A cerebellar-like terminal and postural tremor induced in normal man by transcranial magnetic stimulation

H. Topka,1 S. Mescheriakov,1 A. Boose,1 R. Kuntz,2 I. Hertrich,1 L. Seydel,1 J. Dichgans1 and J. Rothwell3

Departments of 1Neurology and 2Neuroradiology, University of Tübingen, Germany and 3MRC Human Movement and Balance Unit, The Institute of Neurology, London, UK

Summary
Trains of repetitive transcranial magnetic stimulation (TMS) at 10–30 Hz and intensities of 90–120% motor threshold were delivered through a figure of eight coil over the motor cortex while normal subjects made either rapid, self-terminated (ballistic) wrist movements or maintained the position of their wrist at a fixed angle. Movement kinematics and EMG activity in antagonistic forearm muscles were analysed. In the ballistic task, repetitive TMS had little effect on the velocity or acceleration of the initial segment of the movement, although it induced large terminal oscillations (tremor) around the target position at frequencies between 4.4 and 7.2 Hz. The likelihood that tremor would occur increased with increasing stimulus intensities or frequencies. It was maximal with stimulation over the forearm area, and decreased with stimulation over the leg area, or over parietal sites; there was no tremor during stimulation of cervical nerve roots. The frequency of the induced tremor was independent of the rate of stimulation and did not depend on the presence of excitatory and inhibitory motor responses to the stimulus. Stimulation could also induce tremor of the same frequency in the fixed task, but only during co-contraction of forearm muscles. The amplitude of tremor was proportional to the level of co-contraction. Clinically, the tremor induced by repetitive TMS appeared very similar to cerebellar tremors. In order to confirm this we investigated two cerebellar patients, one with autosomal dominant cerebellar ataxia and the other with multiple sclerosis. Both of them had a terminal tremor of 6–7 Hz in the wrist movement task. In the holding task, the amplitude of their postural tremor increased with the level of co-contraction in forearm muscles. Since the frequency of repetitive TMS-induced tremor was independent of stimulus parameters, we conclude that it represents some intrinsic property of the CNS. We suggest that the tremor is caused by disruption of cortical processes involved in terminating a voluntary movement or maintaining a posture. Similarities to cerebellar patients suggest that repetitive TMS may cause tremor by interfering with adaptive cerebellar afferent inflow to motor cortex. Repetitive TMS-induced tremor, therefore, may represent a model of some forms of cerebellar tremor in man.

Keywords: intention tremor; postural tremor; cerebellar; transcranial magnetic stimulation

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; ANOVA = analysis of variance; MEP = motor evoked potential; MT = motor threshold; SMA = supplementary motor area; TMS = transcranial magnetic stimulation

Introduction
Tremor is the most common movement disorder, yet we are surprisingly ignorant of its pathophysiology. Three types of mechanism have been proposed as potential (non-exclusive) sources of tremor: (i) oscillations in peripheral feedback loops, such as the stretch reflex; (ii) oscillations within central neural circuits, such as olivocerebellar or thalamocortical connections; and (iii) oscillations caused by poorly timed feedforward corrections, as postulated by Britton and colleagues (Britton et al., 1994) in essential tremor. One of the problems of studying tremor in man has been that it is not easy to induce tremor in normal individuals. If the latter were possible it might be possible to identify specific neural circuits where disruption produces particular forms of tremor. Tremor during fatigue is relatively common, but this is
thought to involve oscillating activity in reflex circuits. Other techniques are needed to allow investigation of the role of more central structures.

Transcranial magnetic stimulation (TMS) of the human brain was first introduced to study the excitability of motor cortical areas. During recent years, TMS of primary motor cortex has been extensively studied and has been shown to exhibit differential excitatory (Barker et al., 1985; Hess et al., 1987; Rothwell, 1991) or inhibitory effects (Calancie et al., 1987; Mills, 1988; Wassermann et al., 1991; Wilson et al., 1993) in target muscles depending on the subset of cortical neurons activated (Triggs et al., 1992; Wassermann et al., 1993; Wilson, et al., 1993) or depending on the characteristics of the stimulus (Kujirai et al., 1993; Ziemann et al., 1996). Suprathreshold single pulse TMS is capable of delaying the execution of wrist movements (Day et al., 1989), arm movements (Berardelli et al., 1994) or saccadic eye movements (Priori et al., 1993) in simple reaction time tasks and prolongs reaction times in choice-reaction time tasks (Romaiguere et al., 1997). In contrast, sub-threshold single pulse TMS has been shown to shorten simple reaction times (Pascual-Leone et al., 1992) and to introduce a response bias in a forced-choice task (Brasil-Neto et al., 1992) in healthy subjects. Recent studies using repetitive TMS have demonstrated that trains of focal magnetic stimuli delivered to primary motor cortex at rest produce in target muscles a complex pattern of inhibitory and excitatory effects which depends on the frequency and intensity of repetitive TMS (Pascual-Leone et al., 1994). These findings suggest that prolonged series of TMS pulses can exhibit profound effects on motor cortical neurons that differ from the ones that are observed with single pulse TMS. However, despite the essential role of primary motor cortical areas in the processing of motor commands, TMS of the motor cortex has never been shown to produce organized movements.

In the present study, we sought to characterize the effects of repetitive TMS on the execution of simple voluntary movements. We show that repetitive TMS delivered at frequencies between 10 and 30 Hz to forearm areas of primary motor cortex generates low-frequency tremor during termination of rapid wrist flexion or extension movements resembling postural and terminal tremors observed in patients with cerebellar disorders.

**Methods**

Five healthy male subjects (authors S.M., A.B., I.H., L.S. and J.R.; mean age 36 years, range 33–42) and two patients participated in the various aspects of the experiments after giving informed consent. The study protocol was approved by the ethics committee of the Faculty of Medicine, Tübingen. Two normal subjects and the patients were naive with respect to the goals of the study at the time of the experiment. Patient 1 was a 60-year-old male diagnosed as autosomal dominant cerebellar ataxia (ADCA I) according to the results of genetic tests. Disease duration was 20 years and severity of upper limb ataxia was moderate. Patient 2 was a 45-year-old male with an 8-year history of multiple sclerosis. The diagnosis was established on the basis of an abnormal MRI scan showing several small demyelinating white matter lesions in both hemispheres, an additional lesion involving the upper cerebellar peduncle on the right and pathological CSF laboratory findings (elevated IgG, oligoclonal bands). At the time of the study, the patient exhibited moderate upper limb ataxia and severe cerebellar postural and terminal tremor during pointing movements in his right arm. Clinical examination did not detect signs of involvement of cranial nerves, muscle weakness, sensory deficits or additional co-ordination deficits. All subjects (six right-handed, one left-handed) used their right arms throughout the experiments. All healthy subjects were neuroscientists or physicians informed of all known and potential risks of repetitive TMS. TMS was not performed in patients. Subjects were seated comfortably in front of a table and made rapid wrist extensions or flexions by moving a manipulandum (mass 350 g, moment of inertia 0.0026 kg m²; Fig. 1A).

The manipulandum was pivoted at the point of rotation of the wrist and moved in a horizontal arc. Movements were restricted to wrist extensions or flexions by taping and splinting the arm. The forearm was semi-pronated and the fingers extended. Start and target positions were indicated by light-emitting diodes (3 mm diameter) mounted on a board.
in front of the subjects such that the target amplitude of wrist extension or flexion movements were adjusted to 30° horizontal arc. During the movement, hand and forearm of the subjects were covered; however, visual feedback was provided by the light of a laser pointer that was mounted on the manipulandum. Subjects were instructed to start their movements immediately after a visual ‘Go’ signal and to perform the movements ‘as fast as possible’. To familiarize subjects with the apparatus, up to 15 practice trials were allowed that were not recorded and analysed. Joint position was recorded by means of a potentiometer that was attached to the shaft of the manipulandum. Position data were digitized at a sampling rate of 1000 Hz. Joint kinematics were analysed off-line using a custom-made software package. Position-time series were digitally low-pass filtered (cut-off frequency 20 Hz). Angular velocity and acceleration as well as deceleration were computed by differentiating time-position data. Start and end of the initial movement segment were determined in velocity traces using a semi-automated procedure. Start of the movement was defined as the point in time when position values exceeded 5% of peak angular velocity during the acceleration phase of the movement. End of the initial movement segment was defined as the point in time at which the velocity first reached 5% peak angular velocity during the deceleration phase of the movement. To ensure correct positioning of start and end-of-movement markers, automatically set markers were reviewed and manually corrected if necessary (<5% of trials). Occurrence of tremor during termination of the movement was measured by determining angular acceleration peaks that followed the end of the initial deceleration phase. The threshold for accepting an additional acceleration peak was set to 500°/s².

Movement-associated EMG activity was recorded with surface electrodes from flexor carpi radialis and extensor carpi radialis muscles (Nicolet Viking IV; Nicolet Biomedical, Madison, Wis., USA). EMG signals from forearm muscles were amplified, digitized at a sampling rate of 1000 Hz and stored along with position data on a hard disk. Onset of agonist EMG signals was marked manually.

**TMS**

Focal repetitive TMS was delivered through a custom-made poly-foam coated figure of eight coil (diameter 2 × 70 mm, nine turns of wire, peak magnetic field strength 2.2 T, peak electric field strength 660 V/m ) that was connected to a repetitive magnetic stimulator (Magstim Rapid with two booster modules; The Magstim Company, Spring Gardens, Whitland, UK).

Stimulus intensities were adjusted according to individual motor thresholds (MT) for motor evoked potentials (MEP) in wrist extensor muscles. To determine motor thresholds, single TMS pulses were delivered to optimal scalp positions for excitation of MEPs in wrist extensor muscles while subjects were moderately contracting target muscles. Motor threshold was defined as stimulus intensity that evoked MEPs of at least 100 μV peak-to-peak amplitude in four out of six trials. Repetitive TMS is known to potentially trigger epileptic seizures in healthy and unmedicated subjects, particularly if large stimulus intensities and frequencies are used (Wassermann, 1998). As a safety measure, in our study, stimulus intensities were adjusted to active rather than resting motor thresholds. If small amplitude MEPs were masked by ongoing voluntary EMG activity in target muscles, excitatory responses of >100 μV peak-to-peak amplitudes were accepted as MEP if they were immediately followed by a silent period. Voluntary activation of target muscles decreases motor thresholds by 10–20% (Thompson et al., 1991; Wilson et al., 1995). In all experiments, maximum stimulus intensities did not exceed 120% active motor threshold which corresponds to an estimated 100% resting motor threshold. Except for experiment 1 where stimulus intensities and frequencies varied to determine the effects of different stimulus characteristics, repetitive TMS was delivered at 20 Hz and at an intensity of 120% active MT. In all experiments train duration was set to 2 s. Inter-train intervals were at least 20 s. Stimulus intensities and frequencies, therefore, were in compliance with safety guidelines proposed recently (Wassermann, 1998). In initial experiments, we used an additional EMG recording from the biceps muscle displayed on the EMG system monitor at a gain of 100 μV/division to monitor spread of excitation to proximal muscles during stimulation. This additional safety measurement was omitted in later experiments, however, since spread of excitation could not be detected in any subject with the stimulation parameters used. Other additional safety procedures, such as neuropsychological tests after the experiments to monitor cognitive functions, were not employed. The experiments were performed in a clinical neurophysiology laboratory in the setting of a neurology hospital. During all experiments, a qualified neurologist was present in the laboratory.

**Experimental procedures**

As a baseline, subjects performed 10 30° wrist extension movements ‘as fast as possible’ after a visual ‘Go’ signal without applying repetitive TMS. In the patients, the effects of repetitive TMS on movement planning and execution were not studied.

**Experiment 1: effects of varying stimulus parameters**

To determine the effects of different combinations of intensities and frequencies of magnetic stimuli, repetitive TMS was delivered at 10, 20 or 30 Hz and at stimulus intensities of 90, 100, 110 or 120% MT to the forearm area of the left motor cortex for 2 s during planning and execution of wrist extension movements (Fig. 1B). Trains of repetitive TMS began simultaneously with the visual ‘Go’ signal. Given the variability in reaction times between trials and subjects,
there was no fixed temporal relationship between onset of the repetitive TMS train and onset of the movement. Taking into account that mean onset latencies of agonist EMG were 191 ± 90 ms in wrist extension movements without repetitive TMS, there was a period of repetitive TMS lasting ~200 ms prior to onset of the movement. Different combinations of stimulus intensities and frequencies were delivered in randomized order (Table 1). Kinematic data obtained during trials with repetitive TMS were compared with baseline trials. As an additional control, repetitive TMS trials at a rate of 30 Hz were delivered at a stimulus intensity of 1% stimulator output (control repetitive TMS). Subjects performed a total of 60 movements. Each stimulus combination was repeated at least eight times.

**Experiment 2: effects of varying scalp positions**

In order to determine the effects of magnetic stimuli to different cortical areas on rapid wrist movements, repetitive TMS was delivered to either leg representation area of primary motor cortex, or to scalp areas overlying parietal or sensory cortex on the left. Each subject performed at least 12 wrist extension movements. In three subjects, trains of repetitive TMS were delivered with the junction of the coil positioned 3 cm medial to the optimal stimulus position for forearm muscles presumably overlying leg motor representation areas, 3 cm posterior presumably overlying sensory cortical areas and to ipsilateral parietal cortical areas. In two subjects, repetitive TMS was delivered to forearm areas of motor cortex and to parietal cortex. Each of the different scalp positions was stimulated during at least four wrist extension movements in randomized order. In all trials, stimulus parameters were set to 20 Hz, 120% MT and a train duration of 2 s. Data, obtained when stimulating leg motor areas, parietal or sensory cortex, were compared with trials in which repetitive TMS (20 Hz, 120% MT) was applied to motor representations of the forearm muscles.

**Experiment 3: effects of repetitive TMS on co-contracting target muscles**

To determine the effects of repetitive TMS on forearm muscles during voluntary contraction of both wrist flexors and extensors, trains of repetitive TMS were delivered to forearm motor representation areas while subjects were maintaining neutral angular position of the wrist joint by co-contracting antagonistic muscles. In each subject eight trains of repetitive TMS at 120% MT were delivered. In three subjects, stimulus frequencies randomly varied between 20, 13 or 17 Hz. In two subjects all repetitive TMS trains were delivered at a rate of 20 Hz. In three healthy subjects and patient 2 an additional experiment was performed in which subjects were encouraged to alter the level of co-contraction between slight, moderate, severe or no co-contraction. As a control condition, in two subjects trains of rapid-rate magnetic stimulation (20 Hz, 180% cortical motor threshold) were delivered to cervical nerve roots targeting forearm muscles on the right.

**Statistical analysis**

A one-factor analysis of variance (ANOVA) was used to test for differences in the effects of stimulus characteristics and stimulus position on kinematic movement parameters. Post hoc comparisons were done using Student’s t test with the significance level set to 0.05 and adjusted for multiple comparisons using Bonferroni’s procedure.

**Results**

**Kinematics and EMG patterns in wrist extension movements without repetitive TMS in healthy subjects**

During baseline trials without repetitive TMS, healthy subjects performed rapid wrist extension movements that were usually characterized by a large initial and a second smaller velocity peak. Movement durations ranged from 131 ms to 208 ms (mean ± SD: 168 ± 36 ms). Most frequently (95% of trials) subjects overshot the target amplitude of 30° by 2–8° (mean 4 ± 3°). EMG recordings from wrist extensor and flexor muscles were characterized by an initial agonist burst and a subsequent antagonist burst that usually began overlapping with the first agonistic burst. In some trials, a second agonist burst and a second antagonist burst could be differentiated before a steady and slightly co-contracting EMG pattern developed to hold the target position.

**Experiment 1: effects of different stimulus characteristics**

Threshold intensities to evoke MEPs in forearm muscles ranged from 45 to 50% stimulator output (47 ± 2%). There was a trend towards shorter reaction times in trials where repetitive TMS was applied as compared with baseline trials without repetitive TMS or control trials in which repetitive TMS was delivered at 30 Hz and 1% stimulator output ($P = 0.07$). All kinematic movement parameters that characterized the initial movement segment from kinematic movement start to the end of the first deceleration phase of the movement.

**Table 1  Combinations of repetitive TMS stimulus frequencies and intensities investigated**

<table>
<thead>
<tr>
<th>Stimulus intensity (% MT)</th>
<th>Stimulus frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>110</td>
<td>–</td>
</tr>
<tr>
<td>120</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stimulus intensity (% MT)</th>
<th>Stimulus frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>110</td>
<td>–</td>
</tr>
<tr>
<td>120</td>
<td>–</td>
</tr>
</tbody>
</table>
Fig. 2 Effects of trains of rapid-rate TMS to the left forearm representation area on rapid wrist extension movements. Repetitive TMS was delivered at 10 Hz, 120% MT and 20 Hz, 110% and 120% MT. No repetitive TMS indicates baseline trials without TMS. Depicted are wrist angular position (Pos), angular acceleration data (Acc) and EMG recordings from wrist extensor (Ag) and wrist flexor muscles (Ant). Each trace represents averages from eight trials recorded in one subject. For averaging, traces were aligned to movement start.

such as peak movement velocity ($P = 0.743$), peak acceleration ($P = 0.648$) and deceleration ($P = 0.857$) were not affected by trains of repetitive TMS of any frequency or intensity. Repetitive TMS, however, did profoundly alter movement termination (Figs 1B and 2). While in baseline trials without repetitive TMS or control repetitive TMS trials,
Fig. 3 Effects of different stimulus positions on rapid wrist extension movements. Repetitive TMS was delivered at 20 Hz, 120% MT at all scalp positions. Traces set up as in Fig. 2. Traces represent averages from four trials recorded in one subject. F, L, S, P indicate scalp positions stimulated (F = forearm area, L = leg representation area, S = somatosensory cortex, P = parietal cortical areas). The filled circle represents Cz (International 10/20-EEG-system). Depicted are wrist angular position (Pos), angular acceleration data (Acc) and EMG recordings from wrist extensor (Ag) and wrist flexor muscles (Ant).
subjects terminated their movements at the end of the correction movement that compensated for the initial overshoot, in repetitive TMS trials, subjects exhibited several additional acceleration peaks in a tremulous pattern that followed the initial movement component. Tremor during termination of the movement was associated with an alternating pattern of EMG in wrist flexors and extensors.

Table 2 Effects of different repetitive TMS stimulus characteristics on movement termination

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (Hz)</th>
<th>Stimulus intensity (%MT)</th>
<th>No. tremor peaks (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>–</td>
<td>–</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>Control repetitive TMS</td>
<td>30</td>
<td>1</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Repetitive TMS trials</td>
<td>10</td>
<td>100</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>110</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>120</td>
<td>3.7 ± 1.5*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>100</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>110</td>
<td>4.1 ± 1.6*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>120</td>
<td>5.9 ± 1.9*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>90</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>100</td>
<td>2.9 ± 0.7</td>
</tr>
</tbody>
</table>

*Significantly different from baseline—one-way ANOVA and post hoc comparisons using Student’s t test and Bonferroni corrections (significance level set to 0.05).

In some trials with suprathreshold magnetic stimulation, repetitive TMS stimulus artefacts and MEPs could be identified. Since stimulus artefacts and MEPs could not be differentiated from voluntary EMG activity or EMG activity related to the tremulous movements during movement termination, we made no attempt to analyse MEP amplitudes quantitatively. Similarly, silent periods that may have followed repetitive TMS pulses in some instances could not be clearly differentiated.

The likelihood of tremor occurrence and the number of additional tremor peaks was dependent on the stimulus characteristics of the repetitive TMS train with the number of tremor peaks increasing with increasing stimulus intensities or stimulus frequencies (one-factor ANOVA, \(P < 0.0001\); Fig. 3). Post hoc analysis revealed that the repetitive TMS trains at 10 Hz, 120% MT (post hoc comparison, \(P < 0.04\)), 20 Hz, 110% MT (\(P < 0.009\)) and at 20 Hz, 120% MT (\(P < 0.0001\)) significantly increased the number of tremor peaks during attempted movement termination compared with baseline trials (Table 2). Similarly, terminal movement tremor occurred if subjects performed 30° wrist flexion movements rather than extension movements and repetitive TMS trains were delivered at 20 Hz, 120% MT (\(P < 0.0001\)).

Tremor was observed in each subject and terminated at the end of the repetitive TMS train. Within each subject the tremor frequency was similar from trial to trial, but between

---

**Fig. 4** (A) Effects of repetitive TMS (rTMS) to the left forearm representation area on co-contracting forearm muscles. Repetitive TMS was delivered at 13, 17 and 20 Hz. For all frequencies stimulus intensities were set to 120% MT. (B) Effects of cervical root stimulation at 20 Hz, 180% cortical MT. Single trials from one subject. The subject was instructed to maintain neutral wrist angular position while maximally contracting target muscles. Depicted are wrist angular position (Pos), wrist angular acceleration (Acc) and EMG recordings from wrist extensors (Ag) and flexors (Ant). Vertical bars represent repetitive TMS.
different subjects, it varied over a larger range from 4.4 to 7.2 Hz. The frequency of the tremor that was generated during repetitive TMS trains at 10 Hz, 120% MT, 20 Hz, 110% MT and 20 Hz, 120% MT was similar in individual subjects irrespective of the frequency of the repetitive TMS train ($P = 0.756$). Statistical comparisons between baseline trials and control repetitive TMS trials did not yield significant differences with respect to the number of tremor peaks.

**Experiment 2: effects of different stimulus positions**

Terminal movement tremor was generated only when stimulating motor representation areas of forearm muscles (one-factor ANOVA for differences between all stimulus positions, $P < 0.05$; post hoc comparison baseline trials versus forearm motor area stimulation, $P < 0.01$). Repetitive TMS trains delivered to ipsilateral leg representation areas (post hoc comparisons, $P = 0.53$), sensory areas (post hoc comparisons, $P = 0.79$) or parietal cortical areas areas (post hoc comparisons, $P = 0.46$) at 20 Hz, 120% MT did not affect movement termination compared with baseline trials (Fig. 3). In some subjects, repetitive TMS of leg motor representation areas induced mild tremor that was detectable in acceleration traces and, most likely, was due to spread of excitation within the motor cortex.

**Experiment 3: effects of repetitive TMS on co-contracting target muscles**

Repetitive TMS at 20 Hz, 120% MT also evoked tremor if subjects attempted to maintain a target position by maximally co-contracting wrist extensor and flexor muscles ($P < 0.0001$; Fig. 4A). The occurrence of tremor did not depend on the frequency of the repetitive TMS train. The number of tremor peaks associated with trains of repetitive TMS at 120% MT delivered at frequencies of 13, 17 or 20 Hz was similar ($P = 0.53$). Also, the frequency of repetitive TMS had no significant effects on the frequency of the tremor ($P = 0.73$) which was $6.2 \pm 1.5$ Hz for $13$ Hz repetitive TMS, $6.2 \pm 1.3$ Hz for $17$ Hz repetitive TMS and $5.5 \pm 1.5$ Hz for $20$ Hz repetitive TMS. In contrast, rapid-rate magnetic stimulation applied to cervical nerve roots targeting forearm muscles (20 Hz, 180% cortical MT) was not associated with tremor movements at the wrist joint (Fig. 4B).

Movements recorded in patients were characterized by large overshoot (patient 1, $19 \pm 5^\circ$; patient 2, $9 \pm 6^\circ$) and terminal tremor of frequencies between 6 and 7 Hz (Figs 5 and 6). Both terminal and postural tremors were most severe in the patient with the cerebellar outflow lesion (Fig. 6A and B). Characteristics of movement kinematics and EMG patterns of the tremor observed in patients did not differ from the tremors induced in healthy subjects by repetitive TMS.

In three healthy subjects and one patient, the effects of different levels of co-contraction of wrist extensor and flexor muscles were evaluated. Repetitive TMS trains at 20 Hz, 120% MT did not evoke significant tremor when subjects were relaxed or when co-contracting target muscles were at low or moderate levels, but evoked severe tremor if healthy subjects co-contracted maximally while attempting to maintain the targeted wrist position. Similar to healthy subjects, co-contraction of wrist muscles increased the amplitudes of postural tremor in the patient. At rest, no tremor was observed in the patient during the 2 s recording period, whereas during voluntary co-contraction of wrist muscles, tremor amplitudes increased with increasing levels of co-contraction (Fig. 7). In contrast, co-contraction of wrist muscles did not affect the frequency of the postural tremor both in healthy subjects and the patient.

**Discussion**

Repetitive TMS over the motor cortex using intensities slightly above threshold evokes tremor in intact man. The...
tremor occurs at the end of targeted voluntary movement and during maintained posture. Repetitive TMS does not seem to affect the initial acceleration and deceleration phases of the movement but has a profound effect on the damping of terminal oscillations. These findings suggest that repetitive TMS as employed in our study does not significantly affect the initial open-loop phase of the movement but does interfere with the later corrective processes that are involved in terminating the movement. With 10 Hz stimulation one could have argued that the inter-stimulus time interval of 100 ms may have been too long to show significant effects during movement initiation. However, at a rate of 20 Hz, stimuli are given every 50 ms which means that an estimated two to three stimuli occur during the initial part of the movement. Since the same number of stimuli given at 10 Hz can affect movement termination, we conclude that repetitive TMS at low intensities has a relatively specific effect on termination compared with its effect on variables that govern movement initiation.

Several lines of evidence suggest that the constant
frequency of the evoked tremor is an intrinsic property of the CNS rather than some complex sub-harmonic of the stimulation rate. First, the frequency of tremor did not correlate with the frequency at which the stimulus was applied. Indeed, in an earlier study, Alberts (Alberts, 1972) had shown that stimulation of the motor cortex during neurosurgery at a frequency of 60 Hz also evoked a 5 Hz tremor. Secondly, repetitive TMS-induced tremor is associated with an alternating EMG pattern in antagonistic muscles and there is no obvious reason why a train of repetitive TMS stimuli that is delivered to the forearm area of the motor cortex should affect antagonistic muscles in an interleaved fashion. Thirdly, rapid-rate magnetic stimulation to cervical nerve roots targeting wrist flexor and extensor muscles at intensities sufficient to generate large MEPs did not result in postural tremor, indicating that stimulation of central structures was probably important for appearance of tremor.

How does this 5 Hz rhythm arise? One possibility is that the cortex itself tends to ‘resonate’ at ~5 Hz when TMS is applied. Indeed, this can be demonstrated when high intensities of stimulation are used. At intensities of 150% relaxed threshold, Pascual-Leone and co-workers showed that trains at 10 Hz produced alternating large and small amplitude MEPs in relaxed hand muscle (Pascual-Leone et al., 1994). At 20 Hz, two low-amplitude MEPs were followed by a single high-amplitude MEP. Thus, facilitation occurred at 5–7 Hz. The mechanism for this effect is probably related to the 150–200 ms period of cortical inhibition that follows a large shock. Recovery from this effect may tend to synchronize cortical neurons and promote a 5–7 Hz excitatory rhythm (Lytton and Sejnowski, 1991). However, in the present study, the stimulus intensity was never >120% active threshold (which is equivalent to ~100% threshold in relaxed muscle), so we think it unlikely that this effect would be of any importance in producing the present results.

While we cannot exclude the possibility that repetitive TMS may also have had effects on SMA and other pre-motor cortical areas, we do not think that these areas are likely to represent the prime target of repetitive TMS when inducing tremor. SMA, for example, is located close to the midline and much closer to the leg area of the motor cortex than to the wrist area. As stimulation of the leg area was much less effective in generating repetitive TMS-induced tremor, our data suggest that stimulation of the SMA was unlikely to have been the main source of the effects that we saw. Stimulation of other pre-motor areas was not investigated formally. However, during the pilot phase of the experiments, we found that stimulation of frontal areas anterior to the hand area of motor cortex was ineffective in generating tremor.

We hypothesize that the 5 Hz tremor in the present experiments is caused by some characteristic property of the neural circuitry involved in co-contraction or in stabilizing a limb after a rapid movement. We can only speculate on how this might happen. Admittedly, comparisons between the effects of repetitive TMS and the tremors that can be observed in pathological conditions are rather indirect. Similarities on a phenomenological level may still be produced by different mechanisms; however, we were drawn by the similarities of the present tremor in normal subjects and that seen in patients with cerebellar disease. Cerebellar disorders are associated with both a postural tremor and tremor during the termination phase of a voluntary movement at frequencies ranging from 3–8 Hz (postural tremor) to 5–8 Hz (kinetic tremor) (Gilman et al., 1981; Sabra and Hallett, 1984; Cole et al., 1988; Hore et al., 1991). Earlier studies suggest that cerebellar kinetic or intention tremor that occurs when approaching the target is related to lesions in cerebellar outflow pathways consisting of the cerebellar dentate nucleus and its projections to the red and thalamic nuclei in both humans (Bastian and Thach, 1995) and animals (Carrea and Mettler, 1947, 1955; Gilman et al., 1981; Flament et al., 1984; Flament and Hore, 1988).

In our study, we observed repetitive TMS-induced tremor in normal subjects during termination of a ballistic movement and during maintained posture that was similar to the tremors that are associated with degenerative disorders of the cerebellum or a focal demyelinating lesion of the main cerebellar outflow pathway—the upper cerebellar peduncle. Indeed, we were even able to show in the multiple sclerosis patient studied here that the amplitude of postural tremor at the wrist was proportional to the level of co-contraction in wrist muscles, just as in the repetitive TMS-induced tremor of normal subjects.

Hore and Flament (Flament and Hore, 1986; Hore and Flament, 1986) have proposed that terminal and postural tremors might arise in the following way. At the end of a brisk voluntary movement, bursts of muscle activity in agonist and antagonist muscles stabilize the limb at the end position. They are not stretch reflex responses driven by the terminal
oscillations of the limb since they occur before the onset of muscle stretch, but are pre-programmed bursts of activity that are sent out by the CNS to counter terminal tremor. The same occurs during active position holding. Perturbations to the limb produce stretch reflex corrections in the stretched muscle, which tend to compensate for the disturbance. They are followed by later bursts of activity in antagonist muscles that reduce terminal oscillations after the correction. These bursts, like those during voluntary movements, are not stretch reflexes but are pre-programmed in advance by the CNS.

Two results indicate that cerebello-thalamocortical circuits generate this predictive activity. (i) Each burst of EMG is preceded by activity in motor cortex. (ii) Cooling of the cerebellar nuclei disrupts the timing of the corrective bursts in both EMG and cortex. When this activity is absent, the positional corrections of the limb become driven by spinal and transcortical (long-loop) reflex activity (Flament and Hore, 1986; Hore and Flament, 1986) which may, because of delays in the feedback loop, sometimes reinforce the oscillations rather than damp them. Indeed, stretch reflexes themselves are often abnormal in cerebellar disease and this could contribute to the problem of limb stabilization that these patients have. For example, acute cerebellar lesions induced by dentate cooling cause severe depression of long-latency reflex responses (Vilis et al., 1976). Similarly, in man unilateral lesions of the cerebellum are associated with a depression of long latency responses (Marsden et al., 1978). In contrast, degenerative cerebellar disorders are associated with enhancement of long-loop responses (Mauritz et al., 1981; Friedemann et al., 1987).

Given the importance of the motor cortex in mediating the predictive EMG bursts that prevent terminal and postural tremors, we speculate that repetitive TMS may induce tremor by interfering with the cortical processing of cerebellar input to or within motor cortex. This could occur because of an effect of stimulation on (i) the thalamocortical projections from cerebellum, (ii) intrinsic motor cortical circuitry, or (iii) projections from motor cortex back to thalamus or cerebellum. There is some evidence that cerebellar projections are more likely to be found in the anterior portions of motor cortex on the surface of the precentral gyrus (Holsapple et al., 1991). In this position they are nearer the surface of the skull, and would be more readily stimulated by TMS than the neurons within the wall of the sulcus. A direct effect on pyramidal output neurons seems unlikely since there was no effect on the peak velocity or acceleration of the movement.

The final question is why the amplitude of tremor was increased by co-contraction in both cerebellar patients and in normal subjects during repetitive TMS. One possibility is that adjustments to the position of the limb in patients or perturbations due to the repetitive TMS in normal subjects lead to reflex corrective adjustments that require predictive bursts of stabilizing EMG activity (Neilson and Neilson, 1978). If these bursts are reduced or absent then stretch reflexes may occur that reinforce the tremor rather than compensate for it. It is thought that the gain of stretch reflexes is enhanced by co-contraction (Neilson and McCaughey, 1981; De Serres and Milner, 1991). If so, then perhaps the higher the co-contraction, the larger the stretch reflexes, and the more they reinforce any tremor in the absence of cerebellar predictive activity.

From our findings, we hypothesize that low intensity trains of repetitive TMS as employed in our study may induce action tremor in normal man by mechanisms that mimic disordered processing of cerebellar afferent inflow to motor cortex. Repetitive TMS-induced tremor may provide a model of cerebellar kinetic or intention tremor that may help both to understand the pathophysiological mechanisms of cerebellar tremor in man and to develop successful therapeutic strategies.

Acknowledgements
We wish to thank S. Schuch for skilful technical assistance. This work was supported by Deutsche Forschungsgemeinschaft, SFB 307-A3, and by a European Union Large Scale Facility Grant to the Human Movement and Balance Unit.

References


