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Home-based transcranial static magnetic field stimulation of the motor cortex for treating levodopa-induced dyskinesias in Parkinson's disease: A randomized controlled trial

Kewords:
Transcranial magnetic stimulation
tSMS
Parkinson's disease
Dyskinesia
Motor cortex

Dear Editor,

Levodopa-induced dyskinesias are a common complication in patients with Parkinson's disease (PD) treated chronically with levodopa. Even though dyskinesias may be more tolerable than parkinsonism, they can be highly debilitating for some patients. The difficulty to achieve satisfactory pharmacological treatment of dyskinesias often motivates the escalation toward more advanced invasive treatments. However, even with invasive treatments dyskinesias may remain problematic.

A promising approach is offered by non-invasive brain stimulation (NIBS). Several small, randomized studies (sample sizes $\leq$17 patients) suggest that presumably reducing the excitability of motor cortical areas with repetitive transcranial magnetic stimulation (rTMS) may be effective for reducing levodopa-induced dyskinesias [1]. However, rTMS is not portable, which limits its application to a center-based therapeutic model and possibly hindered the path toward larger, longer and more definitive clinical trials.

We recently introduced transcranial static magnetic field stimulation (tSMS), which can reduce cortical excitability in both healthy subjects [2,3] and PD patients OFF medication [4]. Differently from rTMS, tSMS is portable, which makes it attractive for shifting the NIBS paradigm from a center-based to a home-based therapeutic model. We thus aimed to investigate the potential of tSMS as a novel non-invasive home-based treatment to manage levodopa-induced dyskinesias.

Abbreviations: tSMS, transcranial static magnetic field stimulation; NIBS, non-invasive brain stimulation; UDysRS, Unified Dyskinesia Rating Scale; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; P-GRC, Patient's Global Rating of Change.

1. Methods

We conducted a randomized, sham-controlled, double-blind, parallel trial to test the ability of repeated sessions of tSMS to safely reduce levodopa-induced dyskinesias in PD (ClinicalTrials.gov: NCT02657681). Patients received 30-min sessions [3] of either real or sham tSMS, one session per day, for 9 days over two weeks (Fig. 1A). Patients were allowed to receive the treatment in the hospital or self-deliver it at home. All but one preferred home treatment. The data were analyzed with Bayesian statistics (i.e. Bayes factor, BF). For detailed methods, see Online Supplementary Materials.

2. Results

A total of 50 patients were randomized, 25 were assigned to real tSMS, 25 to sham tSMS (Suppl. Table 1). Of them, 42 (21 real, 21 sham) were analyzed for the primary outcome (Fig. 1B). The objective part of the Unified Dyskinesia Rating Scale (UDysRS, primary outcome) displayed moderate evidence of improvement after treatment compared to baseline ($p = 0.008$, $BF_{incl} = 5.4$), but there was also moderate evidence of absence of difference in the improvement between real and sham treatment (Fig. 1C and D; Suppl. Table 2). Changes in motor scores, as assessed by the Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III scale, secondary outcome), were inconclusive (Suppl. Table 2). Conversely, the Patient's Global Rating of Change (P-GRC, secondary outcome) revealed moderate evidence of subjective improvement with real compared to sham treatment ($p = 0.017$, $BF_{+0} = 6.6$; Fig. 1E).

No serious adverse events were reported. Anxiety occurred in two patients (one real, one sham), but was unlikely to be directly caused by the treatment. Transient mild dizziness and headache were reported by one patient, presumably attributed either to the static magnetic field or to the weight of the helmet. The latter was likely the cause of a mild periorbital hematoma transiently observed in one particularly fragile female patient.

For detailed results, see Online Supplementary Materials.

3. Discussion

3.1. Objective evaluation of levodopa-induced dyskinesias

We found non-significant difference in objective improvement (moderate evidence of absence) between patients who received

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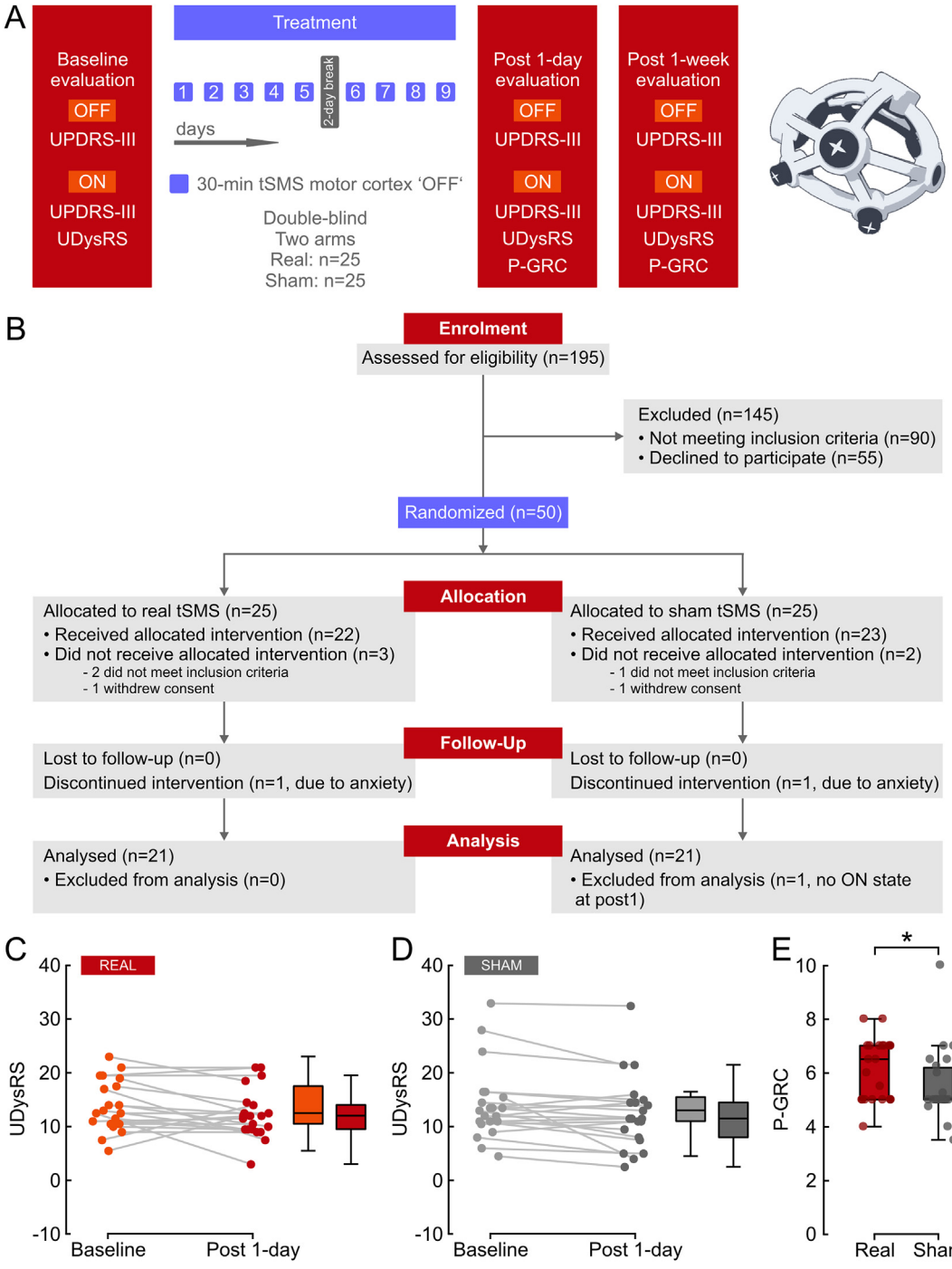

Fig. 1. Methods and results

(**A**) Experimental design and primary/secondary outcome measures. Patients underwent three visits at the hospital for clinical evaluation before (baseline) and after (post 1-day, post 1-week) the treatment with tSMS (real or sham, randomized and double-blind). Clinical evaluations were performed OFF medication (MDS-UPDRS-III) and ON medication (MDS-UPDRS-III, UDysRS) at each visit. For the home-based treatment the patients were instructed to apply the tSMS helmet (shown on the right). The treatment consisted of one 30-min session per day, for 9 days over two weeks, with a two-day rest after 5 days of treatment. The Patient's Global Rating of Change (P-GRC) was also obtained at post 1-day and post 1-week to collect a subjective assessment of the effect of the treatment.

(**B**) CONSORT flow diagram. The flow diagram shows the participant flow through each stage of the randomized trial (real and sham tSMS patient group). The different phases are enrolment, allocation, follow-up and data analysis. The analysis refers to the primary outcome.

(C-D) Objective evaluation of the treatment, as assessed by the objective part of the UDysRS at baseline and post 1-day for patients that received real (A) or sham (B) tSMS treatment (primary outcome). Individual (dots) and median (box plots) values are represented for each treatment group (same colors in dots and box plots refer to the same data). Considering both groups, a moderate evidence of reduction of UDysRS was found comparing post 1-day to baseline (two-way ANOVA, TIME: $F(1,40) = 7.7$, $p = 0.008$, $BF_{incl} = 5.4$), but there also was moderate evidence of absence of difference in the reduction of the UDysRS between real and sham treatment (TIME × TREATMENT, $F(1,40) = 0.1$, $p = 0.82$, $BF_{incl} = 0.3$). (**E**) Subjective evaluation of the treatment, as assessed by the P-GRC averaged between post 1-day and post 1-week, in patients that received real (red) or sham (gray) tSMS treatment (secondary outcome). P-GRC = 5 indicates no change, <5 worsening, >5 improvement. Individual (dots) and median (box plots) values are overlaid. The data showed a moderate evidence of greater subjective improvement in patients that received the real treatment ($n = 21$) compared to patients that received the sham treatment ($n = 20$, excluding the outlier; *t*-test, $t(40) = 2.5$, $p = 0.017$, $BF_{+0} = 6.6$). *($p < 0.05$, $BF_{+0} > 3$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

real compared to patients who received sham treatment. One limitation and two experimental choices might have limited our ability to detect differences in objective improvement between groups. First, overall the patients that participated in the study displayed relatively mild dyskinesias. Our difficulty in recruiting patients with severe dyskinesias is in line with the epidemiologically decreasing prevalence and severity of levodopa-induced dyskinesias, at least in some countries [5]. Second, we assessed dyskinesias after administration of 100% of the morning dose of levodopa, in order maintain real-life conditions and a stable pharmacological schedule. A higher levodopa dose might have decreased the variability of the assessment, at least in some patients. Third, since this was the first study with repeated sessions of tSMS, we conservatively delivered a relatively low number of sessions. With NIBS, it is not uncommon to observe an initial parallel improvement in patients receiving real or sham stimulation, with differences between groups becoming appreciable only after higher number of sessions and longer follow-ups [6]. Future studies should thus test longer home-based treatments, which are feasible with tSMS [7].

3.2. Objective evaluation of motor features

A priori, we did not strongly expect tSMS to improve PD motor features, since excitatory rather than inhibitory NIBS protocols typically provide motor improvement when applied to the motor cortex. Yet, tSMS mechanisms unrelated to cortical excitability could have ameliorated motor features, and we wanted to ensure that possible improvements in dyskinesias did not come at the expense of motor impairment. This did not seem to be the case. An attractive alternative target would be the supplementary motor area (SMA), which can be reached with tSMS [8] and whose stimulation with inhibitory NIBS protocols may improve both dyskinesias [1] and parkinsonian motor features [6].

3.3. Subjective improvement

We found significant subjective improvement (moderate evidence) in patients who received real compared to patients who received sham treatment, also supported by the ability of patients to correctly guess, to some extent, what treatment they had received (see Online Supplementary Materials). Even though we cannot fully exclude unreported unblinding in some patients, this possibility seems unlikely to have driven the evidence of subjective improvement. Interestingly, the primary motor cortex is involved in brain networks responsible for the sense of agency [9]. The observed dissociation between subjective and objective improvement thus suggests that tSMS might have modulated not the dyskinesias per se, but rather the subjective assessment of patients about their dyskinesias (or about other motor/non-motor aspects of their disease). This possibility is admittedly speculative and will require further investigation.

3.4. Safety

Our findings extend the safety of tSMS [10] to repeated sessions. The safety of repeatedly exposing the brain to static magnetic fields is also supported by decades of use of MRI, where the static magnetic fields (1.5–3T or even 7T) are at least one order of magnitude stronger than the field used in tSMS (<200 mT at cortical level).

4. Conclusions

The present results suggest that repeated sessions of home-based tSMS of the motor cortex are feasible, safe and provide no significant objective benefit (moderate evidence of absence) but significant subjective benefit (moderate evidence) for the treatment of levodopa-induced dyskinesias in PD. To seek evidence of objective benefit, future studies should investigate longer tSMS treatments.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Antonio Oliviero and Guglielmo Foffani are cofounders and shareholders of the company Neurek SL, which is a spinoff of the Foundation of the Hospital Nacional de Parapléjicos.

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Appendix A. Supplementary data

Supplementary Materials and Tables to this article can be found online at https://doi.org/10.1016/j.brs.2022.05.012.

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