Transcranial magnetic brain stimulation modulates blepharospasm

A randomized controlled study

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ABSTRACT

Background: Benign essential blepharospasm (BEB) is a common form of focal dystonia. Besides pathology in the basal ganglia, accumulating evidence suggests pathologic changes in the anterior cingulate cortex (ACC).

Methods: This is a randomized, sham-controlled, observer-blinded prospective study. In 12 patients with BEB, we evaluated the effects of a 15-minute session of low-frequency (0.2 Hz) repetitive transcranial magnetic stimulation (rTMS) over the ACC with stimulation intensities at 100% active motor threshold with 3 stimulation coils: a conventional circular coil (C-coil), a sham coil (S-coil), and a Hesed coil (H-coil, which allows stimulation of deeper brain regions. Primary outcome was the clinical effects on BEB (blink rate, number of spasms rated by a blinded physician and patient rating before, immediately after, and 1 hour after stimulation); secondary outcome was the blink reflex recovery curve.

Results: Subjective stimulation comfort was similar for each coil with no stimulation-associated adverse events. Stimulation with the H- and C-coils resulted in a significant improvement in all 3 outcome measures and was still detectable in physician rating and patient rating 1 hour after stimulation. S-coil stimulation had no effects. The active motor threshold was significantly lower for the H-coil compared to the other 2 coils.

Conclusions: rTMS could be used as a therapeutic tool in BEB. Further studies will be necessary to show whether repeated stimulation applications result in lasting clinical effects.

Classification of evidence: This study provides Class II evidence that for patients with BEB, H- and C-coil rTMS is safe and improves clinical symptoms of BEB immediately and 1 hour after stimulation. *Neurology*® 2010;75:1465–1471

GLOSSARY

ACC = anterior cingulate cortex; **BEB** = benign essential blepharospasm; **BRR** = blink reflex recovery; **C-coil** = circular coil; **H-coil** = Hesed coil; **MC** = motor cortex; **OO** = orbicularis oculi; **PMC** = premotor cortex; **rTMS** = repetitive transcranial magnetic stimulation; **S-coil** = sham coil; **SMA** = supplementary motor area; **SNr** = substantia nigra pars reticulata.

Benign essential blepharospasm (BEB) is a common form of focal dystonia and is characterized by excessive involuntary closure of the eyelids.[1] It considerably impacts the health status of the afflicted patient and can lead to significant depression.[2] Despite normal visual acuity, in severe cases, patients are functionally blind.

There is no etiologic therapy for BEB. Currently, the first-line therapy is chemodenervation with botulinum neurotoxin injections. However, this therapy is purely symptomatic, and the effect of the therapy lasts only about 10 weeks.[3] Recently, experimental therapeutic approaches have been implemented with rTMS in focal hand dystonia and other movement disorders.[4,5]

Traditionally, dystonia has been considered a disorder caused by the basal ganglia, since patients with secondary dystonia commonly exhibit lesions within basal ganglia structures. Current concepts of dystonia suggest aberrant brain plasticity and a lack of surround inhibition

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Study funding: Supported by the NIH/NINDS Human Motor Control Section and the Max Kade Foundation, New York (G.K.)

Disclosure: Author disclosures are provided at the end of the article.

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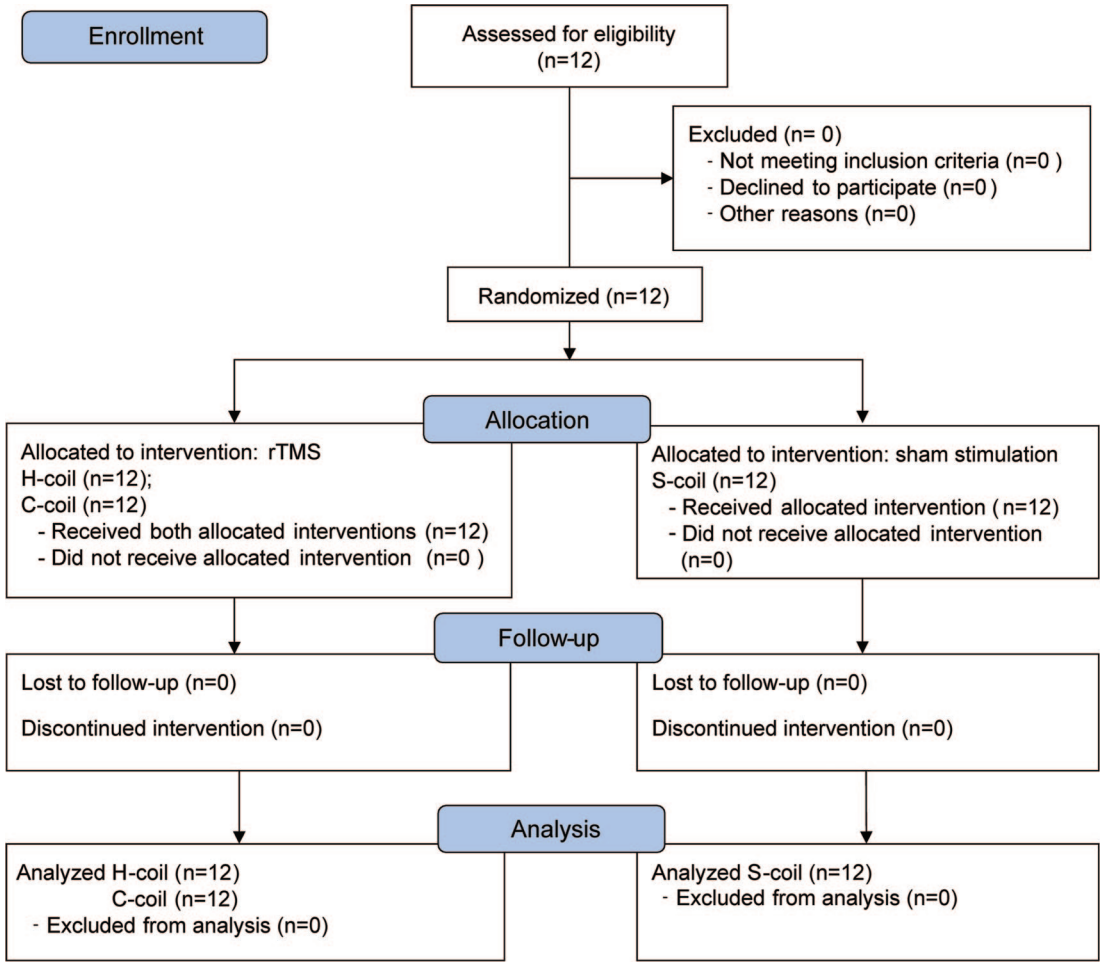
in the motor system.[1] In BEB, earlier studies suggested enhanced cortical excitability, notably in the ACC. PET studies have shown increased glucose uptake in the right posterior and left ACC[6,7] and a fMRI study demonstrated eye-closure–related brain activity in the rostral ACC.[8] Neuroanatomic findings in the monkey indicated that efferents from the supplementary motor areas (SMA) and ACC project bilaterally to upper facial muscles.[9] Hence, reducing cortical excitability in this region may reduce abnormal plasticity and improve symptoms of BEB. In a pilot study, we applied rTMS to reduce cortical excitability over motor (MC), premotor (PMC), SMA, and ACC areas in patients with BEB and found that rTMS over the ACC had the best clinical effects.[10]

METHODS

Primary research question. We conducted the present study to examine whether clinical and electrophysiologic effects of rTMS over the ACC in patients with BEB can be demonstrated in a sham-controlled design, using 3 different stimulation conditions. We stimulated with a 9-cm standard circular coil (C-coil); an H-coil (Hesed coil), a specially designed coil that allows stimulation of deeper brain regions; and a sham coil (S-coil).

Patients. In this prospective, randomized, sham-controlled, observer-blinded study, according to our sample size calculation, 12 right-handed patients with BEB (4 men and 8 women, age 61.4 ± 8.3 years, duration of disease 7.8 ± 5.0 years, last treatment with botulinum toxin 6.7 ± 3.6 months, Blepharospasm Disability Scale 12.8 ± 3.8, Blepharospasm Movement Scale 6.8 ± 2.0, Severity Rating Scale 2.2 ± 0.4)[11] were recruited from our movement disorder clinic between April and November 2007, having met the following inclusion criteria: clinical diagnosis of BEB or cranial dystonia with eyelid involvement (Meige syndrome); age between 18 and 85 years; normal findings in the medical history, physical, and neurologic examinations (except for BEB); no prior use of neuroleptics; and no treatment with antidepressants, antiepileptic medication, anticholinergic drugs, or muscle relaxants within the past 4 weeks. All patients except patient 7 had a history of botulinum toxin injections with good (n = 8) or moderate (n = 3) responses; however, the last injection was >3 months prior to participation. Patients received general information about stimulation

Figure 1 Consort flow diagram



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techniques and coils but no specific information before each particular experiment.

Standard protocol approvals, registrations, and patient consents. Before inclusion in the study, written informed consent was obtained from all patients. A signed patient consent-to-disclose form was obtained for videos of any recognizable patient. This study was approved by the NIH Institutional Review Board.

Procedure. Every patient came for 3 visits, each separated by at least 2 days. In random order (patients were randomly assigned by the primary investigator to 1 of 6 possible treatment orders by having the patient draw a slip from a hat), we performed rTMS over ACC with 3 different stimulation conditions (figure 1).

Stimulation technique. ***rTMS.*** Earlier studies reported suppressive effects on cortical excitability at frequencies as low as 0.2 and 0.3 Hz.[5,12] We applied rTMS with 0.2 Hz, 180 stimuli, 15 minutes per session, with a stimulator output of 100% active motor threshold, which was assessed at the tibialis anterior muscle with the circular coil for the C-coil and S-coil conditions and with the H-coil for the H-coil condition. rTMS was delivered to the ACC in each session. Patients had ear protection throughout all stimulation procedures. As defined earlier, to determine the stimulation site for ACC, the coil was placed over Fz and then moved over the midline of the brain in 0.5-cm steps anteriorly, until the point of maximum motor evoked potential in the orbicularis oculi (OO) muscle (with a latency of 6–8 msec) was reached (about 3.5 cm medial and 5.5 cm anterior to MC).[13]

Stimulation conditions. ***C-coil stimulation.*** After determining the active motor threshold and the hotspot for the ACC with the C-coil (counterclockwise current), rTMS was delivered through the C-coil connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The C-coil was placed tangentially to the scalp with the handle pointing forward and the upper rim touching the stimulating point.

S-coil stimulation. After determining the active motor threshold and the hotspot for ACC with the C-coil, the coil was disconnected from the Magstim. To provide the same stimulation sound, we connected another standard coil to the Magstim through which we delivered rTMS. Whereas the S-coil remained on the patient's head in the identical manner as during C-coil stimulation, the connected coil providing the stimulation sound was placed behind the patient and rotated 90° away from the scalp.[14] In each stimulation condition, the Magstim was placed behind the patient and not visible to him or her.

H-coil stimulation. The H-coil is a specially designed magnetic coil that was developed to reach deep brain regions without increasing the electrical field intensity in the superficial cortical regions. Design principles, theoretical considerations, and safety data of the H-coils are described in earlier studies.[15–18] Briefly, different coil elements are specifically positioned to generate summation of magnetic fields tangential to the surface in a depth of about 4 cm (postero-anterior current). After determining the active motor threshold and the hotspot for ACC with the H-coil, rTMS was delivered. The H-coil was connected to the same Magstim 200 magnetic stimulator.

Outcome measures. The primary outcome measure was the clinical effects on BEB symptoms. Five-minute videos of eye blinks before and after stimulation were assessed by a blinded rater. The secondary outcome was subjective rating by the patients. The primary and secondary outcome measures tested clinical changes in BEB. The blink reflex recovery (BRR) was used as a third measure to evaluate neurophysiologic correlates to the clinical endpoint measures. Evaluation was performed before (T1), immediately after (T2), and 1 hour after stimulation (T3). After 1 hour, no further systematic evaluation was performed. Further, patients rated the stimulation comfort for each stimulation in a 7-point nominal scale: 1) very comfortable, 2) comfortable, 3) slightly comfortable, 4) indifferent, 5) slightly uncomfortable, 6) uncomfortable, 7) very uncomfortable.

Physician rating. An investigator who was not present during the experiments and blinded to the intervention rated the videos. Clinical evaluation was expressed in percent change before and after stimulation, including eye blink rate, number of sustained blinks, and time of eye closure. An eye blink was defined as any visible, bilateral, and synchronous contraction of the OO muscle, causing eyelid drop. Blink rate was expressed as blinks per minute. Sustained spasms of the OO muscle were not considered blinks and were counted separately. The rater counted the time (seconds) of eye closure with a stopwatch whenever blinks caused prolonged eye closure (eyes shut >2 seconds).

Patient rating. Patients rated their symptoms before and after stimulation in a 7-point nominal scale: 1) excellent, 2) very good, 3) good, 4) average, 5) slightly worse than usual, 6) bad, 7) very bad.

Blink reflex recovery. Subjects opened their eyes gently during stimulation and stayed in a relaxed position. Paired electrical stimuli (conditioning and test) were delivered at an interstimulus interval of 0.2 seconds and EMG amplitudes were recorded from the OO muscle. Stimulus intensity was 3 times the threshold of the R2s response (lowest intensity with 5 of 10 R2s responses). Responses with artifacts due to involuntary movements were rejected. To avoid habituation, a rest period of 25–35 seconds was maintained between trials. The low-pass filter was set at 3 kHz and the high-pass filter at 1 Hz. All responses were stored digitally. In an offline analysis procedure performed fully automatically, reflex responses were digitally bandpass filtered within a range of more than 100 Hz to minimize DC offsets and slow eye drifts and below 900 Hz to reduce the high-frequency noise. Then, the responses were full wave-rectified and we computed the average of 6 trials. Peak amplitude of R2 was calculated within a window from 30 to 60 msec to avoid stimulation artifacts. We obtained R2 recovery values by dividing the

Table Mean treatment effects for the 3 outcome measures, stimulation comfort, and active motor threshold for each coil

	S-coil, mean ± SD[a]	C-coil, mean ± SD[a]	H-coil, mean ± SD[a]	*F*	*p*
PhysR	58.1 ± 7.6	45.1 ± 5.5	44.8 ± 5.3	5.382	0.023
PatR	3.8 ± 0.34	2.6 ± 0.27	2.5 ± 0.33	7.478	<0.01
BRR	0.53 ± 0.04	0.39 ± 0.04	0.43 ± 0.035	7.832	<0.01
aMT	66.5 ± 1.2	67.3 ± 1.7	57.8 ± 1.7	17.4	<0.01
StimC	2.83 ± 0.21	3.25 ± 0.3	3.25 ± 0.13	1.21	0.32

Abbreviations: aMT = active motor threshold; BRR = blink reflex recovery; C-coil = standard circular coil; H-coil = Hesed coil; PatR = patient rating; PhysR = physician rating; S-coil = sham stimulation; StimC = stimulation comfort (low values indicate high StimC).
[a] Means show averaged effect after treatment (T2+T3), low values indicate high treatment effects.

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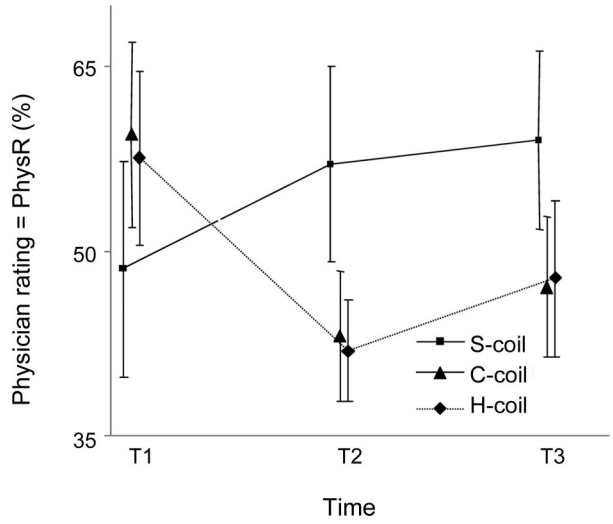
Figure 2 Physician rating

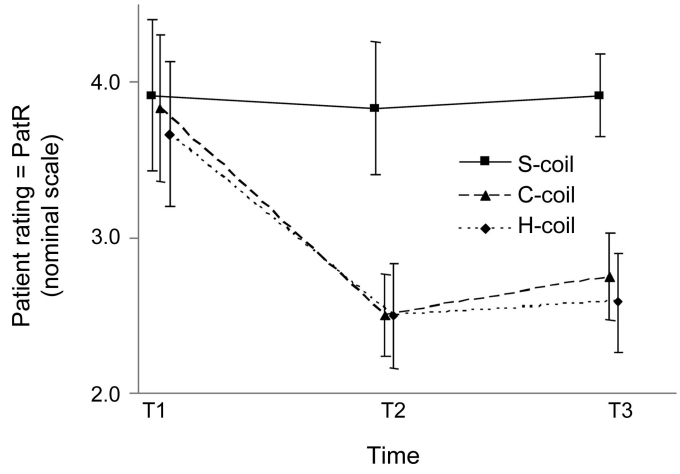


C-coil = stimulation with the standard circular coil; H-coil = stimulation with the Hesed coil; S-coil = stimulation in the sham condition; T1 = baseline, evaluation before stimulation; T2 = evaluation immediately after stimulation; T3 = evaluation 1 hour after stimulation. Data points are staggered to visually separate the 3 coils.

size of R2test [R2t] by the size of conditioning response [R2c]. BRR was measured for both eyes separately.

Statistics. Since physician rating was measured in percentages, an arc sine transformation was used prior to further statistical testing. We conducted a mixed models analysis using time and stimulation technique as repeated factors adjusted for baseline values, and subjects as the random factor. According to Akaike information criterion, repeated measurements were modeled using a Toeplitz covariance structure for the outcome measure patient rating, and using unstructured covariance for physician rating and BRR. Interaction effects between stimulation technique and time were dropped in case of nonsignificance. In case of significant main effects, post hoc pairwise comparisons were corrected using Fisher least significant difference procedure in accordance with the closed test principle; i.e., post hoc comparisons were declared nonsignificant if the global p value of the main effect (testing equality of all 3 simulation techniques simultaneously) was nonsignificant, but carried out without further correction in case of a significant global main effect. SPSS version 15.0 for Windows was used for statistical computations. The 2-tailed significance level was set at 0.05. To examine possible carryover effects of coils, the sequence effects of 2 consecutive coils were compared using unpaired t tests (e.g., H-C vs C-H). To this end, a treatment effect for each coil was computed using the following formula: Coil effect = TP1 − (TP2 + TP3)/2.

Figure 3 Patient rating



C-coil = stimulation with the standard circular coil; H-coil = stimulation with the Hesed coil; S-coil = stimulation in the sham condition; T1 = baseline, evaluation before stimulation; T2 = evaluation immediately after stimulation; T3 = evaluation 1 hour after stimulation.

RESULTS Patients tolerated stimulation with all 3 coils with no stimulation-related significant adverse events. Due to institutional review board requirements for H-coil stimulation, we measured the blood pressure, heart rate, and respiratory rate before and after stimulation with each coil in the first 6 patients. Additionally, hearing tests were performed in the first 6 patients before and after stimulation. There were no relevant changes in any of these measures (data not shown). The stimulation comfort was similar for each coil (table) ($F2 = 1.21$; $p = 0.32$); however, active motor threshold was lower for the H-coil compared to the other coils ($F2 = 17.4$; $p < 0.01$).

Clinical and electrophysiologic improvements were similar for both the C- and H-coil stimulation, but there were no improvements in the sham condition (figures 2–4). In detail, the mixed model analysis showed the following results: for physician rating, we found a main effect of stimulation technique, $F_{2,11.002} = 5.382$; $p = 0.023$, but no main effect of time between T2 and T3, $F_{1,11} = 1.475$; $p = 0.250$, indicating that the stimulation effect lasted until T3. Pairwise comparisons revealed a stimulation effect of the C- and H-coil compared to the S-coil ($p = 0.008$ and $p = 0.024$). However, no difference was found between the effects of the C- and the H-coil ($p > 0.05$).

For patient rating, we found a main effect of stimulation technique, $F_{2,32.544} = 7.478$; $p = 0.002$, but no main effect of time between T2 and T3, $F_{1,13.305} = 0.203$; $p = 0.659$, indicating that the stimulation effect lasted until T3. Pairwise comparisons revealed a stimulation effect of the C- and H-coil compared to the S-coil ($p = 0.007$ and $p = 0.001$). No difference was found between the effects of the C- and H-coil ($p > 0.05$).

BRR was measured separately for each eye. Since BRR was similar in both eyes at T1, T2, and T3, results were calculated with a mean of both eyes for each measurement. We found a main effect of stimulation technique $F_{2,11.000} = 7.832$; $p = 0.008$, and also a main effect of time between T2 and T3, $F_{1,11.001} = 17.899$; $p = 0.001$, indicating that the stimulation effect did not last until T3. Pairwise comparisons revealed a stimulation effect of the C- and H-coil compared to S-coil ($p = 0.005$ and $p =$

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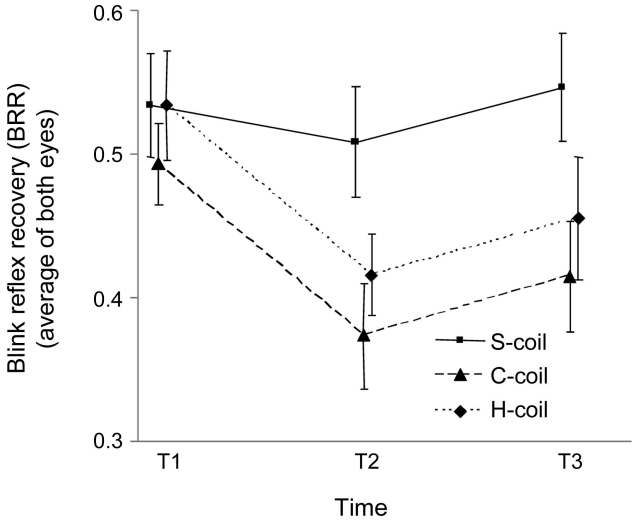
Figure 4 Blink reflex recovery



C-coil = stimulation with the standard circular coil; H-coil = stimulation with the Hesed coil; S-coil = stimulation in the sham condition; T1 = baseline, evaluation before stimulation; T2 = evaluation immediately after stimulation; T3 = evaluation 1 hour after stimulation. H-coil and C-coil showed a main effect of time.

0.007). No difference was found between the effects of C and H ($p > 0.05$).

Comparisons between all pairs of consecutive coils were not different ($p > 0.05$, uncorrected), indicating that carryover effects are unlikely in our experimental setting.

DISCUSSION Contrary to the classic view that the primary motor cortex exclusively controls facial movements, accumulating evidence suggests that significant eyelid control with reduced inhibition and abnormal cortical plasticity in the mesial frontal region, notably the ACC, plays an important role in the pathophysiology of BEB.[6,8,9,19] Models of dystonia suggest disinhibited thalamo-frontal projections due to increased GABA-mediated striato-pallidal inhibition (via the direct pathway) and reduced pallido-thalamic inhibition. This results in increased cortical excitability and disorganized cortical representation. Low-frequency subthreshold repetitive TMS has been well-documented to reduce cortical excitability noninvasively.[5,20] This study was performed to test whether rTMS compared to sham stimulation improves clinical symptoms and normalizes electrophysiologic characteristics in patients with BEB. We found significant improvements with the C- and the H-coils immediately after stimulation for all 3 outcome measures and 1 hour after stimulation in physician rating and patient rating. S-coil stimulation had no effect in any of the outcome measures. Since S-coil stimulation produced the same sound compared to the other coils and the stimulation procedure was performed identically for all coils, most patients whom we asked could not determine which stimulation was the sham treatment immediately after each stimulation.

Our sample size was small (because we anticipated large effects in our power analysis) and differences in baseline values were seen between coils in all 3 outcome measures, especially in physician rating. Additionally, in the sham stimulation condition changes over time were seen in both directions (i.e., in physician rating and BRR). Although all these differences were not significant, certain variability exists in all tests, smallest in patient rating. However, even with this small sample size, we obtained significant results in all—subjective and objective—outcome measures, indicating that the stimulation effect is quite strong and relevant. Carryover effects are unlikely to account for baseline variability, as stimulation effects started to decrease within the first hour, visits were separated by at least 2 days, and statistically, we did not see interactions between study days.

Because the ACC region is located deeper in the brain than the primary or secondary motor areas, we also tested the stimulation effects of the H-coil. H-coils were designed to achieve effective stimulation of deep brain regions without increasing the intensity to levels that stimulate cortical regions to a much higher extent and possibly cause undesirable side effects.[17] An electrical field induced by any coil is always greater in superficial cortical regions; however, its decrease within the brain as a function of the distance from the coil is markedly slower for the H-coil. This was previously confirmed on a phantom brain model.[15] Therefore, it is reasonable that in our study, stimulation with the H-coil had similar effects compared to a standard coil, even with significantly lower stimulation intensities. Since the H-coil is a novel development with only a few published clinical trials and safety data,[16,18] we measured vital signs and hearing thresholds before and after stimulation with each coil in the first 6 patients. Additionally, we asked patients to report any side effects including pain, anxiety, and changes in mood or dizziness. None were reported and patient rating of stimulation comfort was similar for all 3 coils. To stimulate the ACC, in a previous study, we used stimulation intensities based on the motor threshold of the OO muscle (we stimulated with 90% resting motor threshold of the OO, which was 60.6% stimulator output).[10] In this study, we used the tibialis anterior muscle to determine stimulation intensity due to practical reasons. Determining the active motor threshold in the OO is generally possible, but much more elaborate and sometimes bothersome for the patient. The effective stimulation intensity in this study was slightly lower with the H-coil and higher with the C-coil,

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compared to the stimulation intensity used in our last study (table).

rTMS also changed BRR in our patients with BEB to more physiologic levels after C-coil and H-coil stimulation. Diminished BRR habituation, which indicates the state of excitability of facial motoneurons and bulbar interneurons, has been well-documented in patients with BEB and other forms of dystonia.[2,21] An animal model of blepharospasm suggests that a predisposing condition to develop BEB could be a loss of dopamine-containing neurons in the substantia nigra pars compacta causing a decreased inhibition in the blink circuit.[22] The substantia nigra pars reticulata (SNr), the basal ganglia output structure for the eyelids, has an inhibitory influence on trigeminal blink reflex excitability via the superior colliculus and the nucleus raphe magnus.[23] Reducing cortical excitability may modulate corticobasal ganglia-thalamo-frontal loops that include the substantia nigra. Therefore, by modulating the excitability of SNr, the pathologic decreased 5HT projections located on blink reflex interneurons within the spinal trigeminal complex would resume their physiologic activity, which could explain the physiologic changes in BRR after cortical stimulation, as found in our study. It is conceivable that basal ganglia dysfunction can affect the excitability of mesial frontal cortical areas and of the blink reflex circuit in the brainstem. This study demonstrates that rTMS over ACC in a sham-controlled design improves symptoms of BEB and changes pathologic electrophysiologic measures. The C- and H-coils showed similar effects; however, as the H-coil requires lower stimulation intensities for deep brain regions, it might be a better choice with which to stimulate the ACC and could provide a therapeutic tool to treat BEB. However, compared to the well-established and long-lasting effects of botulinum toxin and in view of the time-consuming nature of rTMS and its short-lasting effects, it should not be used in clinical routine at this stage. Further studies will be needed to show whether repeated rTMS applications applied over a longer time period results in lasting clinical effects.

AUTHOR CONTRIBUTIONS

Study concept and design: Drs. Hallett, G. Kranz, and Shamim; acquisition of data: Drs. G. Kranz, Shamim, and Lin; analysis and interpretation of data: Drs. G. Kranz, Hallett, Shamim, and G.S. Kranz; drafting of the manuscript: Drs. G. Kranz, Hallett, Shamim, and G.S. Kranz; critical revision of the manuscript for important intellectual content: Drs. Hallett, Shamim, Lin, and G.S. Kranz; statistical expertise: G.S. Kranz; administrative, technical, or material support: Drs. Shamim, Lin, and Hallett; study supervision: Dr. Hallett.

ACKNOWLEDGMENT

Dr. G. Kranz has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Devera Schoenberg, MSc (NIH), for help in editing the manuscript; and Georg Heinze, PhD (Section of Clinical Biometrics, Core Unit of Medical Statistics and Informatics, Medical University of Vienna), for statistical advice. Trial center and sponsor: Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health.

DISCLOSURE

Dr. Kranz has received funding for travel from the NIH/NINDS and Ipsen; has received speaker honoraria from Allergan, Inc., Ipsen, and Merz Pharmaceuticals, LLC; and has received research support from the Max Kade Foundation and the NIH/NINDS (Intramural Grant). Dr. Shamim receives research support from the NIH/NINDS (Intramural Grant) and holds stock in Amgen, Pfizer Inc., and Medtronic, Inc. Dr. Lin has received research support from the NIH/NINDS (Intramural Grant). G.S. Kranz reports no disclosures. Dr. Hallett serves as Chair of the Medical Advisory Board for and receives funding for travel from the Neurotoxin Institute; serves as Chair of the Medical Advisory Board of the Benign Essential Blepharospasm Foundation; serves on editorial advisory boards for *Clinical Neurophysiology* (Editor-in-Chief), *Western Hemisphere*, *Brain*, *Acta Neurologica Scandinavica*, *Journal of Clinical Neurophysiology*, *Italian Journal of Neurological Sciences*, *Medical Problems of Performing Artists*, *Annals of Neurology*, *Neurology and Clinical Neurophysiology*, *The Cerebellum*, *NeuroRx*, *Current Trends in Neurology*, *Faculty of 1000 Biology*, *European Neurology*, *Faculty of 1000 Medicine*, *Brain Stimulation*, *Journal of Movement Disorders* (Korea), and *World Neurology*; may accrue revenue on patents re: Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders and Coil for magnetic stimulation and methods for using the same; receives royalties from publishing from Blackwell Publisher, Cambridge University Press, Springer Verlag, Taylor & Francis Group, Oxford University Press, John Wiley & Sons, and Elsevier; receives research support from Ariston Pharmaceuticals, NIH/NINDS (Intramural Program), and the US Department of Defense (Army); has received license fee payments from the NIH (from Brainsway) for licensing the patent for the H-coil; and with his spouse held stock in Agilent Technologies, Amgen, Amylin Pharmaceuticals, Merck & Co., Monsanto Co. New Del, Sanofi-Aventis, Coventry Health Care Inc., Sigma Aldrich Corp., Warner Chilcott Ltd., Pfizer Inc., Genentech, Inc., United Health Group, St. Jude Medical, and Eli Lilly and Company.

Received December 30, 2009. Accepted in final form July 1, 2010.

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