

# Modulation of Postural Wrist Tremors by Magnetic Stimulation of the Motor Cortex in Patients with Parkinson's Disease or Essential Tremor and in Normal Subjects Mimicking Tremor

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The effect of magnetic brain stimulation on postural wrist tremor was studied in 10 patients with Parkinson's disease, 12 with hereditary essential tremor, and 10 normal subjects who mimicked tremor by making rapid alternating wrist movements. In all patients and normal subjects, magnetic brain stimulation over the contralateral motor cortex at an intensity approximately 10% above threshold produced the following sequence of events: (1) a small direct electromyographic (EMG) response, followed by (2) suppression of the rhythmic EMG activity responsible for the tremor, before (3) reappearance of the tremor time-locked to the stimulus. It is concluded that magnetic brain stimulation over the motor cortex can modulate the oscillatory mechanisms responsible for the generation of postural tremors. Group analysis revealed that the time to reappearance of rhythmic EMG activity varied significantly with the period of parkinsonian postural tremors, but not with the period of essential or mimicked tremors. Magnetic stimulation also significantly shortened the period of parkinsonian postural tremors, but did not influence the period of essential or mimicked tremors. These behavioral differences indicate differences in the pathophysiological mechanisms underlying parkinsonian postural tremor and essential tremor.

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Some authors have suggested that parkinsonian *postural* tremor and essential tremor have similar origins; their frequencies are similar [1] and are unaffected by mechanical loading of the limb [2]. Both types of tremor are abolished by contralateral thalamotomy [3]. We recently demonstrated that both parkinsonian postural tremor and essential tremor are similarly modulated by brief mechanical perturbations [4] and supra-maximal peripheral nerve shocks [5]. Such studies appear to provide a measure of support for the hypothesis that parkinsonian postural tremor and essential tremor have similar origins.

Other authors have suggested that parkinsonian postural tremor has a similar origin to that of the *rest* tremor [6], based on the finding that voluntary pronation or supination of the wrist could often provoke a tremor with alternating patterns of muscle contraction in agonists and antagonists, similar to that in parkin-

sonian rest tremor. If correct, parkinsonian postural tremor would have a different origin from that of essential tremor, since the pathophysiology of parkinsonian rest tremor differs from that of essential tremor [7-9].

In the present study, we examined the effect of magnetic brain stimulation on parkinsonian postural tremor and essential tremor. We found that stimulation over the contralateral motor cortex modulated both types of tremor, with the rhythmic electromyographic (EMG) activity being suppressed before reappearing time-locked to the stimulus. However, the time to reappearance of rhythmic EMG activity varied with the period of parkinsonian postural tremors but not with that of essential tremors. Furthermore, magnetic stimulation significantly shortened the period of parkinsonian postural tremors but did not influence the period of essential tremors. These differences argue against a similar

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origin for parkinsonian postural tremor and essential tremor. Some of this work was previously published in abstract form [10].

## Materials and Methods

### Patients

Ten patients (mean age, 59 years; range, 33–74 years) with typical Parkinson's disease (defined as an akinetic rigid syndrome of asymmetrical onset and responsive to L-dopa) and tremor were studied with approval of the local ethical committee. All the patients with Parkinson's disease had tremor at rest with frequencies ranging from 4 to 6 Hz, which on posture increased in rate (range, 4.4–6.6 Hz) and tended to decrease in amplitude. Antiparkinsonian medication was not stopped.

Twelve patients (mean age, 53 years; range, 25–73 years) with hereditary essential tremor were also studied. A diagnosis of essential tremor was based on the finding of a postural limb tremor predominantly, if not only, in the outstretched arms, which was absent at rest and unaccompanied by signs of parkinsonism or cerebellar disease. The frequency of tremor ranged from 4 to 7 Hz. Three patients were taking beta-blockers, which they were asked to stop taking for 72 hours before the study.

Ten laboratory staff (mean age, 35 years; range, 28–40 years) without tremor and without a family history of tremor were asked to mimic a tremor by rapidly flexing and extending their wrists. The frequency of these "mimicked" tremors ranged from 4.0 to 6.5 Hz.

There was no significant difference in mean tremor period between the groups (Parkinson's disease, 201 msec; essential tremor, 179 msec; mimicked tremor, 188 msec; analysis of variance [ANOVA],  $F = 1.4$ ,  $df = 2$ , not significant). However, mean tremor amplitudes for each group (Parkinson's disease, 8.3 degrees; essential tremor, 3.3 degrees; mimicked tremor, 14.3 degrees) were significantly different (ANOVA,  $F = 4.67$ ,  $df = 2$ ,  $p < 0.02$ ).

### Experimental Methods

Patients and subjects were seated comfortably and their semi-pronated arms placed in a manipulandum of low inertia coupled to a torque motor (Printed Motors type G12M4-H, Birmingham, UK). The forearm and hand were secured so as to restrict movement to the wrist in a horizontal plane. A background extensor torque of 0.38 Newton-meters was applied to the wrist in order to activate the forearm flexor muscles and bring out the postural wrist tremor. The position of the manipulandum was displayed as a vertical bar on the lower half of an oscilloscope screen placed in front of the patient or subject. Instructions were given to keep this vertical bar under a second stationary vertical bar in the center of the screen. The apparatus was arranged so that when the two vertical bars were in line, the wrist was in approximately 15 degrees of flexion.

The motor cortex was stimulated using the commercially available MAGSTIM 200 (Whitland, Dyfed, UK). The coil (consisting of 19 turns of copper wire; inner diameter, 5.5 cm; outer diameter, 12 cm) was centered over the vertex and the current direction was chosen so as to stimulate preferentially the cerebral cortex contralateral to the arm being stud-

ied. The stimulus intensity was set at about 10% (of stimulator output) above the threshold for EMG responses in relaxed forearm flexor muscles. Fifty magnetic cortical stimuli were given randomly at 5- to 8-second intervals.

Wrist position and velocity, derived by electrical differentiation of the position trace, were recorded 2 seconds before and 2 seconds after delivery of the magnetic brain stimulus. EMG recordings were taken from forearm flexor and extensor muscles using silver-silver chloride (Ag/AgCl) electrodes taped 3 to 4 cm apart over the muscles, and then were amplified and processed (Digitimer D160 [Digitimer, Welwyn Garden City, UK] with bandpass filtering between 80 Hz and 2.5 kHz). EMG signals were subsequently full-wave rectified and smoothed (time constant, 10 msec). All four channels were collected by a CED 1401 A/D converter (Cambridge Electronic Design, UK) at a sampling rate of 150 Hz per channel before being stored on floppy disc for later analysis.

### Display of Results

The rectified forearm flexor EMG of each trial was averaged by computer (Fig 1). Because magnetic stimuli were given at random times within the tremor cycle, this had the effect of "averaging out" the EMG bursts preceding the stimulus, so producing a relatively flat average rectified EMG trace. If magnetic stimuli had no effect on the tremor, there would be a level trace in the period afterward as well. However, if the timing of EMG bursts in the forearm muscle was modulated in a consistent manner (e.g., phase reset) by magnetic brain stimuli, then the average rectified EMG trace after stimulation will show such modulation (lowermost trace of Fig 1).

The latency of the first peak on the average rectified EMG trace following delivery of the stimulus was measured by visual inspection using a cursor.

### Analysis

In order to quantify the effect of magnetic brain shocks on tremors, we employed the "resetting index" [4, 7]. This gives a value that ranges from 0 to 1 and indicates the degree to which the timings of the first five tremor bursts after the shock have been altered from the timings predicted by the prestimulation tremor. It should be noted that there is not a simple relationship between the visual appearance of the average rectified EMG traces and the resetting indexes, as the former will be highly dependent on the frequency variability of the tremor.

Statistical analysis of group data was performed with one-way ANOVA and paired Student's *t* tests as appropriate. Correlation was performed by using linear regression analysis. Significance was judged at a 5% level.

## Results

Magnetic brain shocks altered the timing of rhythmic EMG bursts in all patients studied and in normal subjects mimicking tremor (Figs 1, 2). A stimulus intensity of approximately 10% (of the stimulator output) above the threshold for responses in relaxed forearm muscles was required for this phase resetting of rhythmic EMG activity to be clearly seen. Magnetic stimulation over

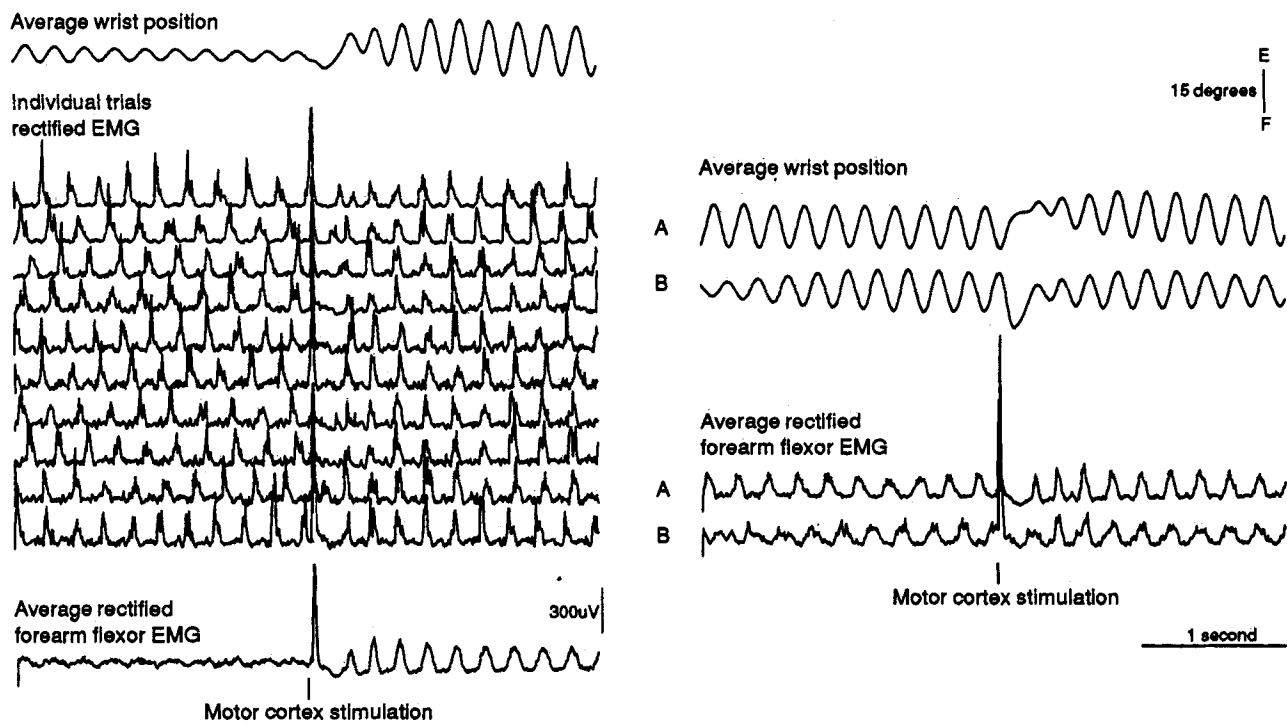


Fig 1. Magnetic stimulation of the contralateral motor cortex modulates the postural wrist tremor and associated rhythmic electromyographic (EMG) activity in forearm flexor muscles of a patient with Parkinson's disease. (Left side) The middle panel shows rectified forearm flexor EMG signals (collected for 2 seconds before and 2 seconds after a magnetic brain shock) from ten consecutive individual trials. Rhythmic bursts of EMG activity at a rate of about 5.5 Hz are seen in the 2-second period before the stimulus is given. The magnetic brain stimulus is given in the middle of each trial, but at random times with respect to the phase of ongoing tremor. Each brain stimulus results in a small short-latency motor response (which for the most part is obscured by stimulus artifact), which is then followed by a period during which EMG activity is suppressed, before rhythmic EMG activity resumes at about 200 msec after delivery of the stimulus. Note that the rhythmic bursts of EMG activity following the magnetic brain shock have a fixed time relationship to the stimulus irrespective of when in the preceding tremor cycle the stimulus was given. The rhythmic EMG activity has become time-

locked to the stimulus. The lower panel shows the average rectified EMG from 50 consecutive trials. The first half of the trace is approximately level as the bursts of rhythmic EMG activity seen in the individual trials have been "averaged out," while the second half of the trace shows clear modulation with peaks occurring at a frequency of about 5.5 Hz, which reflects the change in timing of rhythmic EMG bursts following magnetic brain stimulation in the individual trials. The upper panel shows the wrist position averaged for the same 50 consecutive trials. (Right side) The effect of magnetic brain stimulation on tremor was not dependent on when the stimulus was delivered. Selected trials from the same data as shown on the left side of the figure were averaged depending on whether the stimulus occurred between (A) or during (B) a rhythmic EMG burst. Note that the modulations seen in the average rectified EMG traces are out of phase before the stimulus was given, but are in phase after stimulation. A similar phase change is seen in the average wrist position traces.

the contralateral motor cortex at intensities higher than just above threshold often caused disruption rather than phase resetting of rhythmic EMG activity, so that the tremor and its associated rhythmic EMG activity were abolished for a period of a second or more, with subsequent EMG activity lacking its previous rhythm. In order to concentrate on the phase resetting (rather than the abolition) of tremor, stimulus intensities were set at about 10% above the motor threshold for the remainder of the investigations. There was no significant difference in mean stimulus intensity used in the three groups (ANOVA,  $F = 1.35$ ,  $df = 2$ , not significant).

At an intensity of 10% above the threshold for responses in relaxed muscles, magnetic stimulation over the contralateral motor cortex produced a small direct EMG response in forearm flexor muscles, followed by a brief period in which rhythmic EMG activity was suppressed. This was then followed by the reappearance of rhythmic EMG activity time-locked to the stimulus. Stimuli were delivered randomly with regard to the ongoing tremor; similar behavior was seen irrespective of whether the magnetic brain shock was delivered during or between forearm flexor EMG bursts (see Fig 1, right panel). The movement produced by the small direct EMG response tended to flex the wrist by a few

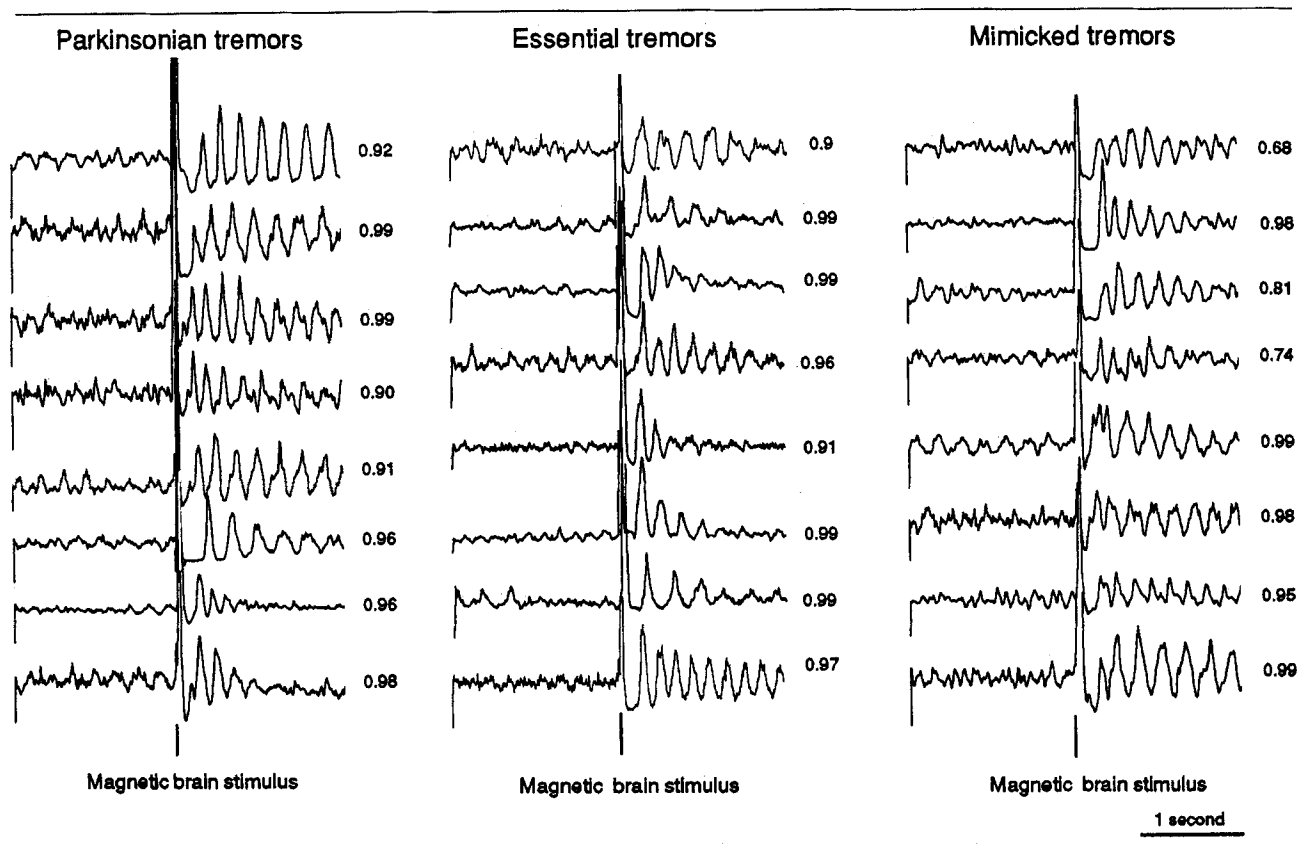


Fig 2. All postural tremors were modulated by magnetic brain stimulation over the contralateral motor cortex using stimulus intensities set at 10% above the threshold for direct electromyographic (EMG) responses. Average rectified forearm flexor EMG traces from 8 representative patients with parkinsonian wrist tremor (left panel), 8 representative patients with essential tremor (middle panel), and 8 normal subjects mimicking a postural wrist tremor (right panel) show time-locked modulations following 50 magnetic stimuli which were given in the middle of each 3-second trace. Such modulations reflect the change in timing of rhythmic EMG activity following magnetic brain stimulation in individual trials such that the rhythmic EMG bursts have become time-locked to the stimulus. The individual resetting index is given beside each trace. Note that there is not a simple relationship between the resetting index and the appearance of the average rectified EMG trace, as the latter is highly dependent on the frequency variability of the tremor.

degrees. Small direct EMG responses were also often, but not invariably recorded in the forearm extensor muscles.

#### Group Analysis

Although the behavior of all the individual tremors appeared similar, a group analysis revealed two significant differences in the behavior of parkinsonian postural tremor compared to that of essential and mimicked tremors (Fig 3). First, the time to reappearance of rhythmic EMG activity, as assessed by the latency of the first peak in the average rectified EMG trace,

correlated significantly with the period of the ongoing tremor in the Parkinson's disease group (linear correlation coefficient,  $r = 0.74$ ,  $p < 0.02$ ) but not in the patients with essential tremor ( $r = 0.5$ , not significant) or the normal subjects mimicking tremor ( $r = -0.54$ , not significant). Second, the average length of the first four tremor cycles after delivery of the stimulus was shorter than the period of ongoing tremor by 17 msec in the Parkinson's disease group (paired  $t$  test,  $t = 3.12$ ,  $p < 0.02$ ), whereas no significant difference was found for essential (average difference in period, 2.75 msec;  $t = 0.7$ , not significant) or mimicked (average difference in period, 0.9 msec;  $t = 0.27$ , not significant) tremors.

#### Resetting Index

The calculated resetting index ranged from 0.90 to 0.99 (mean  $\pm$  standard error of mean,  $0.96 \pm 0.01$ ) for the patients with parkinsonian tremor, from 0.90 to 0.99 ( $0.97 \pm 0.01$ ) for the patients with essential tremor, and from 0.68 to 0.99 ( $0.91 \pm 0.04$ ) for the normal subjects mimicking tremor. There was no significant difference between the mean resetting indexes for each group (ANOVA,  $F = 1.88$ ,  $df = 2$ , not significant). The resetting index did not correlate significantly with either tremor amplitude or tremor frequency.

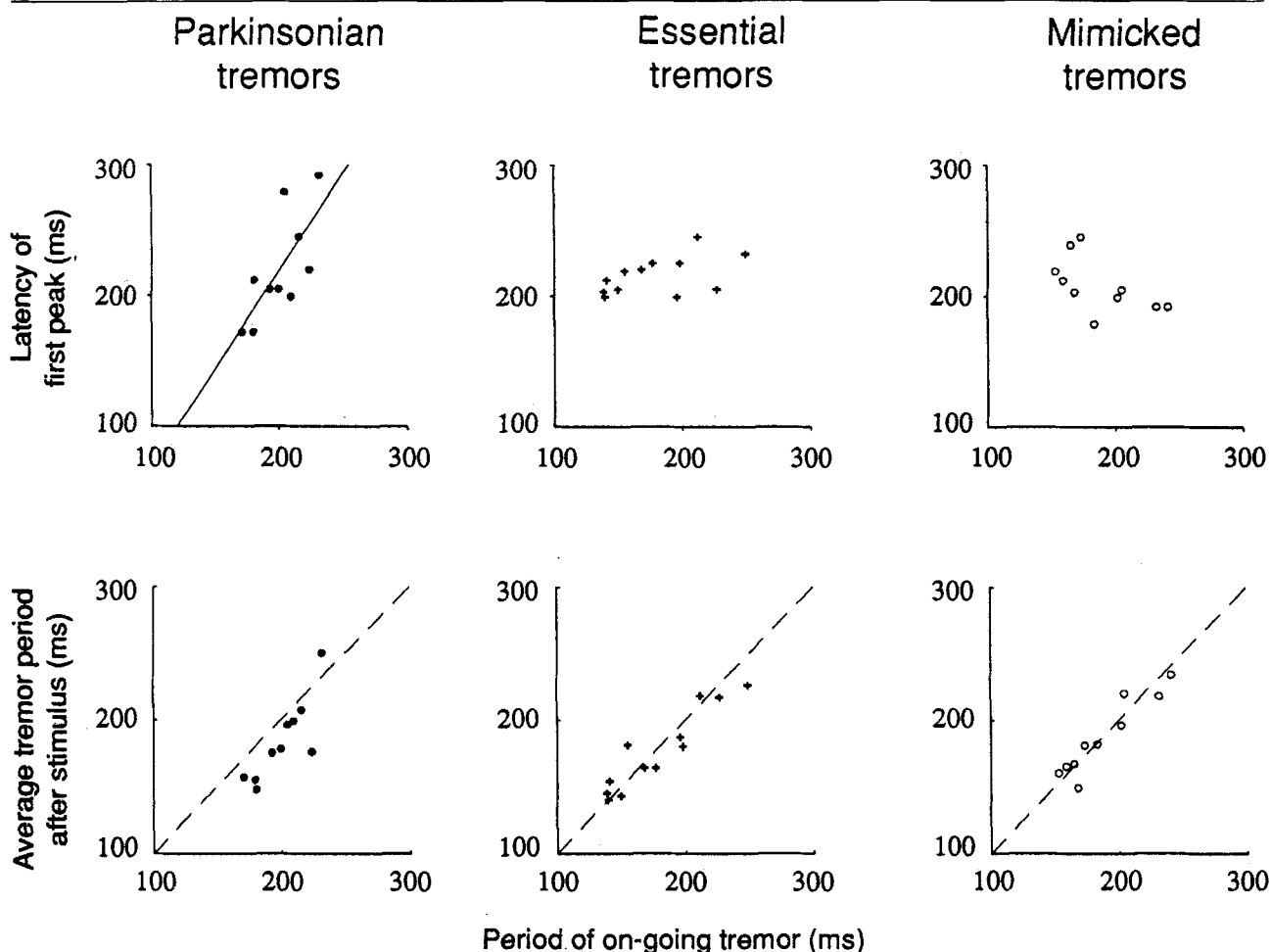


Fig 3. The behavior of parkinsonian postural tremor following magnetic brain stimulation differed from that of essential or mimicked tremors. The time to reappearance of rhythmic electromyographic (EMG) activity following magnetic brain stimulation (as measured by the latency of the first peak in average rectified EMG traces) varied significantly with the period of ongoing tremor in parkinsonian wrist tremors (linear regression line drawn, left upper panel), but not in essential (middle upper panel) or mimicked (right upper panel) postural tremors. In the lower panels, the average period of the first four cycles of tremor after magnetic brain stimulation is plotted against the ongoing tremor period. Lines of equivalence have been drawn (dotted lines) to illustrate that the average tremor period after magnetic brain stimulation was shorter than that before stimulation in parkinsonian postural tremor (left lower panel), but was similar in essential (middle lower panel) and mimicked (right lower panel) tremors.

### Discussion

This study showed that transcranial magnetic brain stimulation can modulate the postural wrist tremors associated with both Parkinson's disease and essential tremor as well as the timing of the rhythmic alternating wrist movements produced by normal subjects (mimicked tremor). Transcranial magnetic brain shocks are therefore capable of interacting with the abnormal oscillatory mechanisms that are responsible for pathological tremors as well as with the oscillatory mechanisms that are utilized by normal subjects in order to produce rapid alternating wrist movements.

Which part of the brain was stimulated to obtain modulation? The upper limb representation in the contralateral motor cortex is the most likely site, since the optimal position of the stimulating coil was over this region and since successful modulation of tremor was always associated with the direct EMG responses in forearm flexor muscles. Furthermore, stimulation of the exposed sensorimotor cortex with single electrical pulses at operation is known to produce long-lasting resetting of phase of parkinsonian resting tremor [11].

The anatomical localization of the site of stimulation to the motor cortex indicates that the motor cortex is intimately related to the oscillatory mechanism(s) responsible for postural tremors, but does not reveal where the interaction occurs. The motor cortex may be part of the oscillator, or its outputs may merely have access to a remote oscillator that could be located at either a spinal or supraspinal level.

The occurrence of direct EMG responses raises the question of whether tremor modulation by magnetic brain stimuli was effected at a spinal motoneuron level or via peripheral pathways. Could the motoneurons discharged by the magnetic motor cortex shock have altered the timing of subsequent rhythmic bursts as a consequence of their refractoriness? This seems unlikely since the evoked EMG responses were small, particularly in comparison with the EMG responses elicited by mechanical wrist stretches that are often ineffective at modulating the tremor at all [4]. Brief mechanical joint displacements [4, 12] can influence the timing of rhythmic EMG activity in both parkinsonian postural tremor and essential tremor. Modulation of tremor in the present study might therefore have resulted from the movement produced by the direct EMG response, but two observations suggest that this was probably not so. First, the size of wrist movement produced by magnetic brain stimulation was small in comparison to the size of wrist displacements required to modulate tremors by externally imposed stretches [4]. Second, large tremors were differentially susceptible, being little influenced by large wrist stretches [4] yet being clearly modulated by magnetic brain shocks. Supramaximal electrical stimulation of peripheral nerves [5, 13] can also modulate parkinsonian postural tremors and essential tremors, and this appears to be irrespective of tremor amplitude [5]. However, it seems unlikely that magnetic brain stimulation could have produced a synchronous volley in afferent fibers similar to that produced by peripheral nerve shocks, since magnetic brain stimulation does not selectively stimulate gamma motoneurons [14]. We therefore believe that peripheral factors probably contributed little to the modulation of tremor produced by magnetic brain stimulation in the present study.

Group analysis revealed two significant differences in the behavior of parkinsonian postural tremors in comparison to that of essential and mimicked tremors. First, the time to reappearance of rhythmic EMG activity following magnetic brain stimulation varied with the period of ongoing tremor for parkinsonian postural tremors, but occurred at a fixed latency in essential or mimicked tremors. Second, the period of parkinsonian postural tremor after delivery of the stimulus was significantly shorter than that before stimulation, whereas the period of essential or mimicked tremors did not change. It is of interest that a shortening of the tremor

period has also been reported in parkinsonian rest tremor after electrical stimulation of the exposed sensorimotor cortex [11]. These results suggest that the pathophysiological mechanisms responsible for parkinsonian postural tremor are different from those responsible for essential tremor.

Why should the time to reappearance of rhythmic EMG activity following magnetic brain stimulation vary with the period of parkinsonian postural tremor and what are the physiological implications? The simplest explanation is that magnetic brain stimulation instantaneously sets the oscillator responsible for parkinsonian postural tremor to some fixed point in its cycle, and the oscillator then restarts such that the next phasic drive to the muscles occurs after a period that is dependent on the cycle length of the oscillator itself. Analogous behavior is exhibited by cardiac pacemaker tissue depolarized by electric shocks. External depolarization resets the cardiac pacemaker so that the next cardiac action potential occurs time-locked to the electric shock and after a time approximately equal to the cardiac cycle length. Whether magnetic brain stimulation truly "resets" parkinsonian postural tremors in the same way as cardiac pacemaker tissue can be reset remains uncertain. Nevertheless, a close interaction of the stimulus with the oscillator responsible for parkinsonian postural tremor seems likely.

The relatively fixed time to reappearance of rhythmic EMG activity following magnetic brain stimulation seen in patients with essential and mimicked tremors requires a different explanation. The behavior can be compared to an oscillator that is held at one point in its cycle before being released after some fixed interval. Two points need emphasizing. First, the oscillator must still be set to some fixed point in its cycle: It is not sufficient merely to "block" the output of the oscillator, since this would not result in subsequent cycles being time-locked to the stimulus. Second, there must be some mechanism that holds the oscillator for the required period. The mechanism by which rhythmic EMG activity is suppressed for a fixed period may be similar to that responsible for the inhibition of tonic EMG activity after magnetic motor cortex stimulation or to the mechanism responsible for the temporary delay in the execution of voluntary movements produced by magnetic brain stimuli [15]: Both of these phenomena are associated with a suppression of EMG activity for around 150 msec, a period that fits well with the period of suppression of rhythmic EMG in the present study.

How do these results fit with our current understanding of the physiological mechanisms underlying tremor? The finding that all tremors could be modulated with centrally delivered magnetic brain stimuli is consistent with the view that central oscillatory mechanisms are responsible for both parkinsonian and essential

tremor as well as voluntary alternating wrist movements. The subtle differences in the behavior of parkinsonian and essential tremors suggest that they have different pathophysiological mechanisms.

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