity and parkinsonian scores after the first and second sessions of c-tDCS + vehicle as compared to sham stimulation + vehicle. No change was detected in the periods 15–30 min, 45–60 min, 75–90 min, 105–120 min and 135–150 min (Figure 3C–G) (all $P > 0.05$); hence, the parkinsonian scores were not detailed into sub-scores.

c-tDCS applied over several sessions affected the anti-PD effect of L-Dopa

Figure 3H and I presents the time course of global motor activity and parkinsonian scores after c-tDCS + L-Dopa as compared to sham stimulation + L-Dopa and to L-Dopa alone. Figure 3J–N shows no change at 15–30 min, 45–60 min, 75–90 min and 135–150 min (all $P > 0.05$) but an increase of PD scores at 105–120 min ($F(3, 4) = 10.88$, $p = 0.021$) during the first session as compared to L-Dopa alone and during the third session as compared to sham stimulation or L-Dopa alone. Sham stimulation did not yield any effect. Hence, there was a reduction of the duration of L-Dopa motor effect specific to c-tDCS.

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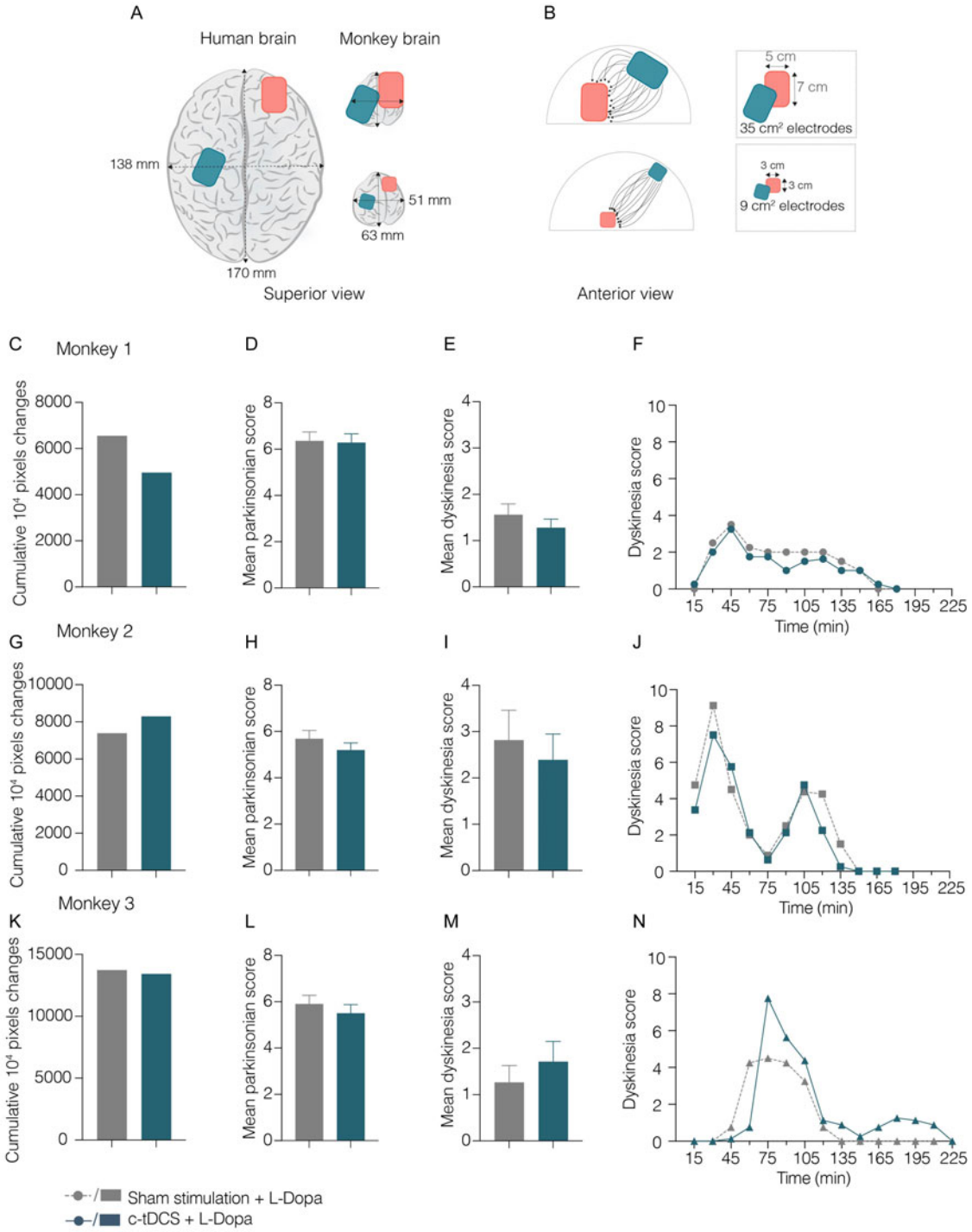

Figure 2. Motor effects of a session of cathodal transcranial direct current stimulation (c-tDCS) + L-Dopa. (A) Schematic representation of a human brain with 35 cm^2 stimulation electrodes and a monkey brain with 9 cm^2 stimulation electrodes selected. (B) Schematic representation, adapted from Solomons et al. [35] on the difference in current flow in the brain as a function of electrode size. (C) Global activity. (D) Mean parkinsonian scores (with SEM). (E) Mean dyskinesia scores (with SEM). (F) Time course of dyskinesia scores for monkey 1 with L-Dopa and sham or with c-tDCS. (G–J and K–N) Same measures as monkey 1 for monkeys 2 and 3, respectively.

c-tDCS applied over several sessions affected dyskinesias

Figure 3O presents the time course of dyskinetic scores after c-tDCS + L-Dopa as compared to sham stimulation + L-Dopa and to L-Dopa alone. At 15–30 min, LID has decreased after c-tDCS + L-Dopa as compared to sham ($t = 2.426$, $df = 3$, $p = 0.046$, Figure 3P). There was no difference at 45–60 min (F (3, 12) = 1.278, $p = 0.326$, Figure 3Q), rather an increase at 75–90 min (F (3, 12) = 6.572, $p = 0.007$, Figure 3R) and a drastic decrease at 105–120 min (F (3, 12) = 4.453, $p = 0.025$, Figure 3S) associated with the decrease motor effect (increase parkinsonian score) of L-Dopa. Dyskinesias were finished in the last 135–150 min in all conditions (F (3, 12) = 0.413, $p = 0.746$, Figure 3T). Sham stimulation did not affect LID. Monkey 4 showed LID in the right and left lower limbs (similarly affected) and trunk but also

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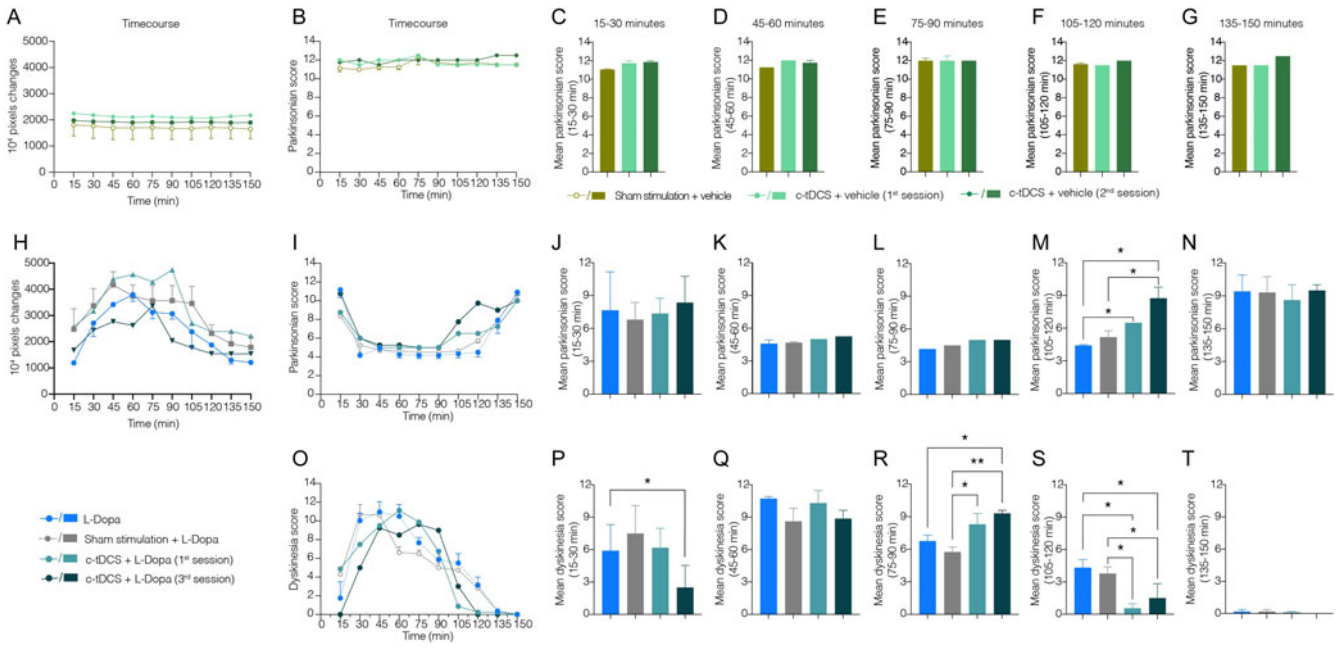

Figure 3. Motor effects of two sessions of c-tDCS + vehicle and three sessions of c-tDCS + L-Dopa. (A) Time course of global motor activity and (B) of Parkinson scores after sham stimulation + vehicle (mean and SEM of the two sessions: Days 2 and 4 of Week 1, see Figure 1) and after c-tDCS + vehicle, in the two sessions separately (Day 2: first session and Day 4: second session of week 2). (C–G) Mean Parkinson scores after sham and c-tDCS administration separated in time segments. (H)Time course of global motor activity and (I) parkinsonian scores after L-Dopa, sham and c-tDCS. (J–N) Mean Parkinson scores after L-Dopa, sham and c-tDCS administration separated in time segments. (O) Time course of dyskinesia scores after L-Dopa, sham and c-tDCS. (P–T) Dyskinesia scores after L-Dopa, sham and c-tDCS administration separated in time segments. Data presented are for monkey 4 as the means and standard error of the mean (SEM) *P < 0.05 and **P < 0.01.

LID in both right and left upper limbs (left side slightly less affected). The decrease of LID at 15–30 min and 105–120 min was observed in all limbs affected. For the 75–90 min period, an increase of LID was observed in all limbs except for the right upper limb.

Experiment 3

cTBS alone improved motor activity (anti-PD effects)

The time course of parkinsonian scores following cTBS is shown in Figure 4A. There was no significant change in the period 0–1 h after cTBS administration ($F(2, 9) = 0.604$, $P = 0.566$) (Figure 4B), an effect in the 1–2 h period (F (2, 9) = 18.69, P value = 0.0006) (Figure 4C) and no effect later in the 2–3 h period ($F(2, 9) = 1.187$, $p = 0.348$) (Figure 4D). In the 1–2 h period post-cTBS, the parkinsonian scores were lower (improved motor behavior) than after vehicle administration and sham stimulation that had no significant effect (Figure 4B). The parkinsonian sub-scores for the 1–2 h period showed that only the mobility score improved with cTBS as compared to vehicle alone and sham stimulation (data unshown) in agreement with the electronic monitoring system measure of global activity, as described below.

The time course of global motor activity following cTBS is shown in Figure 4E. There was an effect in the first two periods: 0–1 h post-cTBS ($F(2, 3) = 10.81$, $p = 0.042$) (Figure 4F) and 1–2 h (F (2, 3) = 14.29, $P = 0.029$) (Figure 4G), while no effect was observed in the 2–3 h period (F (2, 3) = 0.85, $p = 0.854$) (Figure 4H). The global motor activity was increased in the periods 0–1 h and 1–2 h after cTBS, whereas sham stimulation or vehicle yielded no effects (Figure 4 F–H).

cTBS maintained the anti-PD effect of L-Dopa

L-Dopa administered after or before cTBS (real and sham) similarly improved motor behavior (Figure 5A–F). Figure 5A ($F(3, 12) = 10.73$, $p = 0.001$) and 5B ($F(3, 12) = 7.823$, $p = 0.003$) shows that the mean parkinsonian scores were improved after the administration of L-Dopa after or before cTBS or sham in the 0–1 h period. Similar results were obtained in the 1–2 h period after L-Dopa administration (Figure 5C: $F(3, 12) = 20.19$, $p < 0.0001$ and Figure 5D: $F(3, 12) = 21.75$, $p < 0.0001$) and the 2–3 h period (Figure 5E: $F(3, 12) = 15.12$, $p = 0.0002$ and $F(3, 12) = 23.95$, $p < 0.0001$). Similar results as the parkinsonian scores were obtained with measures of global activity showing no effect of sham and no deleterious effect of real cTBS on L-Dopa motor effect (Figure S1).

The time course of LID was not the same when L-Dopa was administered after cTBS or before (Figure 5G and M). The effects of L-Dopa administered after cTBS are shown in Figure 5G–L. Hallucination-like behaviors were observed at 75 and 90 min during the first session, but not during the second, and LID was not decreased. This monkey (5) was known to react sometimes with hallucination-like behavior to L-Dopa administration (head movements following non-apparent stimuli). Thus, this behavior was not new and unlikely related to cTBS. There was no effect within 0–1 h, that is, at 15–30 min ($F(2, 9) = 0.5157$, $p = 0.613$, Figure 5H) or 30–45 min ($F(2, 9) = 3.525$, $p = 0.074$, Figure 5I) or 45–60 min ($F(2, 9) = 0.5780$, $p = 0.580$, Figure 5J), and no effect later at 1–2 h ($F(2, 17) = 2.267$, $p = 0.134$), without the time points with hallucination-like behaviors) after administration (Figure 5K), and no effect of sham stimulation. However, a small reduction of LID was observed later at 2–3 h during the first session

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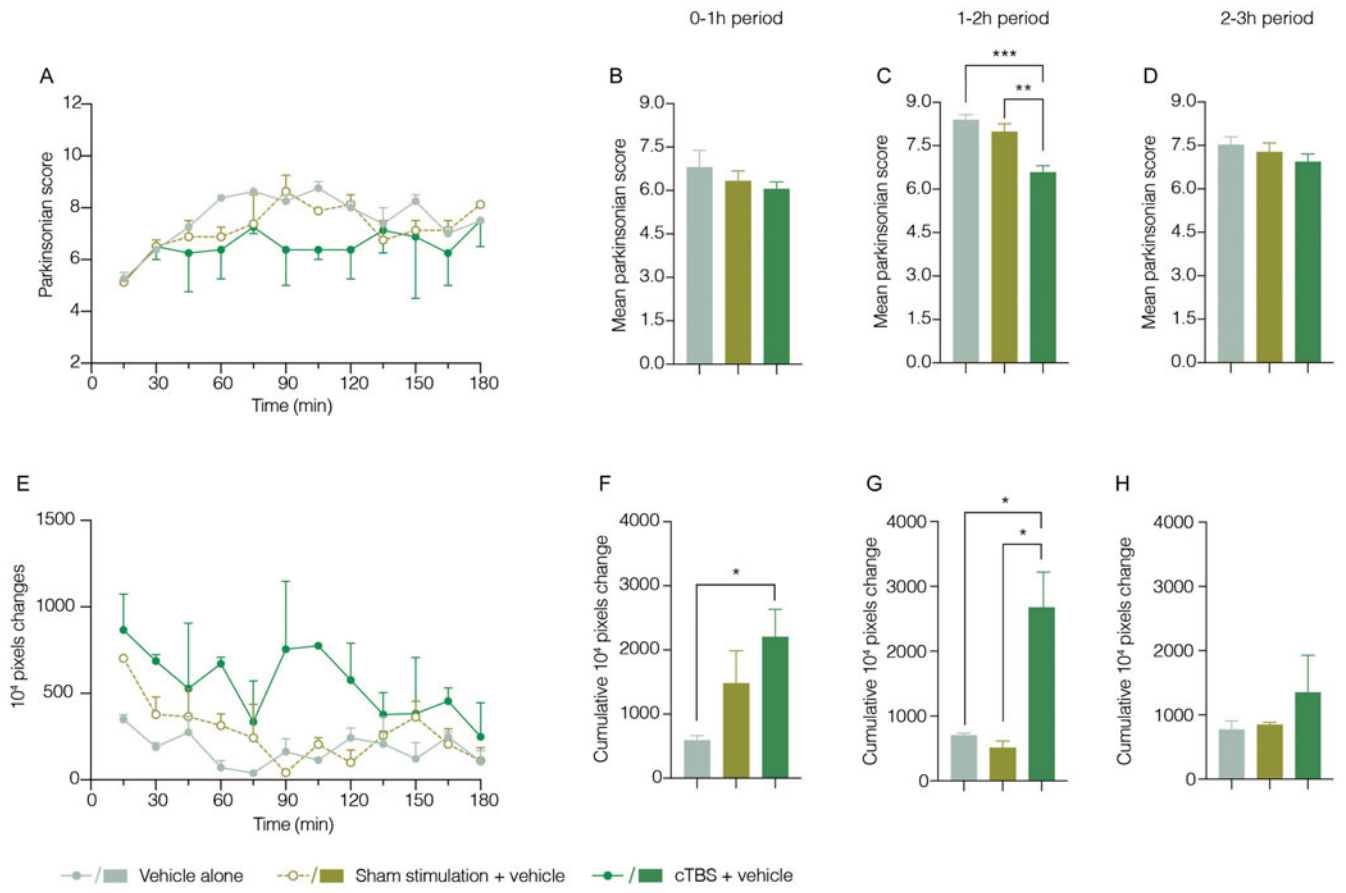

Figure 4. Motor effects of continuous theta-burst stimulation (cTBS). (A) Time course of real compared to sham cTBS on parkinsonian scores. (B–D) Mean parkinsonian scores over 0–1, 1–2 and 2–3 h time periods. (E) Time course of the global motor activity after cTBS compared to sham stimulation. (F–H) Cumulative global motor activity over 0–1, 1–2 and 2–3 h time periods. Data presented are for monkey 5 as the means and standard error of the mean (SEM) for two sessions per condition. *P < 0.05, **P < 0.01 and ***P < 0.001.

(F (2, 21) = 6.796, $p = 0.005$) (Figure 5L) as compared to sham stimulation + L-Dopa.

L-Dopa administered before cTBS did not yield any effect in the first session but decreased the LID in the second session (Figure 5M). This effect was detected within 0–1 h specifically at 30–45 min (F (2, 9) = 12.92, $p = 0.002$, Figure 5O) but not at 15–30 min (F (2, 9) = 2.998, $p = 0.100$, Figure 5N) nor at 45–60 min (F (2, 9) = 3.645, $p = 0.069$, Figure 5P). There was no effect detected later at 1–2 h (F (2, 21) = 0.9517, $p = 0.402$, Figure 5Q) or at 2–3 h (F (2, 21) = 0.4795, $p = 0.625$, Figure 5R) and no effect of sham stimulation. Monkey 5 had mainly bilateral LID in the lower limbs (both sides similarly affected for LID frequency and amplitude) with the trunk affected but less frequently. At post-cTBS, LID was decreased for both lower limbs similarly and also for the trunk.

Discussion

This is the first study testing c-tDCS and cTBS after-effects in the MPTP-lesioned and dyskinetic primate *Macaca fascicularis* on LID and PD motor symptoms. c-tDCS applied during a single session did not show motor improvement or LID reduction and did not alter the motor effect of L-Dopa. c-tDCS applied over five consecutive days reduced LID shortly after administration but later reduced the duration of L-Dopa motor effects. cTBS improved (decreased) the parkinsonian score and increased global motor activity when administered with the vehicle. cTBS applied after L-Dopa reduced LID without affecting the beneficial motor effect of L-Dopa. Hence, under specific conditions, our results denoted better outcomes with cTBS than with c-tDCS.

In patients with PD, studies using rTMS applied over M1 either reported LID decrease[37,38] or no effect,[39] and studies with cTBS over the cerebellum or the inferior frontal cortex reported LID decrease after single[40–42] and repeated sessions.[43] Also, a single session of cerebellar cTBS applied immediately after L-Dopa administration could reduce LID at 30 min and 45 min later.[44] This LID reduction was maintained when bilateral cTBS was applied during 2, 4 or 6 weeks.[44] Our study with bilateral cTBS of M1 also obtained a LID reduction at 30–45 min post-cTBS, thus supporting that the MPTP dyskinetic monkey is a relevant model to study the effects of magnetic brain stimulation in PD. We observed a decrease of LID 15–30 min after c-tDCS, which is coherent with M1 excitability reduction shown 30 min post-c-tDCS in healthy people.[45,46] Higher intensity of c-tDCS or repetition of stimulation could reverse the effects, that is, a reversal of M1 inhibition to excitation with c-tDCS or a reversal of M1 excitation to inhibition with anodal tDCS.[47,48] Thus, depending on the inter-stimulation time interval, it is possible that five sessions of excitatory a-tDCS could turn to inhibitory in this study.[46,48] Hence, our c-tDCS setup

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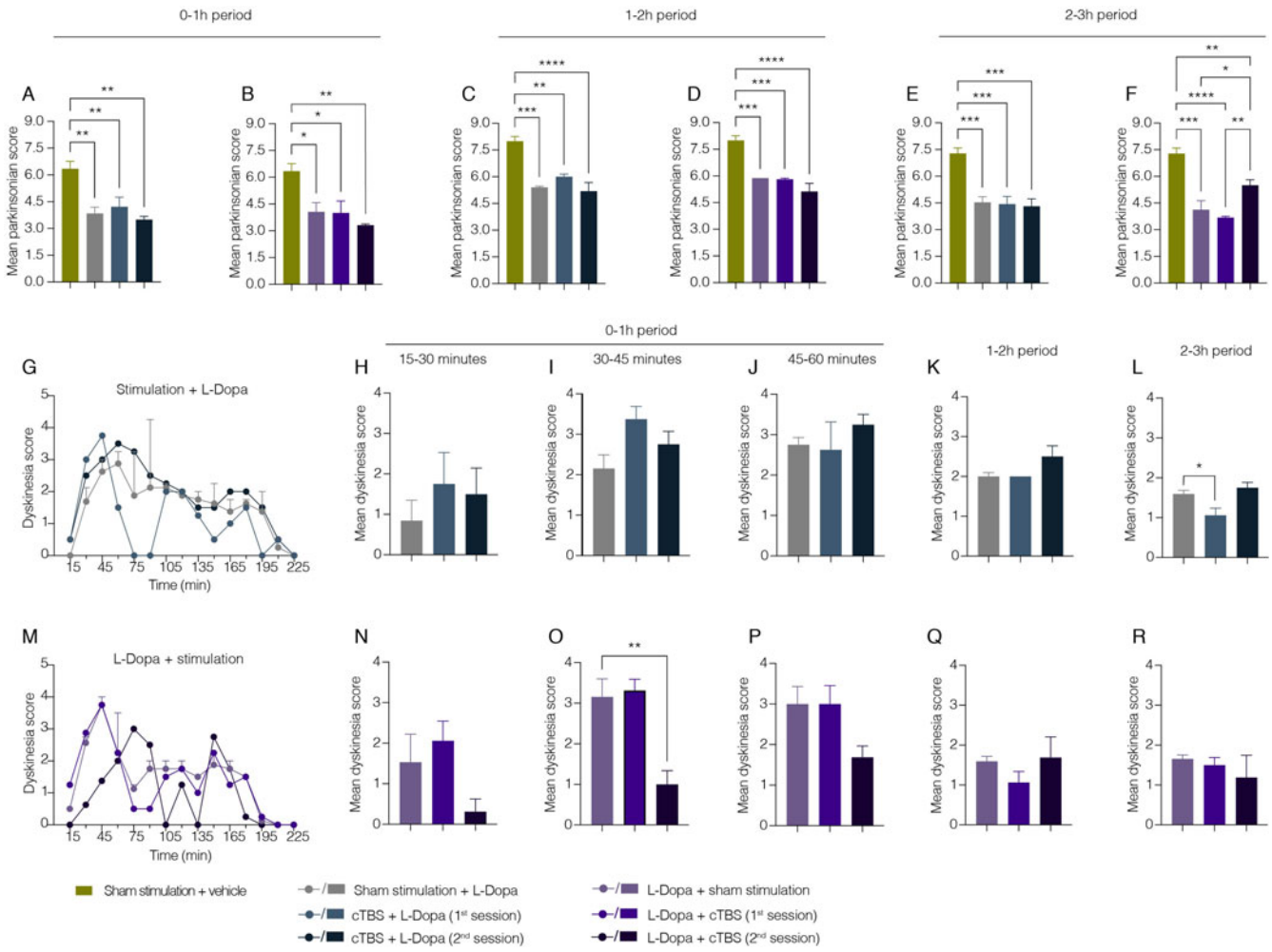

Figure 5. Motor effect of cTBS with L-Dopa administered after or before stimulation. (A–F) Mean parkinsonian scores 0–1, 1–2 and 2–3 h time periods with L-Dopa administration (after and before) and cTBS and sham stimulation. (G) Time course of dyskinesia scores with L-Dopa administered after cTBS and sham stimulation. (H–L) Mean dyskinesia scores 0–1, 1–2 and 2–3 h time periods with L-Dopa administered after cTBS and sham stimulation. (M): Time course of dyskinesia scores with L-Dopa administered before cTBS and sham stimulation. (N–R) Mean dyskinesia scores 0–1, 1–2 and 2–3 h time periods with L-Dopa administered before cTBS and sham stimulation. Data presented are for monkey 5 as the means and standard error of the mean (SEM) *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001.

in MPTP monkeys could be useful to delineate the most efficient protocol for persistent LID reduction in terms of stimulation number and intersession time interval.

cTBS alone had a significant beneficial motor effect in MPTP monkeys. This was observed in human studies where rTMS of the M1 hand area improved walking[49] and freezing of gait.[50] We did not observe motor symptoms improvement with c-tDCS (Figure 3), but it has been reported that anodal tDCS of M1 in MPTP rhesus monkeys improved parkinsonian motor symptoms.[51] This study, the only tDCS study reported to date in MPTP monkeys, showed that a transient improvement of motor symptoms could be enlarged by accumulated stimulations; however, this study did not test LID.[51]

TBS protocols had never been applied in parkinsonian monkeys before our study, but two studies were conducted in the 6-hydroxydopamine lesioned rat as a model of PD.[52,53] The first used cTBS of M1 (inhibitory protocol, like us) and iTBS (excitatory, i.e., intermittent theta-burst stimulation) to test that the mechanisms of neuroplasticity induced were altered and even progressively deteriorated along with the disease progression.[52] The second tested iTBS once daily for 21 days[53] and showed improvement in motor and emotional behaviors as well as learning and memory[53] that were accompanied by an increase of striatal levels of DA, serotonin and glutamate transporters, as well as an alteration of the NMDA receptor subunit composition.[53] Of note, DA release following magnetic stimulation of M1 was also reported in patients with PD,[54] which improved motricity. Like iTBS, cTBS acts via the NMDA receptors,[30] that is, inducing a glutamatergic dysfacilitation that reduces M1 excitability,[28] thus favoring LID reduction. This explains our results of concurrent post-cTBS motricity improvement and LID reduction. This supports that our cTBS setup in MPTP monkeys is a feasible and efficient model to study anti-LID treatment involving cTBS.

A previous study reported that participants with more advanced PD presented with less responsiveness to NIBS protocols, that is, a lesser potential of the brain for plasticity.[55] This study included participants with a stable response to dopaminergic medication, participants with a fluctuating response but without dyskinesias and participants with fluctuating response to medication accompanied by dyskinesias.[55] While no correlation was found between M1 responsiveness to TBS in the OFF condition and disease duration or motor score in OFF, differences

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related to L-Dopa response complications were observed: in the OFF condition, L-Dopa stable responders exhibited long-term potentiation (LTP)- and long-term depression (LTD)-like plasticity, whereas fluctuating non-dyskinetic responders exhibited only LTP and fluctuating dyskinetic responders none. That said, given that cTBS and c-tDCS protocols used in the present study are referred to as LTD-like protocols,[56] they could influence the mechanisms of brain plasticity, such as synaptogenesis and axonal growth, at least in L-Dopa stable responders, to entrain motor improvements and reduce associated motor complications.

In our study, it was possible to administer L-Dopa before or after cTBS. Indeed, as abovementioned, cTBS is of short duration, and the L-Dopa effects on parkinsonian motor symptoms do not appear before minutes; thus, the application of twice 40 s of cTBS after the administering L-Dopa was safe (no motor activation yet during cTBS application). cTBS effects can last 40–60 min after stimulation; thus, in both combinations, L-Dopa + cTBS or cTBS + L-Dopa, the L-Dopa effects on motor symptoms occurred during the after-effects of cTBS. It was shown that none of the two combinations altered the L-Dopa antiparkinsonian effects (Figure 5A–F) and that L-Dopa administered before cTBS reduced LID earlier and more importantly (significantly, see Figure 5N–R) than when L-Dopa was administered after cTBS (Figure 5H–L). Further investigations are warranted to investigate the mechanisms of action underlying this difference, such as molecular and multi-omics analyses of postmortem brains.

We administered c-tDCS (5 min duration per hemisphere, 10 min total) only before the L-Dopa injection because of the risk of monkeys to express motor activation and LID during the procedure. Hence, in our MPTP monkeys at an advanced stage of disease, the brain may have had very little DA release[23] during c-tDCS administration. Accordingly, when patients with PD are in an OFF-medication status, the phenomena of LTP/LTD characterizing brain plasticity could be hampered.[55] Further, patients with less severe PD in the OFF condition, and a shorter duration of the disease, show a better responsiveness of M1 to TBS in the ON condition (with L-Dopa treatment).[55] In corollary, DA can prolong the neuroplastic effects induced by magnetic and electrical stimulation in healthy controls.[57] Thus, it is possible that c-tDCS applied before L-Dopa administration, that is, without exogenous intake of DA, may have had lesser after-effects, as compared to cTBS after-effects during L-Dopa after-effects.

Limitations of the study

Our study demonstrated the feasibility of cTBS and c-tDCS alone and combined with L-Dopa administration in MPTP dyskinetic monkeys. As the objective of the study was to set up a NIBS paradigm, we used a very small number of animals (ethical limitations, four of the five monkeys investigated had participated in many studies over the years in our laboratory), and future studies are warranted to replicate the present results in larger samples. Further, due to these same ethical limitations, we could not apply cTBS and c-tDCS in the same animals, thus preventing any intra-animal comparison of after-effects. Special caution will have to be taken with respect to the movements of the monkeys' heads during cTBS and smaller coils (than the 70 cm diameter used in humans) should be bioengineered. For c-tDCS, the electrode diameter and the stimulation intensity and duration were adapted to the animals' brain volume: this montage induced after-effects of a similar duration than with patients (circa 1 h) tested with 5 × 7 cm electrodes mounted over M1 and the contralateral orbitofrontal area during 9 min at 1 mA.[58] However, smaller tDCS electrodes (4 cm^2 instead of the 9 cm^2 used here) should be tested to better adapt to the size of the MPTP monkeys' heads. The parameters of the cTBS application were identical to those used with patients. Future studies should investigate different cTBS or c-tDCS parameters per animal (duration, intensity) to decipher the most efficient protocol to induce plastic mechanisms in MPTP monkeys. Another way to potentiate tDCS after-effects that could also be tested is the repetition of sessions within the time interval of after-effects,[47,48,51,59] which is referred to as temporally contiguous tDCS or during after-effects condition.[48]

Monkeys in our study received chronic MPTP until motor symptoms stabilized, thus leading to almost a total loss of DA neurons. Given that the levels of striatal denervation correlate with symptom severity,[60] our model could be compared to an advanced stage of human PD. It is therefore warranted to test whether the beneficial effects we observed in MPTP monkeys with advanced PD could be more important in MPTP monkeys at earlier or intermediate stages of the disease. More studies in MPTP monkeys will thus contribute to tailored neuromodulation treatment combined with L-Dopa administration at all the stages of the disease, from early to advanced.

Conclusion

This pilot study showed the feasibility of NIBS administration, specifically cTBS and c-tDCS in MPTP dyskinetic monkeys as an animal model of PD. Our data illustrate motor improvement and LID reduction, these results warrant replication in larger sample studies with *de novo* monkeys to delineate the influence of the stage of the disease and of medication, the sexual differences, the optimization of stimulation parameters and conditions maximizing LID reduction. Also, postmortem analyses of the brain could shed light on the molecular mechanisms underlying LID and NIBS.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.284.

Author contributions. Conceptualization: TDP, EG and CS. Methodology: TDP, MB, EG and CS. Data collection: EG and MB. Writing – original draft preparation: TDP, MB, EG and CS. Writing – review and editing: TDP and CS.

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Competing interests. None.

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