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Bi-hemispheric repetitive transcranial magnetic stimulation for upper limb motor recovery in chronic stroke: A feasibility study

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Dear Editor,

With the emerging of a crucial role of non-primary and contralesional motor areas in the recovery of upper extremity (UE) after acute stroke [1,2], the "bimodal-balance recovery model" has been proposed [3], with the hypothesis that the contribution of ipsi- and contralesional primary and secondary motor areas might vary according to the structural reserve of the ipsilesional corticospinal tract. This model opens to novel non-invasive brain stimulation approaches for improving the effects of neurorehabilitation, targeting bilateral, wide motor cortical regions rather than focusing on the ipsilateral or contralesional M1. We tested safety, feasibility and efficacy of simultaneous high-frequency rTMS of bilateral motor/premotor areas using the H5-coil, associated with unilateral motor training of the paretic UE.

Methods

We enrolled 20 patients with UE motor involvement from first-ever chronic stroke occurred 36.6 ± 21.3 before. Exclusion criteria were: Fugl-Meyer assessment UE (FM-UE) score <16 at baseline [4], other neurological disorders, contraindications to undergo rTMS. They underwent 11 sessions of 30 minutes of upper limb motor training (MT) of the paretic UE, each followed by rTMS with the symmetric H5-coil, designed to stimulate both hemispheres simultaneously [5,6] (40 2s-trains at 20 Hz, 20 sec inter-train interval, 1600 pulses), at 90% of resting motor threshold (RMT) determined with electromyographic recording of first dorsal interosseous (FDI) muscles bilaterally or a twitch on any other upper limb muscle at visual inspection. Stimulation intensity was further reduced at 1% decrements of stimulator output if TMS-related twitches involving other UE muscles were observed. The H-coil helmet also contained a sham coil, delivering a superficial cutaneous stimulation accompanied by a magnetic click. The operation mode was switched using unlabelled magnetic cards assigned individually to each patient on a pseudorandomized fashion (50% real and 50% every 10 patients) to ensure blindness of patients and operators, who recorded side effects after each session. Clinical measurements were collected before the first (T0) and after the last treatment session (T1), plus one-month follow-up (T2) and included: FM-UE score, modified Ashworth scale (MAS) global score as the sum of shoulder, elbow and wrist scores (range 0–12), handgrip strength (JAMAR® dynamometer). To ensure blindness of clinical assessments, the latter were performed by a neurologist not involved in rTMS and post-session side effect reporting. A blindness questionnaire was administered to all patients at T1.

Results

No significant group differences in baseline variables were found (see Supplementary data-Table 1). No serious adverse events were reported. During real rTMS, 2 patients reported transitory dizziness, 1 toothache and the treating personnel detected muscle twitches on the unaffected UE in 3 subjects, on both arms in 3 subject and on shoulders for 1 subject. For these patients, intensity was lowered to a comfort level (84.6%RMT ±5.8) and all subjects completed the whole treatment cycle (Supplementary data-Table 2). At the blinded questionnaire, patients receiving active rTMS did not guess their group assignment more accurately than those receiving sham (chi-square: $p = 0.3$). FM-UE scores significantly improved over time in both real ($F = 13.5$; $p < 0.001$) and sham ($F = 6.3$; $p = 0.008$) groups. Patients in the real group improved significantly at T1 ($t = -6.1$; $p < 0.001$) and at T2 ($t = -3.3$; $p = 0.009$), while in the sham group only at T1 ($t = -3.5$; $p = 0.006$). Compared with sham stimulation, real rTMS was associated with a larger FM-UE improvement (F: 6.4, $p = 0.02$) (Fig. 1-A), and with a larger proportion of subjects with a clinically important change (improvement of at least 6 points [7]) of FM-UE score (real 7/10, sham 1/10; X^2 test $p = 0.01$). For the real group, the lower the FM-UE (e.g. more severe impairment at baseline) the greater the extent of recovery at T1 ($r = -0.6$; $p = 0.05$) and even better at T2 ($r = -0.8$; $p = 0.004$), while the opposite was observed for the sham group at T2 ($r = 0.6$; $p = 0.034$) (Fig. 1-B). Spasticity significantly decreased only in the real group ($F = 6.5$; $p = 0.028$; T1: $t = 2.6$; $p = 0.027$; T2: $t = 2.5$; $p = 0.032$), as well as handgrip strength ($F = 3.8$; $p = 0.04$) at T1 ($t = -3.9$; $p = 0.03$). See Supplementary data-Table 3 for statistical analysis.

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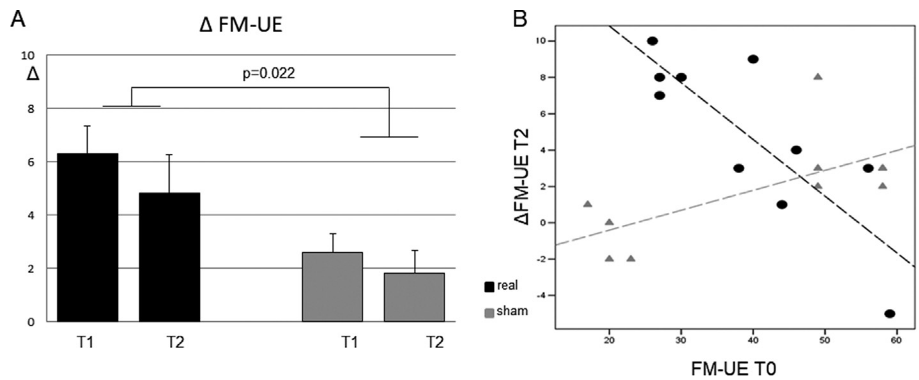

Fig. 1. (A) Change from baseline (Δ) of FM-UE after real (black) and sham (grey) rTMS at the end of treatment (T1) and 1 month follow-up (T2). (B) Pearson's correlation between baseline upper extremity Fugl-Meyer (FM-UE) score and its change at 1 month follow-up-T2.

Discussion

In the present study, including participants with mild to severe-moderate UE motor impairment, bilateral high-frequency rTMS of motor/premotor areas, following motor training, was associated with greater and more sustained motor improvement compared with MT followed by sham. Such improvement was clinically relevant (FM-UE≥ 6 point) for 70% of subjects in the real group (vs 10% of the sham group). No serious adverse events occurred and no patient dropped the study due to side effects. For 9/10 subjects receiving real rTMS, the intensity of stimulation had to be lowered below 90% RMT (84% RMT on average) due to reversible side effects or to movements observed in proximal UE muscles, the latter possibly related to the bilateral, wide H5-coil configuration. In fact, the fixed distance between the two H5-coil active wings does not match in every individual the distance between the two hand motor areas. However, the wide extension of the H5-coil fields could grant reaching safely both hand and forearm motor representations without the need of correspondingly increasing the stimulus intensity or increasing the number of stimulation sites, as it would be needed with using a focal coil. Patients' blindness was not significantly affected, as from questionnaires. Moreover, clinical evaluators were not involved in performing rTMS or side effect reporting. Real rTMS was also associated with improvements in UE spasticity, consistently with the reported modulation of spinal reflex circuits [8].

It is hypothesized that the motor cortex surrounding the ischemic lesion can vicariate function of the damaged neurons [9], while extended lesions with poor corticospinal reserve may lead to recruitment of non-primary and contralesional motor areas [10] [3]. To explain the present results, we cannot disentangle the relative contribution of rTMS to the ipsilesional or contralesional hemisphere. It is also possible that the wide bilateral, simultaneous stimulation may improve functional intra- and interhemispheric synchronization between motor and premotor areas and promote the unmasking of cortico-cortical and descending pathways. Interestingly, we found that bilateral stimulation of motor/premotor areas was associated with a greater FM-UE improvement in more severely impaired patients, opposite to what observed in the sham group. This pilot evidence prompts the extension of the present protocol to larger samples to further establish the role of bihemispheric stimulation in improving the effects of motor training and to gain insights on mechanisms of the effects.

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Disclosures

A. Zangen is a key inventor of deep TMS H-coils and has financial interest in Brainsway Ltd. All other authors have no disclosures related with the present work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2018.03.013.

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