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CASE REPORT

Video evidence of improved hand function following repetitive transcranial magnetic stimulation combined with physical therapy in stroke: a case report

James R. Carey[1], Mo Chen[2] & Christopher D. Streib[3]

[1]Division of Physical Therapy and Division of Rehabilitation Science, University of Minnesota, Minneapolis, Minnesota
[2]Department of Psychiatry, Institute for Engineering in Medicine, University of Minnesota, Minneapolis, Minnesota
[3]Department of Neurology, University of Minnesota, Minneapolis, Minnesota

Correspondence
James R. Carey, Division of Physical Therapy and Division of Rehabilitation Science, University of Minnesota, Minneapolis, 55455 MN.
Tel: 651 276 5563;
E-mail: carey007@umn.edu

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Key Clinical Message

In a 46-year-old female 6 months poststroke who presented with minimal paretic hand function, repetitive transcranial magnetic stimulation (rTMS), and exercises considerably improved her function beyond that accomplished with conventional rehabilitation. However, intermittent rTMS (2 sessions/week) was required to sustain the benefits. Research is required to determine the critical frequency of intermittent rTMS needed to sustain functional gains long term.

Keywords

Case report, hand, physical therapy, repetitive transcranial magnetic stimulation, stroke.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been studied as an adjunct to conventional stroke rehabilitation to elevate excitability in surviving cortical motor neurons that have been down-regulated by learned non-use [1], abnormal interhemispheric inhibition (IHI) [2], and deafferentation [3]. The logic is that enhancing excitability in the ipsilesional primary motor area (M1), either through high-frequency facilitatory rTMS of ipsilesional M1 [4] or low-frequency suppressive rTMS to contralesional M1 to rebalance IHI [5], can augment the effectiveness of conventional therapies. Meta-analyses of the many studies exploring the effectiveness of rTMS combined with rehabilitation in stroke have reported both significant benefits [6, 7] and no benefits [8, 9]. According to Ridding and Ziemann [10], the cause of inconsistent findings across studies is high variability in neurophysiological and behavioral responses both within and between subjects. They reviewed many factors beyond the obvious differences in pathology that contribute to this variability, including differences in age, sex, attention levels, prior activity levels, medications, genetics, time of day, and unexplained endogenous brain oscillations.

Due to variable findings, rTMS has not yet attained mainstream clinical use as a reimbursable intervention for stroke rehabilitation. To allow patients with stroke the possibility for further improvement of hand function following completion of their conventional rehabilitation, we recently implemented an off-label, private-pay rTMS clinical service. The purpose of this case report was to describe the characteristics, treatment, and outcome, evidenced through performance videos, of the first patient referred to this clinical service.

Case Description

The patient was a 46-year-old female who sustained a stroke in June of 2016. Imaging revealed an ischemic stroke secondary to right middle cerebral artery occlusion with a large infarct in the right frontal lobe, temporal lobe, insula, caudate, and putamen (Fig. 1). Initially, she

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had severe weakness of the entire left side. Gradually, she became able to ambulate and move her left arm; however, her hand remained nonfunctional. She was referred by her neurologist for rTMS and physical therapy in January of 2017 to improve her hand function.

She presented with high communication skill and motivation. She scored 30 of 30 on the Mini-Mental State Examination [11]. She showed moderate spasticity in the left finger and wrist flexor muscles with Modified Ashworth Scale [12] ratings of 2. She had 20 degrees of active flexion/extension at the metacarpophalangeal joints of the fingers but no prehensile function. She did not have any of the following conditions that would have excluded her from receiving rTMS: seizure within the past 2 years, pregnancy, nondental metal in the head, indwelling medical device incompatible with rTMS, receiving tricyclic antidepressant or neuroleptic medications. The project was approved by the institutional Internal Review Board. The patient gave informed consent, including consent for the videos.

Measurements

We attempted to measure her grasp and release function in the paretic hand with the Box and Block Test [13]; however, this proved to be overly difficult for her. Instead, we monitored her changes in hand function with videos of her performing grasp, release, and manipulation of small objects.

We measured her corticospinal excitability at ipsilesional M1 through transcranial magnetic stimulation (TMS) testing of resting motor threshold (RMT). The optimal TMS location (hotspot) for the extensor digitorum muscle (ED) of the paretic hand was explored using single pulses of TMS from a 70-mm figure-of-eight, Airfilm coil connected to a Magstim Rapid^2 stimulator (Magstim Co., Whitland, UK). The coil was oriented 45° to the sagittal line. Adhesive electromyography (EMG) electrodes placed in a bipolar arrangement on the skin overlying the paretic ED recorded motor-evoked potentials (MEPs). EMG signals were amplified and displayed on a laptop computer. The RMT was determined as the lowest stimulator intensity at which MEPs of at least 50 μV in peak-to-peak amplitude could be elicited in at least 3 of 5 attempts [14, 15]. On the first day only, as a screening test, we checked for the possibility of an ipsilateral MEP from the paretic ED when stimulating the contralesional M1, which would have contraindicated the use of suppressive rTMS treatment to contralesional M1 [16].

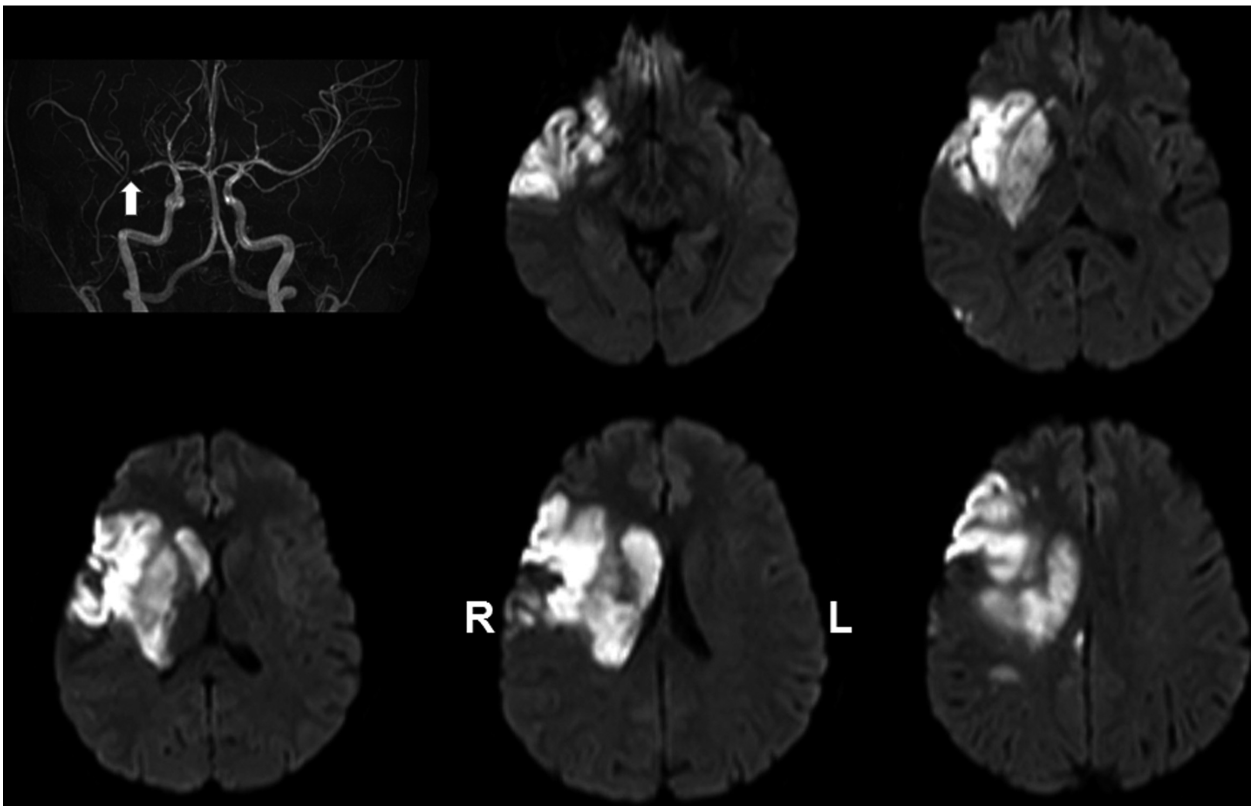

Figure 1. Patient's magnetic resonance imaging scan on hospital day #2 showing right middle cerebral artery occlusion (arrow) and infarction of the right temporal and frontal lobes, insula, basal ganglia, internal capsule, and corona radiata.

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However, no such ipsilateral MEP was found, even at 100% of MSO, and so we proceeded with contralesional rTMS.

At the conclusion of each series of treatments, the patient gave her own opinion of the outcome using the Global Rating of Change (GROC) scale [17]. Possible ratings range from +7 ("a very great deal better") to −7 ("a very great deal worse").

Treatment

For each daily rTMS treatment, the patient sat in a regular armchair wearing earplugs. One uniqueness of our protocol was that we used both contralesional and ipsilesional modes of rTMS on separate treatment sessions, as identified in the Table 1, to leverage both the suppressive effects on contralesional M1 and facilitatory effects on ipsilesional M1, respectively. Khedr et al. [18]. showed that low-frequency rTMS to contralesional M1 in one group of stroke patients and high-frequency rTMS to ipsilesional M1 in another group were both effective in producing higher functional gains than sham rTMS.

For contralesional rTMS, EMG electrodes were placed over the nonparetic ED and the hotspot and RMT for contralesional M1 were determined as described above. The therapist held the coil over the hotspot. Neuronavigation was not used. Another uniqueness applied during contralesional rTMS was that we preceded the principal rTMS phase with a phase of priming rTMS [19, 20]. Priming consisted of intermittent (5 sec on, 25 sec off) trains of 6-Hz stimulation for 10 min (total pulses = 600) with an intensity generally at 90% of RMT. Principal rTMS followed 1 min later and consisted of constant 1-Hz stimulation for 10 min (total pulses = 600) at the same intensity. The logic for preceding the low-frequency stimulation with high-frequency priming was to capitalize on metaplasticity principles [21], specifically the Bienenstock–Cooper–Munro theory of bidirectional synaptic plasticity [22], whereby the aftereffects of the intended suppressive stimulation can be heightened by first facilitating the neuronal network [19].

For ipsilesional rTMS, EMG electrodes were placed over the paretic ED and we attempted to find the hotspot and RMT for ipsilesional M1. Throughout the early treatments, a definitive (at least 50 μV) and consistent (at least three of five attempts) MEP could not be elicited from ipsilesional M1 even at 100% of MSO and so the hotspot was then deemed to be the site that mirrored the hotspot for contralesional M1. Treatment intensity was generally set at 70% of MSO. rTMS was then applied intermittently (5 sec on, 25 sec off) at 6-Hz for 10 min (total pulses = 600). So as to not over-facilitate ipsilesional M1, and risk a possible seizure, we did not precede the facilitatory stimulation with low-frequency priming.

As with the majority of the studies cited in the four meta-analyses [6–9], motor training followed the rTMS to capitalize on the state of heightened cortical excitability immediately following the rTMS. Training tasks, generally lasting 30–45 min, were intentionally made to be difficult, repetitive and variable to promote neuroplasticity [23]. Exercises included grasping/releasing blocks, handling finger food/drink items, playing cards, turning pages, etc. We also used computerized virtual reality tasks including the RAPAEL Smart Glove [24] (Neofect, Yong-in, Korea), Leap Motion Controller [25] (Leap Motion, San Francisco, CA), and finger tracking [26].

Ultimately, the patient received three treatment series of rTMS combined with physical therapy, totaling 32 treatments (Table 1). Treatments were 5 days/week for 2 weeks for the first and second series with a 1-month

Table 1. Identification of treatment dates and rTMS modes

First series		Second series		Third series	
Date	rTMS mode	Date	rTMS mode	Date	rTMS mode
1/23/2017	Contralesional	3/6/2017	Contralesional	3/21/2017	Contralesional
1/24/2017	Contralesional	3/7/2017	Contralesional	3/22/2017	Contralesional
1/252017	Contralesional	3/8/2017	Contralesional	4/5/2017	Contralesional
1/26/2017	Contralesional	3/9/2017	Contralesional	4/13/2017	Contralesional
1/27/2017	Contralesional	3/10/2017	Contralesional	4/18/2017	Contralesional
1/30/2017	Ipsilesional	3/13/2017	Ipsilesional	4/20/2017	Contralesional
1/31/2017	Ipsilesional	3/14/2017	Contralesional	4/24/2017	Contralesional
2/1/2017	Ipsilesional	3/15/2017	Ipsilesional	4/26/2017	Contralesional
2/2/2017	Ipsilesional	3/16/2017	Contralesional	5/2/2017	Contralesional
2/3/2017	Ipsilesional	3/17/2017	Ipsilesional	5/4/2017	Ipsilesional
				5/9/2017	Ipsilesional
				5/11/2017	Ipsilesional

rTMS, repetitive transcranial magnetic stimulation.

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break between those series. The original plan was to give only one series of 10 treatments. However, the patient observed a loss of the gains in her paretic hand performance, as described below, in the weeks following her first series. Consequently, she requested a second series of 10 treatments that was started 1 month after the first series. The patient was pleased with her gains and wanted to try to maintain them through treatments at a lower frequency because of cost and schedule commitments. Thus, a third series began the week after completing the second series at roughly 2 days per week but stopped after 12 treatments because of the cost.

Outcomes

The Box and Block Test was used only on the first day because, as shown in Video S1, the patient had extreme difficulty in performing this task. She used only an ulnar grasp involving just the ring and little fingers; there was no pincer grasp between the fingertips and the thumb. However, as shown in Video S2, which occurred after seven treatments, she was able to execute a pincer grasp between the thumb and the index and middle fingers to pick up grapes. She was successful in bringing a grape to her mouth but with much effort (Video S3). On the last day of the first series, she was able to add supination and bring a grape to her mouth easily (Video S4). Despite this improvement in the first series, assessment of her corticospinal excitability at ipsilesional M1 showed no MEP on the first or last day. She rated her GROC at +7 (“a very great deal better”).

On the first day of the second series, 1 month after the first series, slight regression of her grasp and release was observed. Video S5 shows that her fingertip prehension of marshmallows was not as skillful as it was with the grapes earlier. As a new task, Video S6 shows that she was not able to turn over playing cards. However, on the last day of the second series, the patient showed much improvement in fingertip grasp and release of marshmallows (Video S7) and turning over of cards (Video S8). Additionally on that day, for the first time, the patient showed consistent and definitive MEPs from the paretic ED following stimulation of ipsilesional M1 (Fig. 2A). Her RMT was 85% of MSO. She rated her GROC at +5 (“a good deal better”).

After the third series, the patient was able to execute a more refined pincer grasp between the index finger and the thumb to pick up walnut pieces (Video S9). She once again showed MEPs following stimulation of ipsilesional M1 (Fig. 2B) with a RMT at 83% of MSO. She rated her GROC at +5.

Throughout the three series of treatments, there were no adverse events.

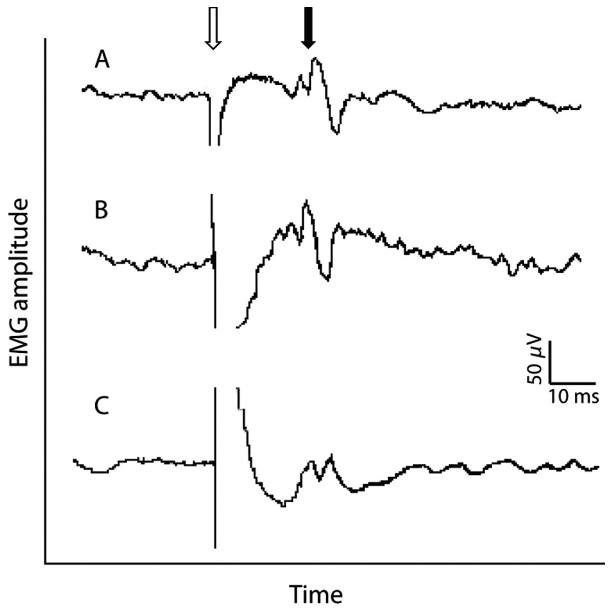

Figure 2. Motor evoked potentials (MEPs) (black arrow) from single-pulse transcranial magnetic stimulation (white arrow) to the patient’s ipsilesional primary motor area on the last day of the second (A) and third (B) treatment series of repetitive transcranial magnetic stimulation. Stimulation intensity was at resting motor threshold, which was 85% of maximal stimulator output (MSO) for A and 83% for B. At the 7-month follow-up (C), only a small MEP was inconsistently elicitable at 100% of MSO.

The patient returned for a follow-up assessment 7 months after completing the third treatment series. No therapy occurred during this time interval. Video S10 shows that her prehension of marshmallows had regressed to using a gross clenching of all fingers on the object compared to the more refined pincer grasp between fingertips and thumb in Video S7. Video S11 shows a decline in turning over cards compared to Video S8. And Video S12 shows a gross clenching of all fingers on the walnut pieces instead of the more delicate pincer grasp in Video S9. Only inconsistent, low-amplitude MEPs were elicitable from ipsilesional M1 (Fig. 2C) and required maximal stimulation (100% MSO).

Discussion

We believe that this patient’s improvement can be attributed to the combination of rTMS and physical therapy. However, we acknowledge that, without a control or sham condition, it is impossible to be absolutely certain of the source of her gains. A placebo effect cannot be excluded but the change in her prehension from a low-level ulnar grasp at the initiation of treatment to a fairly refined pincer grip at the culmination of treatments seems unlikely to be explained by a placebo, especially in light

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of the observed corticospinal excitability change. We believe that the development of consistent MEPs at ipsilesional M1 provides physiologic plausibility that her improved hand function most likely resulted from active neural plasticity induced by rTMS combined with physical therapy.

The fact that the gains following the culmination of treatments were not sustained at the 7-month follow-up was disappointing. However, this actually suggests that the effects of rTMS combined with hand training were real, albeit not permanent if not occasionally reinforced. The observation that the third series given at roughly two treatments per week did continue the benefits from the second treatment series gives hope that occasional treatment may be effective in sustaining earlier gains. This calls for more research exploring the critical treatment frequency needed to sustain treatment gains long term.

Despite the inherent limitations of case reports, our video findings of improved hand function and increased cortical excitability in an individual who had previously demonstrated minimal hand recovery in her initial 6 months poststroke contribute to advancing the nascent field of rTMS for stroke recovery. These promising individual results, tempered by the possible confoundment from placebo effects, warrant continued but vigilant application of rTMS as an off-label rehabilitation service while randomized trials more definitively determine the clinical utility of rTMS for people with stroke.

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Informed Consent

Copies of the patient's informed consent and permission to show videos are available through the corresponding author.

Conflict of Interest

The authors declare no conflict of interest.

Authorship

JRC: contributed treatment applications, measurements of outcomes, and manuscript writing. MC: contributed engineering of equipment, software support, and manuscript writing. CDS: contributed neurological and medical consultation and manuscript writing.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Video S1. Shows poor grasp and release of blocks at baseline before any treatment.
Video S2. Shows pincer grip of grapes after 7 treatments.
Video S3. Shows ability to bring grape to mouth but without supination after 7 treatments.
Video S4. Shows improved ability (with supination) to bring grape to mouth at end of first series.
Video S5. Shows reduced prehension following one month of no treatments.
Video S6. Shows inability to turn over cards prior to starting second series.
Video S7. Shows improved ability to grasp and release marshmallows at end of second series.
Video S8. Shows improved card turning at end of second series.
Video S9. Shows refined pincer grip in picking up walnut pieces at end of third series.
Video S10. Shows reduced prehension of marshmallows at 7-month follow-up.
Video S11. Shows reduced card turning at 7-month follow-up.
Video S12. Shows reduced prehension of walnut pieces at 7-month follow-up.