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6-Hz primed low-frequency rTMS to contralesional M1 in two cases with middle cerebral artery stroke

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ABSTRACT

This case study contrasted two subjects with stroke who received 6-Hz primed low-frequency repetitive transcranial magnetic stimulation (rTMS) to the contralesional primary motor area (M1) to disinhibit ipsilesional M1. Functional magnetic resonance imaging (fMRI) showed that the intervention disrupted cortical activation at contralesional M1. Subject 1 showed decreased intracortical inhibition and increased intracortical facilitation following intervention during paired-pulse TMS testing of ipsilesional M1. Subject 2, whose precentral knob was totally obliterated and who did not show an ipsilesional motor evoked potential at pretest, still did not show any at posttest; however, her fMRI did show a large increase in peri-infarct zone cortical activation. Behavioral results were mixed, indicating the need for accompanying behavioral training to capitalize on the brain organization changes induced with rTMS.

Functional deficits following stroke are due not only to the ischemic loss of neurons but also to maladaptive brain reorganization associated with compensatory "learned non-use" [34] behaviors. Exaggerated interhemispheric inhibition of the ipsilesional primary motor area (M1) by contralesional M1 can lead to down-regulation of excitability in neurons that have survived the stroke and a worsening of the functional deficit [13,23,30]. Low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to contralesional M1 has been shown to reduce its inhibition on ipsilesional M1 [14,31,33], leading to improved function in the paretic hand. Importantly, Iyer et al. [22] showed in healthy humans that the disruptive effect of low-frequency stimulation could be magnified if it was preceded (primed) with high-frequency stimulation. We recently have shown that 6-Hz primed low-frequency rTMS is safe in subjects with stroke [7]. The purpose of this case report was to contrast findings in two subjects who volunteered for a larger study examining the efficacy of 6-Hz primed low-frequency rTMS to contralesional M1.

Both subjects had right middle cerebral artery strokes with dense paresis of the left upper extremity. For both, the stroke duration was 10 years and both were right-handed pre-stroke. Subject 1 was a 71-year-old male (upper extremity Fugl-Meyer [16] score = 36). Subject 2 was a 52-year-old woman (Fugl-Meyer = 35). The experiments were conducted in accordance with the Declaration of Helsinki and both subjects signed informed consent forms approved by our IRB. The study was conducted under an investigational device exemption (IDE# G050260) from the United States of America Food and Drug Administration.

For subject 1, testing occurred at pretest and two weeks later at posttest with five intervention sessions given every other day between the two tests. His posttest occurred 72 h after his last session. Testers were blinded. In subject 2, we could not elicit a motor evoked potential (MEP) at pretest when applying TMS to ipsilesional M1 and so this person was not included in the larger. But as a case study, two pretests were given—one when she volunteered for the larger study and four months later after IRB approval as a case study. For subject 2, the five intervention sessions occurred daily after the second pretest and the posttest occurred 24 h after the last session.

fMRI. Anatomical and functional images were acquired using a 3 T magnet. The details of the data acquisition have been reported earlier [6]. Briefly, with electrogoniometers applied to the paretic and nonparetic index fingers, each subject attempted to track a target waveform displayed on a screen using finger flexion/extension movement. The task consisted of alternating 30-s blocks of rest (7 blocks), paretic (3 blocks) and nonparetic (3 blocks) finger tracking. We evaluated nonparetic finger tracking to screen for a possible adverse effect in the nonparetic hand. A total of 130 T_2-weighted

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scans of the blood-oxygen-level-dependent signal were taken over the brain volume divided into 36 slices. Voxel resolution was 3 mm × 3 mm × 3 mm. Finger tracking was quantified with an accuracy index [5] (maximum = 100%).

Brain Voyager software was used for fMRI analysis as described previously [6]. The 3D functional volume was co-registered with the corresponding 3D anatomical volume, and both were normalized to standard Talairach space. A general linear model was run that created an activation map showing active voxels with significantly different signal intensity between paretic finger tracking and rest using a false discovery rate (FDR) [18] of q(FDR) < 0.05.

TMS. With EMG electrodes recording from the paretic extensor digitorum (ED) muscle, TMS was delivered to the scalp ipsilesionally using two Magstim 200^2 stimulators coupled by a Bistim module (Magstim, Dyfed, UK) and a figure-of-eight coil (wing diameter: 70 mm). Single-pulse stimulation was applied at 0.1 Hz starting at an intensity of 60% of machine maximum. The scalp location and stimulus intensity were adjusted until the optimal location was found for producing the resting motor threshold (RMT), defined as the lowest intensity that induced MEPs of at least 50 μV (peak-to-peak) on at least 5 of 10 trials in the target muscle [3].

Once the ipsilesional RMT was found (subject 1 only), 10 single pulses at 120% of his RMT were applied at 0.1 Hz. Then, paired pulses were applied with the conditioning pulse set at 80% of RMT and the test pulse at 120%. Short and long interpulse intervals between the conditioning and test pulses were used to assess intracortical inhibition (ICI) and facilitation (ICF), respectively [24]. We chose two short intervals (2 and 3 ms) and two long intervals (10 and 15 ms), consistent with Hamzei et al. [20], to ensure capturing of the suspected effects. Each MEP amplitude from 10 paired pulses applied randomly at each interval was normalized to the average of the 10 single-pulse MEPs.

Behavioral. Subjects performed three trials each of the Box and Block Test (BBT) [28], involving grasp and release of small cubes with the paretic hand over 1 min, and a maximal finger extension force test against a calibrated load cell. The Motor Activity Log (MAL) [25] measured "real-world" function as judged by subject responses to structured interview questions on the amount of use and quality of movement (both rated 0–5) in using the paretic arm in 30 activities. The Test Évaluant la performance des Membres supérieurs des Personnes Âgées (TEMPA) [12] was used to assess manual skill, recorded as the total time to complete only those tasks that involved using both hands together (neither subject could perform the paretic-hand-only tasks).

The RMT for the nonparetic extensor digitorum muscle was determined by stimulating the contralesional M1. rTMS intervention involved two phases, priming and low-rate stimulation. Priming consisted of 10 min of intermittent 6-Hz rTMS given in 5-s trains with 25-s intervals between trains (i.e. 30 pulses/train × 2 trains/min × 10 min = 600 priming pulses) at an intensity of 90% RMT. Immediately following priming, 10 min of continuous 1-Hz rTMS (i.e. 600 low-frequency pulses) was given at 90% RMT. We did not calculate a new RMT between the

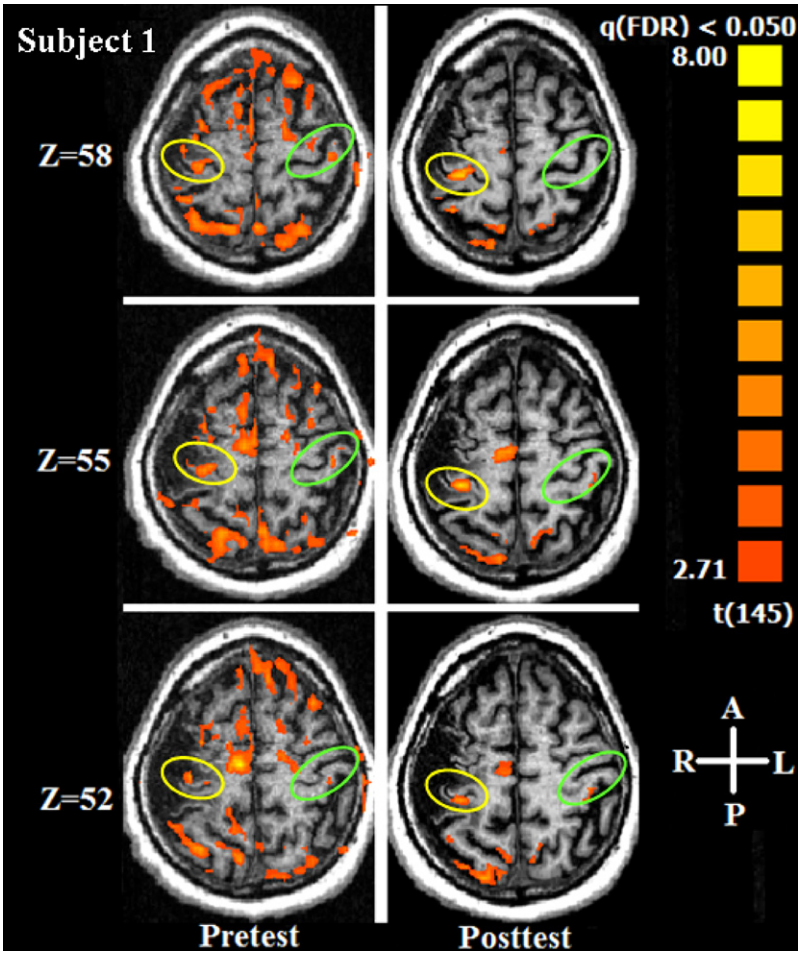

Fig. 1. Activation for subject 1 before (pretest) and after (posttest) intervention. Maps show a reduction in active voxels in left (contralesional) sensorimotor cortex (green circles) from pretest to posttest and an increase in active voxels and intensity in right (ipsilesional) sensorimotor cortex (yellow circles). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
fMRI and behavioral results before and after five sessions of 6-Hz primed low-frequency rTMS to contralesional primary motor area.

Measurement	Subject 1		Subject 2		
	Pretest	Posttest	Pretest 1	Pretest 2	Posttest
fMRI active voxels					
Contra SMC	101	59	981	1393	841
Ipsi SMC	322	314	2	28	85
Wt Avg intensity					
Contra SMC	3.60	3.66	3.8	4.10	3.59
Ipsi SMC	3.52	4.28	2.65	3.25	3.59
Behavioral					
AI (%)	−53.0 ± 6.7	−18.5 ± 10.4	30.3 ± 11.9	−16.6 ± 34.0	−47.3 ± 23.1
BBT (blocks)	11.3 ± 0.6	9.0 ± 1.7	3.0 ± 1.0	6.0 ± 3.0	7.0 ± 2.7
Force (N)	8.4 ± 1.1	to 10.7 ± 0.4	5.1 ± 1.6	7.2 ± 2.9	8.3 ± 1.8
MAL					
Amount	0.6	0.4	0.9	0.9	1.2
Quality	0.4	0.7	0.9	1.1	1.6
TEMPA (s)	149.9	164.9	139.5	172.1	233.9

fMRI = functional magnetic resonance imaging, Contra = contralesional, Ipsi = ipsilesional, Wt Avg = weighted average, BBT = Box and Block Test, N = Newtons, s = seconds, TEMPA = Test Évaluant la Performance des Membres Supérieurs des Personnes Âgées, MAL = Motor Activity Log.

priming and low-frequency stimulation because we wanted to replicate the procedure used by Iyer et al. [22] and not risk losing the priming effect that may depend on the immediacy of low-frequency following high-frequency stimulation.

For fMRI, we restricted the location of our analysis to the active voxels located in the contralesional and ipsilesional sensorimotor cortex (SMC) at the level of the precentral knob because it is considered to be the focal area of M1 representing the hand [36]. We identified three brain slices in the transverse plane showing the precentral knob in both subjects (Z = 52, 55, 58). At these slices, we used Brain Voyager analysis features to record the active voxel count in the SMC and their average signal intensity (average *t* statistic reflecting difference between the paretic finger tracking and rest conditions).

For TMS paired-pulse testing (subject 1 only), following confirmation that the data were normally distributed, a one-tailed paired *t*-test was applied to the paired-pulse/single-pulse ratios of MEP amplitude.

For all fMRI results, cortical activation corresponds to the paretic finger tracking condition. Subject 1 showed a decrease in active voxels in contralesional SMC following intervention (Fig. 1 and Table 1) with little change in intensity, whereas ipsilesional SMC showed little change in active voxels but an increase in intensity. Subject 2 showed a relatively small increase in activation in con-

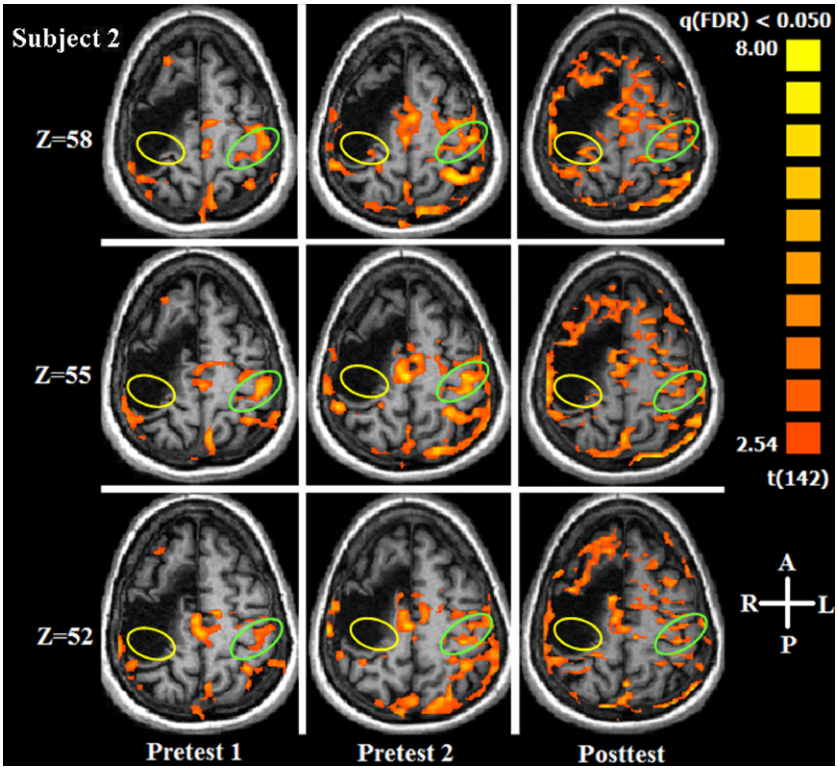

Fig. 2. Activation for subject 2 before (pretests 1 and 2) and after (posttest) intervention. Maps show a small increase in activation in the left (contralesional) sensorimotor cortex (green circles) from pretest 1 to pretest 2, followed by a reduction at posttest. In the ipsilesional hemisphere, an increase in peri-infarct zone activation is seen at posttest, including in the small amount of surviving sensorimotor cortex (yellow circles). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

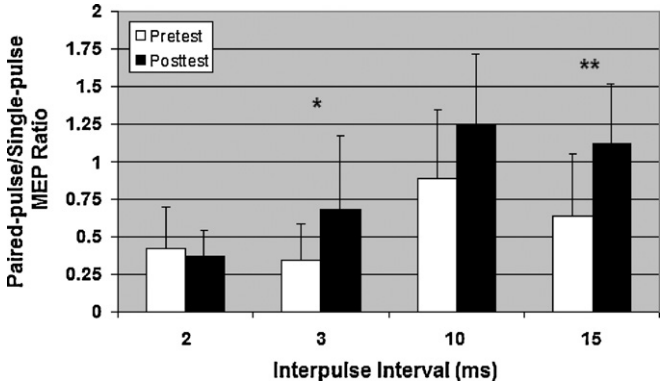

Fig. 3. Excitability of ipsilesional primary motor area in patient 1 before (pretest) and after (posttest) intervention. Each bar represents mean ± standard deviation of 10 measurements (MEP = motor evoked potential, $^{*}p = 0.029$, $^{**}p = 0.017$).

tralesional SMC from pretest 1 to pretest 2 (Fig. 2 and Table 1) followed by a more substantial decrease in active voxels and intensity after intervention. Ipsilesionally, the small amount of available SMC substrate showed an increase in activation across the three tests; however, the more notable observation is the absence of change in peri-infarct zone activation from pretest 1 to pretest 2 but then a sizeable increase after intervention.

Subject 1's paired-pulse/single-pulse MEP ratios are shown in Fig. 3. For 2-ms and 3-ms interpulse intervals, Kujirai et al. [24] showed on healthy subjects that conditioned MEPs were reduced to roughly 20–30% of unconditional MEPs and our pretest values were close to that range. At posttest for the 3-ms interval, with the ratio increasing toward 1.0, there was a significant reduction ($p = 0.029$) in ICI relative to pretest. For 10-ms and 15-ms intervals, Kujirai et al. found that conditioned MEPs were facilitated to roughly 125–160% of unconditioned MEPs but our pretest values, being less than 1.0 on average, showed no facilitation. However, at posttest, both the 10-ms and 15-ms intervals showed increased ICF, relative to pretest, with the latter interval being significant ($p = 0.017$). For subject 2, no single-pulse MEP could be elicited at pretest 1, pretest 2 or posttest even at intensities as high as 100% of machine maximum and with a broad search area. She then did not receive paired-pulse testing.

Subject 1's paretic hand tracking accuracy and finger extension force improved from pretest to at posttest but this did not translate into improved BBT or TEMPA scores (Table 1). His own rating of motor function (MAL) decreased in the amount of use but increased in the quality of movement. Subject 2's paretic hand tracking accuracy and TEMPA scores showed general decreases in skill across her three tests, whereas her BBT scores, finger extension force and MAL ratings showed general increases.

There were no adverse effects in either subject.

The important finding of this study was that 6-Hz primed low-frequency rTMS to contralesional M1 was able to produce physiologic effects that were measurable 72 h (subject 1) and 24 h (subject 2) after their last intervention. However, the actual physiologic effects were different between the two subjects and this may relate to whether the precentral knob was damaged [20]. The fMRI results for both subjects suggest that the intervention disrupted the voluntary recruitment of contralesional M1, which was intended and is consistent with Nowak et al. [31]. Furthermore, in subject 1 only, there was an increase in BOLD signal intensity of the active voxels in ipsilesional SMC at the precentral knob, possibly as a consequence of the reduced voluntary recruitment of contralesional M1 leading to reduced interhemispheric inhibition from ipsilesional M1 [9,21]. Indeed, paired-pulse TMS testing to his ipsilesional M1 showed reduced ICI and increased ICF (Fig. 3), which is consistent with Wu et al. [35] in healthy subjects following 15 Hz rTMS.

Contrarily, whereas the ipsilesional precentral knob was largely spared in subject 1, it was obliterated in subject 2. Loss of this neural substrate likely accounts for the absence of any MEPs with single-pulse TMS to ipsilesional M1 at pretest 1 and pretest 2, which has also been reported by Butefisch et al. [4]. At posttest, we were uncertain whether the small area of spared SMC at the medial edge of the infarct (Fig. 2) might, through vicariation of function [15], respond to the rTMS intervention and elicit MEPs during TMS testing. Although an increase in cortical activation of some of this spared SMC was observed (Fig. 2, $Z = 58$), there still was no MEP. Instead, conceivably as an alternative brain reorganization strategy in the absence of precentral knob substrate, there was an increase in peri-infarct zone activation extending into the ipsilesional premotor area [15]. The decreased tracking performance with her paretic hand at posttest may actually be a reflection of this large change in brain organization without sufficient time or training to capitalize on it. Other studies have reported on the rich potential for neuroplasticity in the peri-infarct zone, possibly leading to higher functional recovery if up-regulated [8,10,17,26]. Our speculation of different brain reorganization strategies between the two subjects being dependent on the presence or absence of the precentral knob is consistent with the findings of Hamzei et al. [20] in their use of constraint induced movement therapy in stroke.

Behavioral changes in our study were inconsistent, as some tests showed gains and others showed declines in both subjects. The upward trends in the BBT and finger force for subject 2 makes it unclear whether the improvement at posttest reflects an intervention effect or a learning effect from repeated exposure. With data from only two subjects, it is difficult to draw any conclusions on the functional effectiveness of the intervention. We postulate, however, that to fully capitalize on the rTMS-induced brain reorganization, it may be necessary to complement the rTMS intervention with behavioral training.

Studies on groups of subjects with stroke have found improved function in the paretic hand measured immediately after a single session of low-frequency rTMS to contralesional M1 [27,31,33]. But this raises the important therapeutic concern about the duration of the rTMS-induced after-effects, as Romero et al. [32] showed in healthy subjects that effects lasted only up to 15 min. Fregni et al. [14] addressed this concern in subjects with stroke by applying five sessions of low-frequency rTMS over two weeks. They found improvements in hand function two weeks after the last intervention. Although they found reduced excitability in contralesional M1 immediately after the last intervention, they did not do excitability testing at the two-week follow-up. Thus, to our knowledge, there are no studies in people with stroke that have determined the duration of cortical excitability changes beyond the day of intervention. In light of the transient effect found by Romero et al. [32] (albeit in healthy subjects), our findings in subject 1 of excitability effects 72 h after the last day of intervention suggest that there may be value to the inclusion of priming, as shown by Iyer et al. [22] in healthy subjects. However, our design did not directly compare priming to no priming and so we are unable to conclude that priming was key to the observed duration of excitability after-effects. Future studies will need to explore this concern.

The exact mechanism of priming is not yet clear, but growing evidence [19,29] suggests that it operates through the Bienenstock–Cooper–Munro theory of bidirectional synaptic plasticity [1], which states that neuronal reactivity to conditioning stimuli depends on the recent history of activity. Restated, low levels of prior (i.e. prior to conditioning) neuronal activity bias the synapse toward long-term potentiation and high levels bias toward long-term depression [29], consistent with the underlying principle of preserving synaptic homeostasis. We believe that our results

measured 72 h (subject 1) and 24 h (subject 2) after intervention suggest that the intended physiological effects were achieved but the mixed behavioral effects indicate that rehabilitative training should accompany the stimulation. Indeed, the extended duration of physiological after-effects gives the opportunity to apply other rehabilitative interventions during a critical time when the ipsilesional M1 is up-regulated. The duration of up-regulated excitability remains unknown for now in humans with stroke. Nonetheless, the theoretical principle remains strong in capitalizing on Hebbian-based rules for synaptic plasticity [2,11], which emphasize the importance of temporally correlated coactivation of presynaptic and postsynaptic activity (i.e. behavioral training amidst cortical disinhibition) to maximize excitability change. Ideally, surviving neurons in the ipsilesional SMC (and possibly other ipsilesional areas) could then emerge from their diaschisis and re-enter voluntary recruitment leading to improved function, even in chronic stroke [20]. Further studies are needed to verify contralesional excitability changes and direct evidence of transcallosal inhibition.

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