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Background. Suppression of activity in the contralesional motor cortex may promote recovery of function after stroke. Furthermore, the known depressant effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) can be increased and prolonged by preceding it with 6-Hz priming stimulation. *Objective.* The authors explored the safety of 6-Hz primed low-frequency rTMS in 10 patients with ischemic stroke. *Methods.* Priming consisted of 10 minutes of 6-Hz rTMS applied to the contralesional hemisphere at 90% of resting motor threshold delivered in 2 trains/min with 5 s/train and 25-second intervals between trains. Low-frequency rTMS consisted of an additional 10 minutes of 1-Hz rTMS at 90% of resting motor threshold without interruption. Possible adverse effects were assessed with the National Institutes of Health Stroke Scale (NIHSS), the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III), the Hopkins Verbal Learning Test–Revised (HVLT-R), the Beck Depression Inventory–Second Edition (BDI-II), a finger movement tracking test, and individual self-assessments. Pretest, treatment, and posttest occurred on the first day with follow-up tests on the next 5 weekdays. *Results.* There were no seizures and no impairment of NIHSS, WAIS-III, or BDI-II scores. Transient impairment occurred on the HVLT-R. Transient tiredness was common. Occasional reports of headache, neck pain, increased sleep, reduced sleep, nausea, and anxiety occurred. *Conclusion.* Because there were no major adverse effects, the authors concluded that the treatment was safe for the individuals in this study and that further investigation is now warranted to examine efficacy and safety of serial treatments of 6-Hz primed low-frequency rTMS.

Key Words: *Stroke—Seizure—rTMS—Safety—Recovery—Primary motor area.*

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Part of the motor deficit following stroke is due to the death of neurons that serve bodily movement, but part also stems from the down-regulation of excitability of surviving neurons due to deafferentation[1,2] or nonuse.[3,4] The possibility exists that viable neuronal pathways may remain after stroke but cannot be recruited voluntarily.

A growing topic related to this inability to recruit available pathways in stroke is interhemispheric inhibition. In healthy individuals, both evoked[5] and voluntary[6] activity in the primary motor cortex (M1) of one hemisphere exerts an inhibitory effect on the contralateral M1. In people with stroke, voluntary activation of the contralesional M1 has a pronounced inhibitory effect on the ipsilesional M1.[7] Inasmuch as restoring function in the ipsilesional M1 is associated with higher recovery from stroke,[8-10] it is reasonable to seek rehabilitation strategies that disrupt excitability contralesionally in an effort to promote excitability ipsilesionally.

It is known that repetitive transcranial magnetic stimulation (rTMS) at 1 Hz in healthy individuals disrupts excitability of the stimulated M1[11-14] and induces disinhibition (excitation) of the contralateral M1.[15,16] Indeed, studies in patients with stroke have applied 1-Hz rTMS to the contralesional hemisphere to enhance ipsilesional excitability and found significant behavioral improvements in the paretic hand.[17-19] To the contrary, one study that used only 5 patients did not find favorable effects.[20] Overall, these works are encouraging and invite further work with 1-Hz rTMS to the contralesional M1 to decrease interhemispheric inhibition from that hemisphere on the ipsilesional M1 and, thereby, improve paretic hand function.

Notably, based on work showing that long-term depression of synapses can be enhanced by pretreatment with stimulation in the 5-6 Hz range,[21,22] Iyer et al[23] demonstrated in healthy individuals that immediately preceding 1-Hz rTMS with "priming" trains of 6-Hz rTMS caused significantly greater depression of excitability in the stimulated hemisphere than without such priming. The important corollary in stroke is that the desired disinhibition of the ipsilesional M1 might be

enhanced by combining priming rTMS at 6 Hz with low-frequency rTMS at 1 Hz to the contralesional M1, possibly leading to greater clinical benefits.

However, the safety of 6-Hz priming stimulation is unknown in people with stroke. It is known that brain stimulation carries a risk of seizure and this risk is increased at frequencies above 1 Hz.[14] It is also known that people with stroke carry a higher risk of seizure than the general population.[24] Consequently, the United States Food and Drug Administration has not given approval to use rTMS above 1 Hz in people with stroke. Therefore, before undertaking a definitive efficacy study of 6-Hz primed low-frequency rTMS, its safety must first be explored. The purpose of our study, following proper approvals, was to determine the safety of one treatment of 6-Hz primed low-frequency rTMS to the contralesional M1 in patients with stroke.

MATERIALS AND METHODS

Participants

Inclusion criteria were individuals with an age range between 30 and 80 years and a history of stroke at least 6 months previously. The location of the stroke could be cortical or subcortical. Participants needed to be able to walk at least 100 feet independently and have at least 10 degrees of voluntary finger extension at the index finger metacarpophalangeal joint of the paretic hand. If the voluntary finger extension was of normal range, the movement needed to be slower compared to the nonparetic side. Exclusion criteria were hemorrhagic stroke because of its higher risk of seizure.[25] Other exclusion criteria were receptive aphasia, personal or immediate family history of seizures, metal inside the head (except dental), indwelling medical devices, increased intracranial pressure, bipolar disorder, and pregnancy.

Twenty candidates responded initially to distributed notices. Three were rejected because medical records indicated that the stroke was hemorrhagic in origin, 2 could not participate because of scheduling conflicts, and 5 did not respond to requests for further information. Ten patients (5 male, 5 female) were enrolled and completed the study. Table 1 identifies the participant characteristics. We used the National Institutes of Health Stroke Scale (NIHSS)[26] to assess the overall severity of stroke, the Mini-Mental State Examination[27] to screen for cognitive function, and the modified Ashworth Scale[28] to grade spasticity in the paretic hand. The mean (±SD) age of participants was 64.8 (±10.1) years, and the mean interval since stroke was 54.6 (±27.3) months. Nine participants were right-handed before the stroke, and 1 (#1) was left-handed based on the Edinburgh Inventory.[29] The hemiplegia was on the left in 6 participants and on the right in 4. Two participants (#1 and #2) had anticoagulation-associated hemorrhagic transformation of primary ischemic strokes. The study was approved by the institution's Committee on the Use of Human Subjects in Research. Also, we received approval from the United States Food and Drug Administration to conduct this investigation as an initial safety study in 10 patients with stroke. All participants signed a statement of informed consent.

Testing Instrumentation and Procedure

On the first day, testing occurred before treatment (pretest) and immediately after treatment (posttest). Follow-up testing occurred on each of the next 5 weekdays (follow-up 1-5). Participant schedules did not permit starting each participant on the same weekday. Thus, the first day was a Monday for all participants except participant #1 (Wednesday), participant #2 (Thursday), and participant #4 (Friday). We used subtests of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III)[30] to evaluate neurocognitive function. Specifically, we tested perceptual organization with the Picture Completion subtest, in which the patient identified missing parts in pictures of common settings (best possible score = 25 points). Verbal comprehension was tested with the Similarities subtest, requiring the participant to explain the similarity of pairs of words presented orally (best possible score = 33 points). Working memory was tested with the Digit Span subtest, requiring the participant to repeat orally presented numbers forward (16 sequences) or backward (14 sequences) (best possible score = 30 points). Processing speed was tested with the Symbol Search subtest, in which the participant indicated on as many test items as possible over 120 seconds whether a specified symbol appeared across a group of symbols (best possible score = 60 points). Because these tests do not have a variety of forms, and therefore are prone to practice effects, we applied these WAIS-III subtests only at pretest and follow-up 5.

To measure for possible adverse cognitive effects daily without practice effects, we used the Hopkins Verbal Learning Test–Revised (HVLT-R),[31] which checked for memory of a word list presented orally to the participant. We chose this test because it has 6 distinct forms. With a total of 7 measurement points (1 pretest, 1 posttest, and 5 follow-ups), the form used at pretest was repeated at the last follow-up. For each test, a single list of 12 nouns was presented orally to the participant 3 times and the participant attempted to recall as many nouns as possible after each presentation. Four scores were obtained. For Total Recall, the best possible score is 36. Delayed Recall is the number of nouns recited on a fourth trial 20 minutes after trial 3 (best

Table 1. Participant Characteristics

Participant	Age (Years)	Sex	Interval Since Stroke (Months)	Stroke Description	NIH Stroke Scale Score	MMSE Score	Modified Ashworth Score	Resting Motor Threshold (% of machine maximum)
1	79	F	31	R cortical (parietal/ temporal)	2	30	0	60
2	74	M	36	R cortical in distribution of R MCA	6	30	2	52
3	54	M	61	L subcortical (pons)	3	30	1	65
4	50	F	96	R cortical in distribution of MCA and ACA	3	30	2	53
5	66	F	84	R cortical with ICA occlusion	4	30	3	67
6	73	M	192	1st stroke: small L cortical (frontal) (asymptomatic)	4	19	0	48
			35	2nd stroke: R cortical in distribution of MCA (R hemiparesis)				
7	57	M	36	L cortical/subcortical (parietal/corona radiata)	3	25	0	56
8		F	28	1st stroke: L cortical (frontal) (asymptomatic)	6	30	3	73
			16	2nd stroke: R subcortical (pons) (R hemiparesis)	1	29	1+	38
9	69	M	95	R cortical with ICA occlusion				
10	77	F	44	L subcortical (putamen, internal capsule corona radiata)	2	29	2	48

M = male; F = female; NIH = National Institutes of Health; MMSE = Mini Mental State Examination; MCA = middle cerebral artery; ACA = anterior cerebral artery; ICA = internal carotid artery.

possible score = 12). Retention is the number of nouns recalled on trial 4 expressed as a percentage of the higher score on either trial 2 or 3 (best possible score can exceed 100%). The fourth score is the Recognition Discrimination Index. For this, a list of 24 nouns was presented orally to the participant, half of which were on the original list and the other half having similarity to the original list but not being on the list. The Index is calculated as the number of nouns correctly identified from the original list minus the number incorrectly identified (best possible score = 12).

Mood was evaluated with the Beck Depression Inventory–Second Edition (BDI-II),[32,33] requiring the participant to select a response from different depression levels on 21 items. This test was applied once each day (best possible score = 0).

We assessed motor performance in each hand with a finger movement tracking test. For this test, the participant wore an electrogoniometer on the hand and attempted to guide a computer screen cursor as accurately as possible along a displayed target waveform (variable amplitude, 0.4 Hz sine wave) using careful finger extension and flexion movements for each 10-second trial. After 3 practice and 3 test trials with the nonparetic hand, the procedure was repeated with the paretic hand. Performance was quantified with an accuracy index based on the root-mean-square error between the target and the response. The best possible score is 100%. Negative scores occur when the response line falls on the opposite side of the midline from the target.[34] Finger tracking tests were applied at pretest, posttest, and all follow-up tests.

A neurologist examined the participant using the NIHSS (best possible score = 0)[26] to give final clearance for participant's participation in the study and to screen for possible adverse effects not detected by the above tests. The neurologist examination occurred at pretest, posttest, and all follow-up tests.

The participant's self-assessment of his or her response to the treatment was obtained during interviews at posttest and each follow-up test. Participants responded to questions on whether they experienced problems with seizure, headache, neck pain, dental pain, hearing, nausea, abnormal muscle contractions, dizziness, tiredness, sleep, concentration, anxiety, memory, mood, balance, use of nonparetic hand, or any other problem.

rTMS Treatment Instrumentation and Procedure

All 10 participants received rTMS treatment. We did not include a sham treatment because the primary purpose of the safety study was to determine whether there were serious adverse effects from real rTMS treatment. Participants were positioned in a reclining chair in a private outpatient room of the General Clinical Research Center at the University of Minnesota, which was fully equipped with emergency resources if the need arose. Each treatment was video recorded. As finger extension is a significant problem following stroke,[35,36] we selected the extensor digitorum of the nonparetic forearm as our target muscle for stimulation. The recording site for this muscle was determined by applying a low-intensity electrical current from the stimulating electrode of a Cadwell Sierra II 4-channel EMG machine (Cadwell Laboratories, Kennewick, WA). The site that produced a trace finger extension movement of the index finger with the least amount of current was identified as the recording site, and self-adhesive, tab EMG electrodes (Cadwell Laboratories, Kennewick, WA) were secured there.

We also attached electrodes to the biceps brachii muscle of the nonparetic arm and to the extensor digitorum and biceps brachii muscles of the paretic side. To establish the proper intensity for rTMS treatment, the target muscle (nonparetic extensor digitorum) alone was monitored. Once rTMS treatment was initiated, all 4 muscles were monitored to detect possible intracortical spread of excitation.[14]

To determine the optimal brain stimulation site (hotspot) and threshold for eliciting a motor-evoked potential (MEP) in the target muscle, the EMG amplifier sensitivity was set to 50 μV/div with a bandpass filter of 20 to 2000 Hz and a notch filter at 60 Hz. The participant wore a tight-fitting Lycra swim cap (Invista, Inc, Wilmington, DE) to help map out the hotspot. The participant and investigators wore earplugs. A Magstim Rapid magnetic stimulator (Magstim Company Limited, Spring Gardens, UK) with 2 boosters and a 70-mm figure-eight coil were used to deliver the stimulation. The investigator positioned the coil on the contralesional side of the participant's head over the presupposed region of the hotspot with the handle pointing posterolaterally 45 degrees to the mid-sagittal line. The resting motor threshold (RMT) of the contralateral nonparetic extensor digitorum muscle was determined using a stimulation rate of approximately 0.1 Hz. The region was searched and the intensity adjusted to find the lowest intensity that induced MEPs of at least 50 μV peak-to-peak amplitude on at least 3 of 5 trials. The hotspot was then marked, intensity was decreased to 90% of RMT, and rTMS treatment was initiated at this site. The RMT for each participant is shown in Table 1. The mean value in percentage of machine maximum output was 56.0 (±10.5).

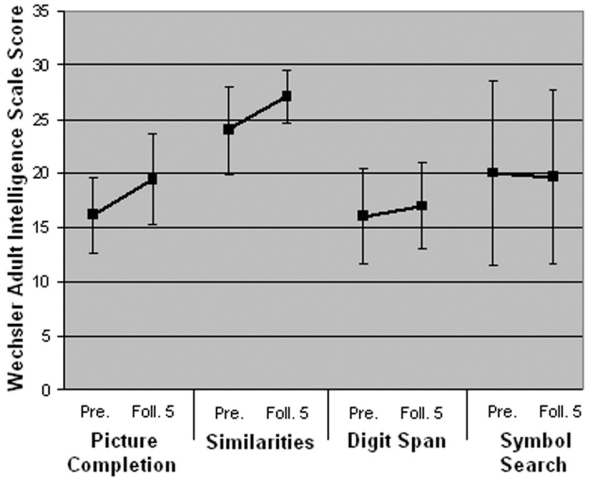

Figure 1. Wechsler Adult Intelligence Scale–Third Edition scores showing essentially no decline in performance (lower scores = decline) from pretest (Pre.) to follow-up (Foll.) test 5 on the 4 subtests.

rTMS treatment involved 2 phases, priming and low-rate stimulation. Priming stimulation consisted of 10 minutes of 6-Hz rTMS at 90% RMT delivered in 2 trains/min with 5 s/train and 25-second intervals between trains (total = 600 priming pulses). Immediately following priming, low-rate stimulation commenced, consisting of an additional 10 minutes of 1-Hz rTMS at 90% RMT without interruption (total = 600 low-frequency pulses).

Data Analysis

We analyzed the safety of this study by (1) observing for any seizures, (2) plotting individual and group data for each dependent measure and examining for any decline at posttest or follow-up compared to pretest, (3) recording clinical assessments by the neurologist, and (4) recording any and all adverse responses reported by participants during their interviews.

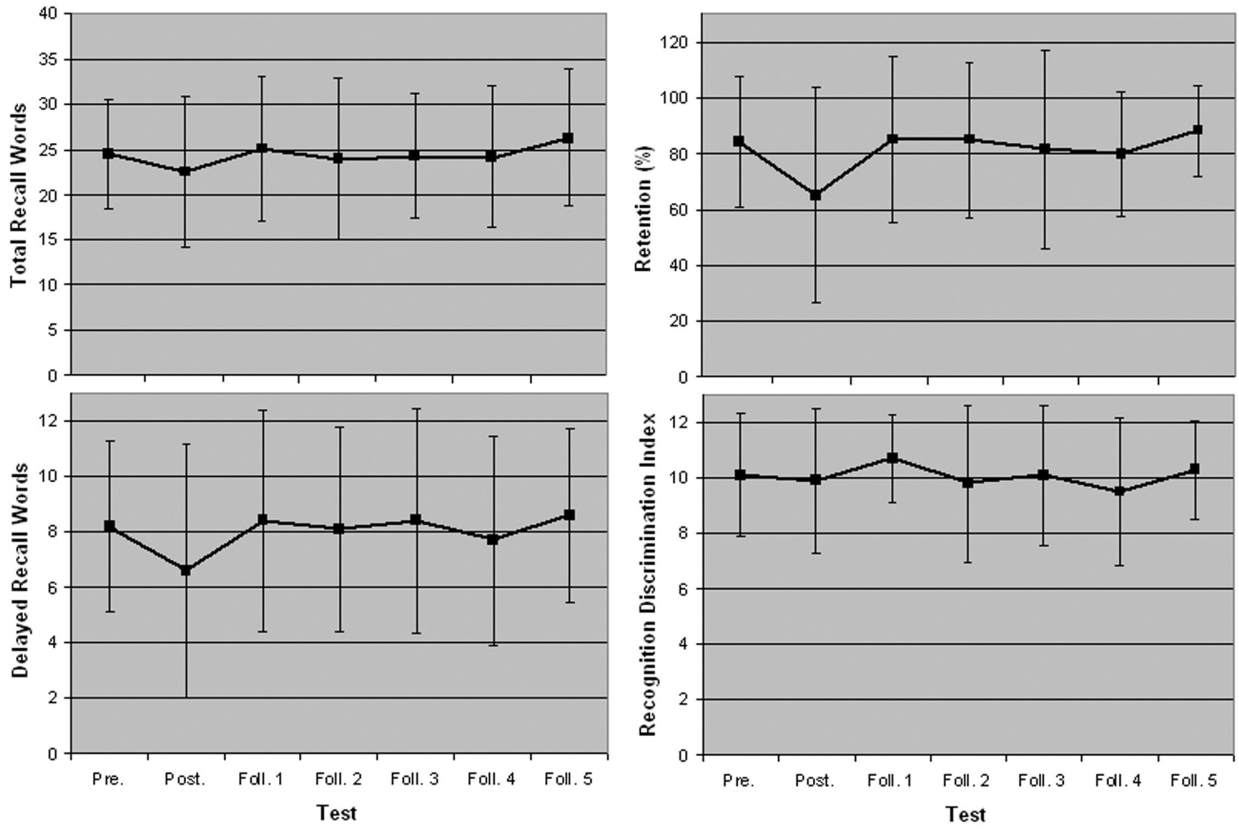

Figure 2. Hopkins Verbal Learning Test–Revised scores showing a decline in performance (lower scores = decline) from pretest (Pre.) to posttest (Post.) on 3 of the 4 test components but with a return to pretest values on follow-up (Foll.) tests, suggesting a transient adverse treatment effect on verbal memory.

RESULTS

No seizures were observed in any participants. WAIS-III subtests for neurocognitive function showed no decrease in group performance at follow-up 5 compared to pretest (Fig. 1).

HVLT-R tests of day-to-day neurocognitive function showed a decline in performance on each of the 4 parameters from pretest to posttest (Fig. 2). Inspection of individual scores revealed that the impairment of word-list memory occurred in all individuals, including those with left hemisphere lesions and right hemisphere lesions. However, at follow-up 1, all scores returned to pretest levels, where they stayed for the remaining follow-up days.

Measurement of mood using the BDI-II showed no adverse response (no increase) at each follow-up test compared to the pretest (Fig. 3). We interpret the appearance of improvement in mood as a possible release from the heightened anxiety before treatment, stemming from the risks identified to each participant in advance.

Figure 4 plots the group finger-tracking performance for the paretic and nonparetic hands. No impairment of motor control was evident at posttest or follow-up tests compared to pretest in either hand.

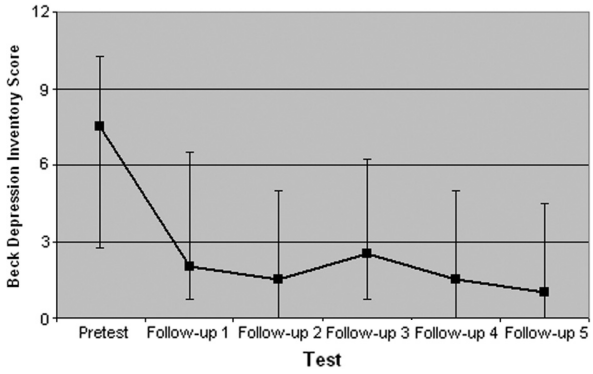

Figure 3. Beck Depression Inventory–Second Edition scores showing no decline in mood (higher scores = decline) from pretest to follow-up tests, indicating no adverse treatment effect on mood.

Beyond these group assessments, we also assessed individual responses in the above dependent measures and found no responses suggestive of an adverse effect in

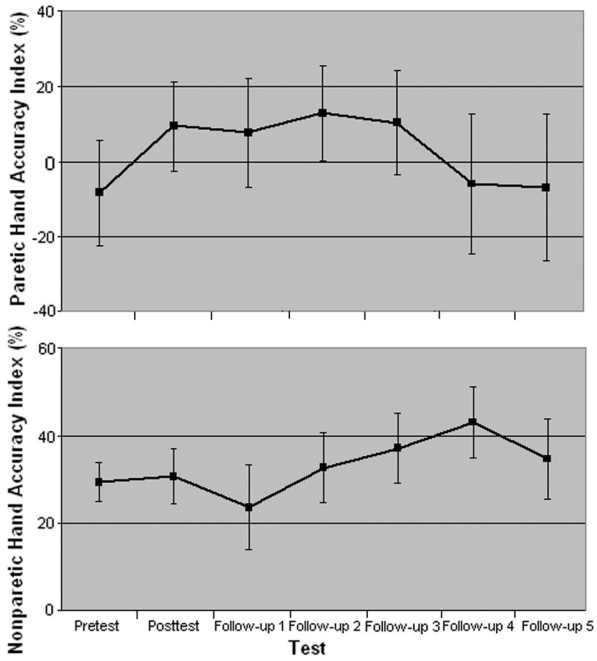

Figure 4. Finger-tracking accuracy in paretic hand (upper) and nonparetic hand (lower) showing no decline in performance (lower scores = decline) from pretest to posttest or follow-up tests, indicating no adverse treatment effect on motor control.

any one person. Furthermore, the neurologist assessment using the NIHSS at posttest and each follow-up test indicated no change from each participant's pretest measurement. Participants' self-assessment during interviews of their response to treatment indicated that 4 individuals (#3, 4, 5, 10) reported a mild headache on the treatment day or at follow-up 1. One (#9) reported mild neck pain on the treatment day. One (#3) reported more sleep than normal on the night of the treatment. One (#2) reported less sleep, mild nausea, and mild anxiety on the night of the treatment. Investigators observed that nearly all 10 participants showed tiredness at the end of the treatment day. One participant (#7) reported a favorable decrease in his normal restlessness and also an improvement in his speech, which was corroborated by investigators. One participant (#8) remarked on her noticeable decrease in spastic finger flexor tone (resistance to passive extension), which was also observed by investigators at follow-up 1, but the effect subsided thereafter.

DISCUSSION

This study is the first to examine the safety of a single treatment of 6-Hz primed low-frequency rTMS in people with stroke. We studied only safety because it would be premature to conduct an efficacy study involving serial treatments without first examining for adverse effects from a single treatment. Our main finding was that no individuals experienced a seizure. We reduced the risk of inducing a seizure by applying the stimulation to the contralesional hemisphere. Furthermore, whereas Iyer et al[23] followed priming with low-frequency rTMS at 115% of threshold in their healthy participants, we applied a more cautious intensity at 90% of threshold. It is not yet clear whether this subthreshold level of treatment is too conservative to be effective for down-regulation of excitability in the contralesional hemisphere with consequent up-regulation in the ipsilesional hemisphere.

Neurocognitive testing showed an impairment of word-list learning/memory (HVLT-R) immediately following the treatment (Fig. 2). Although our work did not include sham rTMS, our finding is consistent with the work of Grafman et al.[37] They applied 20-Hz rTMS in trains of 500 ms duration at an intensity of 120% of motor threshold (abductor pollicis brevis) during the presentation of word lists to healthy participants. The stimulation was applied at specified cortical sites (dorsolateral, temporal, occipital) in both hemispheres. Compared to sham treatment, they found that rTMS resulted in a significant reduction in word-list recall. No significant interhemispheric differences occurred. They suggested that rTMS-induced impairment of word recall may stem from its disruptive effect on cortical semantic and contextual consolidation processes leading to more shallow stimulus encoding. They did not report how long the effect lasted. Their finding from rTMS to multiple cortical sites, combined with our similar finding at M1, suggests that impaired word-list recall may be a side effect of rTMS across widespread stimulation sites. Importantly, our results indicate that the effect is quite transient.

WAIS-III testing for perceptual organization, working memory, verbal comprehension, and processing speed showed no treatment-induced impairment. Nor did participant mood, as measured by BDI-II scores. Motor control testing showed no treatment-induced impairment of finger-tracking performance in either hand.

Individual clinical assessment by a neurologist showed no treatment-induced impairments. Although there were common reports of tiredness on the day of treatment and occasional reports of headache, anxiety, nausea, and altered sleep, it is not clear whether these complaints resulted from the actual rTMS or possibly from other nonspecific treatment conditions, such as wearing a tight-fitting swim cap or keeping the head perfectly still for the lengthy treatment. Indeed, Anderson et al[38] found an equivalent report rate of headache in healthy individuals receiving real rTMS compared to sham rTMS. We did not include a sham group because our primary concern was whether 6-Hz primed low-rate rTMS would produce a seizure, which stems from the inherent risk of

seizures during brain stimulation[14] combined with the heightened propensity for seizures in people with stroke.[24] Sham stimulation would not lend value to answering our primary concern.

In summary, because there were no seizures and the observed adverse effects were transient and did not impact daily function, we conclude that 6-Hz primed low-frequency rTMS treatment to the contralesional hemisphere was safe for the participants in this study. This finding invites further work with serial treatments involving priming. Based on work showing that the effect of low-rate stimulation on neural excitability is potentiated by the inclusion of priming,[23] the possibility is real for achieving greater treatment effects in people with stroke by preceding low-rate stimulation with priming stimulation. But progress must occur cautiously as subtle differences in individual characteristics, such as infarct volume, location, and so on, from the people in this study may be a critical factor. Further studies are now needed to examine the efficacy, mechanisms, and safety of serial rTMS treatments *with priming* to determine whether the magnitude and duration of treatment effects can be extended beyond those demonstrated by Fregni et al[17] *without priming*.

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