Transcranial Magnetic Stimulation of the Cerebellum in Essential Tremor

A Controlled Study

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**Background:** Growing evidence implicates an overactivity of the cerebellum in the pathophysiology of essential tremor. In a small series of patients, we explored the acute effects and therapeutic possibilities of low-frequency repetitive transcranial magnetic stimulation (rTMS) of the cerebellum in patients with essential tremor in a double-blind, crossover, placebo-controlled design.

**Methods:** Ten patients with essential tremor underwent an active and a sham rTMS session, at a 1-week interval. The rTMS was performed with a focal double 70-mm butterfly coil (maximum peak field of 2.2 T) applied 2 cm below the inion. Each session consisted of 30 trains of 10-second duration separated by 30-second pauses, at 100% of the maximum output intensity and at 1-Hz frequency. Major evaluation outcomes were the score on the Tremor Clinical Rating Scale and accelerometric recordings obtained before (−5 minutes), immediately after (+5 minutes), and 1 hour after (+60 minutes) each rTMS session. Both clinical and accelerometric measurements were obtained by a blinded neurologist.

**Results:** On the +5-minute assessment, active rTMS produced a notable tremor improvement compared with sham rTMS, as evidenced by a significant reduction in scores on the clinical rating scale and accelerometric values. At +60 minutes, no clinical or accelerometric benefit was evidenced. No adverse effects of rTMS were observed.

**Conclusions:** This exploratory study of the potential therapeutic properties of rTMS on essential tremor showed an acute antitremor effect. Further investigation in search of a more lasting benefit is warranted.

Arch Neurol. 2002;59:413-417

Repeat transcranial magnetic stimulation (rTMS) has become a useful noninvasive tool to study the physiology of the human cortex. In healthy control subjects, fast rTMS at a frequency of 5 Hz and higher induces an increase in cortical excitability beyond the time of stimulation, whereas low-frequency rTMS at 1 Hz gives rise to a lasting decrease in cortical excitability. Several recent reports have suggested that this modulation of cortical excitability by rTMS might have therapeutic potential in patients with major depression, Parkinson disease, or focal dystonia.

Essential tremor (ET), characterized by tremor during the maintenance of posture and active movement, is one of the most common movement disorders. Pharmacologic treatment is poor and often unsatisfactory, usually failing to achieve adequate tremor control. There is a clear need for new therapies for ET.

Evidence of the overactivity of deep nuclei and cerebellar cortex in the pathophysiology of ET is growing. In this preliminary exploratory study, we evaluated the acute effects and therapeutic possibilities of low-frequency rTMS over the cerebellum in patients with ET with a double-blind, crossover, placebo-controlled design.

**RESULTS**

**CLINICAL EXAMINATION AND MOTOR TASK PERFORMANCE (TCRS PARTS 1 AND 2)**

The analysis of variance showed significant time \( (P = .001) \) and interaction (treatment × time) \( (P = .007) \) effects. Treatment effect showed a tendency toward significance \( (P = .09) \).

Although no significant differences in TCRS scores between the interventions were observed at baseline (sham, 23.8 ± 13.2; active, 25.2 ± 11.8) and at +60 minutes (sham, 23.4 ± 13.9; active, 22.9 ± 11.1), the TCRS scores were significantly lower at +5 minutes after...
PATIENTS AND METHODS

Ten outpatients (7 men and 3 women; mean age, 67.9 years; range, 57-77 years; mean tremor duration, 12.2 years; range, 3-25 years) attending the Movement Disorders Section of the Sant Pau Neurology Department, Barcelona, Spain, with moderate (sufficient to cause mechanical or social disability) to severe ET were included in the study between June 1, 1999, and June 30, 2000, according to a previous sample size calculation. All 10 patients completed the study. Diagnosis was established on the basis of chronic (ie, longer than 5 years), persistent (although the amplitude could fluctuate), bilateral (although it could be asymmetric) postural tremor with or without kinetic tremor involving hands or forearms (although tremor of other body parts could be present in addition to upper limb tremor), with no other neurologic abnormalities related to systemic or other neurologic disease (with the exception of the presence of tremor, cogwheeling, and Froment sign) and no other explanation for tremor (eg, the presence of known causes of enhanced physiologic tremor, concurrent or recent exposure to drugs known to cause tremor, or the presence of drug withdrawal state).14

The study protocol was approved by the hospital ethics committee and was performed in accordance with international ethical regulations.15 The study was proposed to 42 patients. Twenty-eight patients refused to participate, mainly because of the nature of the procedure, and 4 patients were excluded from the trial for one of the following exclusionary criteria: seizures (n=1), cardiac pacemakers (n=2), and tremor-active drugs (n=1). Tremor-active drugs included central cholinergic drugs (acetylcholine chloride, muscarinic and nicotinic agonists, anticholinesterases, and aminopropranolols), central monoaminergic drugs (neuroleptics, phenylethylamines, and indoles), peripheral adrenergic drugs (lithium carbonate, amphetamine sulfate, adrenocorticosteroids, and thyroid hormone supplements), and others such as anticonvulsants (valproic acid), bronchodilators (theophylline and terbutaline sulfate), or antidepressants (amitriptyline hydrochloride). Patients with dystonia were also excluded. Patients were requested to avoid alcohol, caffeine, and smoking for 24 hours before testing. Finally, 10 subjects gave written informed consent to participate after the nature of the procedure had been fully explained.

Patients were systematically asked about family history of ET. Three patients reported a history in first-degree relatives. In addition to hand tremor, tremor was present in the head in 3 patients. Kinetic tremor of the upper limbs was present in all patients in addition to postural tremor. Four patients were newly diagnosed, and the rest had been treated with antitremor medication (5 with propranolol hydrochloride [mean dosage, 135 mg daily] and 1 patient with diazepam [15 mg daily]). Antitremor medication and doses were not changed after the end of the study.

The rTMS was performed with a high-speed stimulator (Magstim Rapid, Carmarthenshire, England) by means of a focal double 70-mm butterfly coil with a maximum peak field of 2.2 T. The electrical field induced by this coil was maximal beneath the center of the figure of 8.16 Use of this type of coil stimulates a small area of the cortex of approximately 2 cm in diameter.16,17 We presumed it was unlikely that the coil placed over the occiput would stimulate structures much deeper than 2 cm; ie, the cerebellum (at least 1.5 cm deep) would be preferentially stimulated rather than the brainstem (at least 3.0 cm deep)15,19. The inion was taken as a landmark of the boundary between the posterior cerebellum and the occipital cortex. We therefore stimulated the area caudal to the inion to stimulate the posterior cerebellum. The coil was oriented vertically and the current was directed upward with respect to the head. The coil was applied 2 cm below the inion (placement was based on previous studies that demonstrated effective stimulation of the cerebellum).20,21

At the beginning of each rTMS session, single stimulations were administered at the theoretical stimulation point. Motor effects (activation of pyramidal tract or upper cervical motor roots) were monitored at this point by means of electromyographic recording of the right abductor pollicis brevis muscle. If motor effects appeared, the stimulation point was repositioned 2 cm upward, and if photoparoxysms were observed, the stimulation point was repositioned 2 cm lower. Each session consisted of 30 trains of 10 seconds in duration separated by 30-second pauses. Stimulation was applied at 1-Hz frequency, at maximal (100%) stimulator output intensity. These stimulation variables were to some extent outside of the safety guidelines developed for rTMS of the motor cortex to avoid the risk of epilepsy.21 Nevertheless, we assumed that the risk of producing epileptic crisis with cerebellar stimulation would

active rTMS (20.7±11.8) than after sham rTMS (23.4±13.9) (t=2.77; P=.02). When the time course of intervention effects was assessed, no significant differences were obtained when sham rTMS was applied. However, significant effects were observed after active rTMS, with scores at +5 minutes (t=4.70; P=.001) being significantly lower than those at baseline (Figure 1 and Figure 2).

NEUROPHYSIOLOGIC DATA

The mean dominant frequency peak was 5.9 Hz (range, 4.4-7.8 Hz). Tremor frequency was not altered by treatments and did not predict treatment response.

The analysis of variance showed significant time (P=.01) and treatment (P=.04) effects. The interaction (treatment×time) effect showed a tendency toward significance (P=.08).

Although no significant differences in accelerometer values between the interventions were observed at baseline (sham, 4905±7120 µV²; active, 3637±4272 µV²) and at +60 minutes (sham, 3687±3959 µV²; active, 3497±7017 µV²), the absolute power of the dominant frequency peak was significantly lower at +5 minutes after active rTMS (1348±1886 µV²) than after sham rTMS (4654±7614 µV²) (t=2.32; P=.05). When the time course of intervention effects was assessed, no significant differences were obtained when sham rTMS was applied. However, significant effects were observed after active rTMS at +5 minutes (t=2.79; P=.02). This decrement reached a mean value of approximately 60% (Figure 3).
be low. To obtain a more homogeneous administration of the rTMS variables and to ensure the cerebellum was reached, we decided on this protocol of stimulation.

Stimulation was applied either with the coil resting flat on the scalp, as required to achieve induction of adequate cortical stimulation (active rTMS), or with the coil angled at 90° and with only the edge of the coil resting on the scalp (sham rTMS). The sham rTMS induces a mild contraction of the scalp muscles and a subjective sensation similar to that achieved with active rTMS, but fails to induce a significant cortical stimulation.16,24 Each stimulation session lasted nearly 20 minutes, and each subject received a total of 300 stimuli per session. Stimulation sessions were performed by a trained neurologist (A.G.) in a room equipped with the necessary instruments and medications for the prompt treatment of a possible seizure. All patients wore earplugs during the stimulation session.

The study design was double blind (both patient and examiner were blinded to study arms, although the neurologist who administered active and sham rTMS was obviously not), crossover, and placebo controlled. Active and sham rTMS were administered in random order (Latin square design) with a 1-week period between sessions.

If the patient was taking antitremor medication, this was stopped 72 hours before the rTMS session and re-started after study measurements were completed at each rTMS session.

Main outcome measures consisted of the comparison of results of a Tremor Clinical Rating Scale (TCRS) and accelerometric recordings evaluated at baseline (5 minutes before) and at +5 minutes and +60 minutes after rTMS session. Adverse events were carefully monitored throughout the trial, with patients being questioned about common side effects of rTMS.

The TCRS consisted of the scale proposed by Fahn et al23 with minimal modifications. To study acute effects of rTMS, we used parts 1, 2, and 4 of this scale. Specifically, clinical examination was performed by visual inspection of postural and kinetic tremor of the hands (fingers), legs, head, and trunk (part 1), according to the following scale: 0, none; 1, mild (amplitude, <0.5 cm); 2, moderate (amplitude, 0.5-1.0 cm); 3, marked (amplitude, >1.0-2.0 cm); and 4, severe (amplitude, >2.0 cm) (maximum score, 40). Scores for face, tongue, and voice were not included. Pos- sibilities and times of the corresponding 1-way repeated-measures analyses of variance and paired t-tests. The results of TCRS part 4 were analyzed by means of the nonparametric Wilcoxon matched-pairs test. Any P<.05 was considered significant. Data are presented as mean (SD) unless otherwise indicated.

A significant treatment effect (P = .03) was observed in the analysis of subjective assessments by the patient; the score after active rTMS (+0.8±0.7) was higher (ie, better) than that after sham rTMS (0.0±0.0).

When patients were asked about the treatment course they preferred, no patient indicated sham rTMS as the most effective treatment, 6 (60%) indicated active rTMS, and 4 (40%) found both treatments similar.

ADVERSE EVENTS

Slight headache was mentioned by 1 patient after active rTMS; it disappeared within 48 hours after the rTMS session without the need for analgesics. The remaining patients did not report any adverse events during the study.

No motor effects were observed during stimulation in any patient or in any stimulation condition. One patient experienced photopsias during active rTMS stimulation at the theoretical stimulation point, and the coil was repositioned 2 cm downward.

The findings of this preliminary study showed that low-frequency rTMS of the cerebellum can induce a moderate, transient, significant reduction of tremor in patients with ET.

In addition to the small number of patients included as a result of the exploratory nature of the study,
2 further limitations of the study should be pointed out. The first of these is the intrinsic difficulty in assessing tremor in clinical trials, especially with accelerometric assessments, which may have great intrasubject variability. Nevertheless, this problem was minimized with our crossover controlled design, and both accelerometry and clinical data showed a consistent beneficial effect of rTMS, a pattern of changes sufficiently reliable to ensure the significant active therapy effect obtained. Second, there have been conflicting reports regarding whether it is possible to stimulate the human cerebellum through the intact scalp by means of TMS. However, recent works have clearly demonstrated that the cerebellum is accessible to TMS when butterfly coils that permit deeper stimulation are used and when a stimulating coil is positioned on the inion area. A limitation of the present study is that we collected no direct evidence to ensure that we had stimulated the cerebellum. Moreover, other structures could also be affected by the stimulation strength used. However, placement of the stimulating coil in accordance with previous studies, together with the monitoring during rTMS sessions of brainstem or occipital adverse effects, led us to suppose that cerebellar hemispheres were actively stimulated. We did not compare cerebellar stimulation with stimulation of other brain regions. However, the central pathways involved in the pathophysiology of tremor are incompletely known and cortical regions might be implicated. Thus, to preserve the singular stimulation of cerebellar areas, we used the coil placed on edge to produce the sham stimulation.

The cerebellum is one of the regions within the central motor pathways that demonstrates oscillatory behavior and is a main candidate for the origin of any pathologic central tremor. The candidate role of the cerebellum in the genesis of ET is further supported by the animal model of harmaline tremor, by regional blood flow studies, and by functional imaging data that provide evidence that ET is associated with abnormal bilateral overactivity not only of deep cerebellar nuclei but also of the cerebellar cortex. Overall, these findings support the notion of a central oscillator inducing bilateral overactivity of cerebellar connections in ET, even when subjects are at rest. Furthermore, a recent study using single-pulse TMS over the cerebellum in ET showed normal excitability of the cerebellolothalamocortical pathways, suggesting an abnormal firing pattern of the efferent pathway or abnormalities in the cerebellar afferent input.

The frequency of stimulation may be a critical factor in determining the effect of rTMS. Studies in animals with electrical stimulation at frequencies in the single-hertz range produced a long-term decrease in the efficiency of synaptic neuronal transmission (long-term associative depression). In rats, seizure thresholds were lowered with 1-Hz stimulation, a phenomenon that has been called 
quenching\textsuperscript{31}. In humans, rTMS may induce transient changes in neocortical excitability. Specifically, long trains of low-frequency rTMS (0.9 or 1.0 Hz) led to a reduction in motor cortex excitability evidenced both by a decrease in motor evoked potential amplitudes and by a decrease in the cerebral metabolic rate. The physiologic mechanism of this phenomenon is unknown, but it is supposed to be reminiscent of long-term associative depression. However, the extrapolation of these effects, observed in animal studies and in human motor cortex, to human cerebellum is plausible, but not yet demonstrated.

Similar mechanisms could be alleged to explain the transient antitremor effect of rTMS of the cerebellum observed in our patients with ET. First, rTMS may interfere with the synchronicity level of oscillatory cerebellar neurons. It has been reported that synchronous oscillatory membrane activity in a large population of olivary neurons is needed to create relevant oscillatory activity on the motor system. Second, rTMS stimulation...
can locally increase the level of γ-aminobutyric acid (GABA) in the cerebellum. It is known that the dentritic spines through which the inferior olivary cells are electrotonically coupled receive GABAergic input from the deep cerebellar nuclei. Changes in the activity of these systems may also increase or decrease the population of neurons that entrained at a particular frequency, thus increasing or decreasing the amplitude of the tremor oscillation. Moreover, rTMS can provoke synaptic changes that alter the neuronal function of the cerebellar structures. In fact, TMS can create temporary functional circulations. Moreover, rTMS can provoke synaptic changes increasing or decreasing the amplitude of the tremor os- 
neurons that entrained at a particular frequency, thus in-

Accepted for publication October 8, 2001.

Author contributions: Study concept and design (Drs Gironell, Kulisevsky, and Lorenzo); acquisition of data (Drs Gironell, Lorenzo, Pascual-Sedano, and Otermin); analy-
sis and interpretation of data (Drs Gironell, Kulisevsky, and Barbanoj); drafting of the manuscript (Drs Gironell, Kulisevsky, and Otermin); critical revision of the manu-
script for important intellectual content (Drs Gironell, Kulisevsky, Lorenzo, Barbanoj, and Pascual-Sedano); statistical expertise (Drs Barbanoj and Otermin); admin-
istrative, technical, or material support (Drs Gironell and Lorenzo); study supervision (Drs Gironell, Kulisevsky, Barbanoj, and Pascual-Sedano).

Presented in abstract form at the 52nd Annual Meet-

We thank Ignasi Gich, MD, Epidemiology Depart-
ment, Sant Pau Hospital, for his assistance with statistics.

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