Effects of Repetitive Transcranial Magnetic Stimulation on Movement-related Cortical Activity in Humans

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Several lines of evidence suggest that low-rate repetitive transcranial magnetic stimulation (rTMS) of the motor cortex at 1 Hz reduces the excitability of the motor cortex and produces metabolic changes under and at a distance from the stimulated side. Therefore, it has been suggested that rTMS may have beneficial effects on motor performance in patients with movement disorders. However, it is still unknown in what way these effects can be produced. The aim of the present study is to investigate whether rTMS of the motor cortex (15 min at 1 Hz) is able to modify the voluntary movement-related cortical activity, as reflected in the Beretischaftspotential (BP), and if these changes are functionally relevant for the final motor performance. The cortical movement-related activity in a typical BP paradigm of five healthy volunteers has been recorded using 61 scalp electrodes, while subjects performed self-paced right thumb oppositions every 8–20 s. After a basal recording, the BP was recorded in three different conditions, counterbalanced across subjects: after rTMS stimulation of the left primary motor area (M1) (15 min, 1 Hz, 10% above motor threshold), after 15 min of sham rTMS stimulation and following 15 min of voluntary movements performed with spatio-temporal characteristics similar to those induced by TMS. The tapping test was used to assess motor performance before and after each condition. Only movement-related trials with similar electromyographic (onset from muscular 'silence') and accelerometric patterns (same initial direction and similar amplitudes) were selected for computing BP waveforms. TMS-evoked and self-paced thumb movements had the same directional accelerometric pattern but different amplitudes. In all subjects, the real rTMS, but neither sham stimulation nor prolonged voluntary movements, produced a significant amplitude decrement of the negative slope of the BP; there was also a shortening of the BP onset time in four subjects. The effect was topographically restricted to cortical areas which were active in the basal condition, irrespective of the basal degree of activation at every single electrode. No changes in the tapping test occurred. These findings suggest that rTMS of the motor cortex at 1 Hz may interfere with the movement-related brain activity, probably through influence on cortical inhibitory networks.

Introduction

In 1965, Kornhuber and Deecke described a slowly increasing surface negative potential starting ~2 s prior to a voluntary movement, called the Bereitschaftspotential (BP) (Kornhuber and Deecke, 1965). The initial part of the BP is thought to reflect movement-related preparatory activity of the cerebral cortex, involving the supplementary motor area (SMA) [for a review see (Shibasaki and Ikeda, 1996)] (Ball *et al.*, 1999; Cui *et al.*, 1999). At ~300–400 ms before the movement onset, the slow negative potential becomes steeper and shows a preponderance over the sensorimotor areas contralateral to the movement (Deecke *et al.*, 1969) [negative slope, NS (Shibasaki *et al.*, 1980)]. Previous intracortical electroencephalogram (EEG) recordings (Neshige *et al.*, 1988), and magneto-EG (Kristeva-Feige *et al.*, 1994, 1996) and high-resolution EEG (Urbano *et al.*, 1996; Ball *et al.*, 1999; Cui *et al.*, 1999) studies have shown that this late asymmetric part of the pre-movement negativity is mainly related to the functional activation of the primary motor cortex (M1). Therefore, the BP is considered to represent an appropriate paradigm to investigate non-invasively voluntary movement organization in humans (Kristeva-Feige *et al.*, 1997).

Magnetic transcranial stimulation (TMS) is now routinely used in clinical settings and for research purposes, since it provides useful information on the excitability and conductivity of the entire motor pathway from the cortex to the target muscle(s) [for a recent review see (Rossini and Rossi, 1998)], even when motor output is minimal, such as during motor imagery tasks (Rossi *et al.*, 1998; Rossini *et al.*, 1999). Repetitive TMS (rTMS) of M1 produces a number of local or trans-synaptic effects which, depending on the combination of frequency/intensity parameters applied, result in a relatively long-lasting modulation of both electrical and metabolic activity of the brain. For example, when the M1 is stimulated with trains of rTMS at low frequency and near-threshold intensity, the excitability of both the stimulated ipsilateral (Chen *et al.*, 1997) and the unstimulated contralateral motor cortex (Wassermann *et al.*, 1998) are reduced. Similarly, reduction of cerebral blood flow can be detected both in the vicinity of and at a distance from the stimulating site (Fox *et al.*, 1997); the dimension of such effects is dependent on the amount of the delivered stimuli at higher frequencies (Paus *et al.*, 1998).

Since these effects may last minutes or hours after the stimulation period, some attempts have been made to apply rTMS as a therapeutic procedure in patients with movement disorders, such as focal dystonia (Siebner *et al.*, 1999a), epilepsy or myoclonus [for a review see (Zieman *et al.*, 1998)]. Contrasting results have been reported about possible beneficial effects of rTMS in patients with Parkinson's disease (Pascual-Leone *et al.*, 1994a; Ghabra *et al.*, 1999; Siebner *et al.*, 1999b). The rapidly growing interest in applying rTMS as a therapeutic procedure in patients with movement disorders has bypassed the investigation of the possible neurophysiological mechanisms which may underlie the therapeutic effect. Therefore, in the present study we have made an attempt to investigate whether, and in what way, the movement-related cortical activity (as reflected in the BP) can be externally modulated by low-frequency rTMS of the motor cortex.

Materials and Methods

Five healthy right-handed volunteers (four men and one woman) aged 25–50 years (mean age 35 years) gave their informed consent for the study, after the approval of the protocol by the institutes participating in the research project. Their neurological history and examination were normal and they had no history of using neuroactive drugs.

Experimental Paradigm

Subjects lay on a reclining chair with their head stabilized by a head restraint. They kept their elbows slightly flexed and their forearms resting

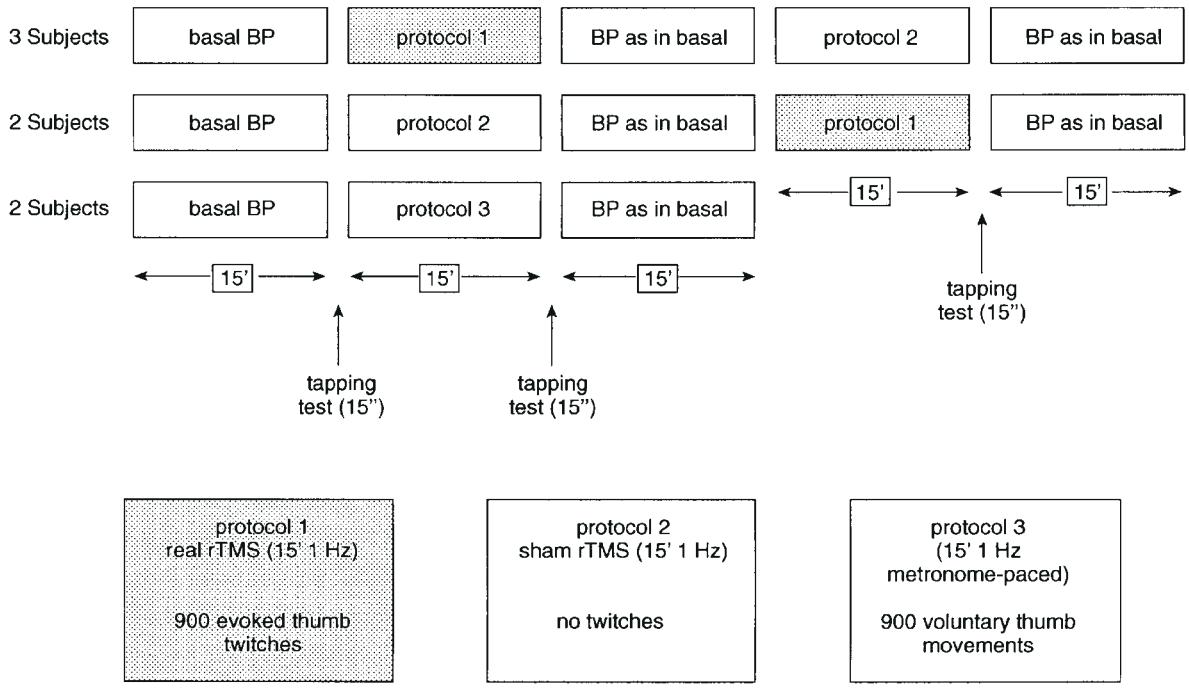

Figure 1. Scheme and timing of the experimental design. Basal BP represents the movement-related cerebral activity preceding self-paced movements (thumb oppositions), randomly executed between 8 and 20 s. Grey areas represent active rTMS.

on chair arms. They were instructed to fix their gaze on a light diode in front of them and to avoid blinking. They wore cotton earplugs to prevent excitability threshold shifts and arousal that was eventually linked with the noise of the discharging stimulator during TMS.

Subjects were instructed to perform self-paced right thumb oppositions at irregular intervals between 8 and 20 s [a typical BP-paradigm; for more details see (Kristeva-Feige *et al.*, 1997)]. Movements were performed with a very sharp onset starting from a complete muscular relaxation. Each subject was given the opportunity to practice prior to the experiment, in order to obtain a consistent electromyographic (EMG) pattern. The EEG and EMG signals were recorded in a continuous mode (see below) and stored on disk for offline analysis. The EMG was recorded by surface electrodes glued on the skin in a short bipolar montage, with the active electrode placed on the thenar muscles belly. The amplitudes and directions of the movement were monitored by an accelerometer placed on the tip of the right thumb.

Figure 1 summarizes the experimental design: after the first BP recording (basal condition), subjects underwent three experimental protocols given in a pseudorandom order and counterbalanced across subjects: protocol 1 (the real rTMS condition), protocol 2 (a control, sham rTMS condition) and protocol 3 (run with two of the investigated subjects), including 15 min of continuous thumb oppositions with rate characteristics similar to those induced by rTMS but without the stimulation. Before applying rTMS, individual thresholds of stimulation were determined for each subject. Following the suggestions of *International Guidelines*, the threshold was defined as the minimal intensity of the stimulator output (1.5 Tesla in our case) that was capable of evoking a motor evoked potential (MEP) of >50 μV in the tested muscle in at least 50% of 15–20 trials (Rossini *et al.*, 1994). In search of the most appropriate site, stimuli were delivered on the left perirolandic region with the same coil used for rTMS and with an interstimulus interval of at least 7 s. The coil rested tangential to the scalp surface, with its handle directed posteriorly. The position corresponding to the lower threshold for the tested muscle (= hot spot) was individually marked on a transparent tightly fitting skullcap – the one utilized for electrodes placement – fixed with reference to anatomical landmarks (inion, nasion, left and right tragus). In all subjects, hot spots roughly corresponded to the C3 position, the scalp area overlying the hand M1.

Stimuli were delivered with the Dantec MagPro repetitive stimulator, connected with a commercially available Dantec eight-shaped coil. The safety of this kind of stimulator for the rTMS study has been tested recently (Wassermann *et al.*, 1996). In order to prevent excessive heating of the coil and of the underlying electrodes during rTMS, the coil was cooled to <15°C before starting the experiment; a watertight plastic bag containing dry ice was then taped onto the coil itself and kept there for the whole period of stimulation. This procedure did not change the intensity of stimulation – this was verified by comparing the amplitude of MEPs recorded during median nerve stimulation at the forearm with a fixed intensity before and after the coil cooling.

In protocol 1, the rTMS was delivered over the left M1 hot spot for 15 min at a frequency of 1 Hz (900 total delivered stimuli), with an intensity of 10% above individual thresholds. During this period, the coil was fixed by Velcro strips in the same position and MEPs were simultaneously recorded from the right thenar and deltoid muscles. In our experimental protocol, MEPs were only present in thenar muscles; the employed montage permitted the monitoring in real time of both the eventual progressive amplitude increases in MEP size and any unwanted spread of excitation at the cortical level to the deltoid muscle, outside the hand area of M1. Both signs have been considered as warnings to prevent seizure induction (Chen *et al.*, 1997), although the combination of frequency/intensity stimulation that we used in the present study is safe according to safety tables (Wassermann, 1998). A four-channel system (Amplaid MK VI) was used both for MEP recordings and for driving the repetitive stimulator.

Thumb twitches evoked by transcranial stimuli and self-paced movements performed during the BP paradigm had the same initial direction as measured by the accelerometer. Due to the relatively low intensity of the TMS, accelerometric peak-to-peak amplitudes were larger for voluntary movements.

Protocol 2 was performed (15 min, 1 Hz, with the same intensity used for the real stimulation) by positioning the coil slightly anterior to the left M1, tilted away (~45°) from the effective orientation tangential to the scalp surface and resting on one of the wings. In this condition, acoustic noise and scalp contact were perceived by subjects almost identically as during protocol 1, but there was no motor response in the contralateral hand muscles and subthreshold stimulation was avoided.

At the end of the rTMS session as well as after the sham session, the same BP paradigm as in basal condition was run for 15 min (see Fig. 1).

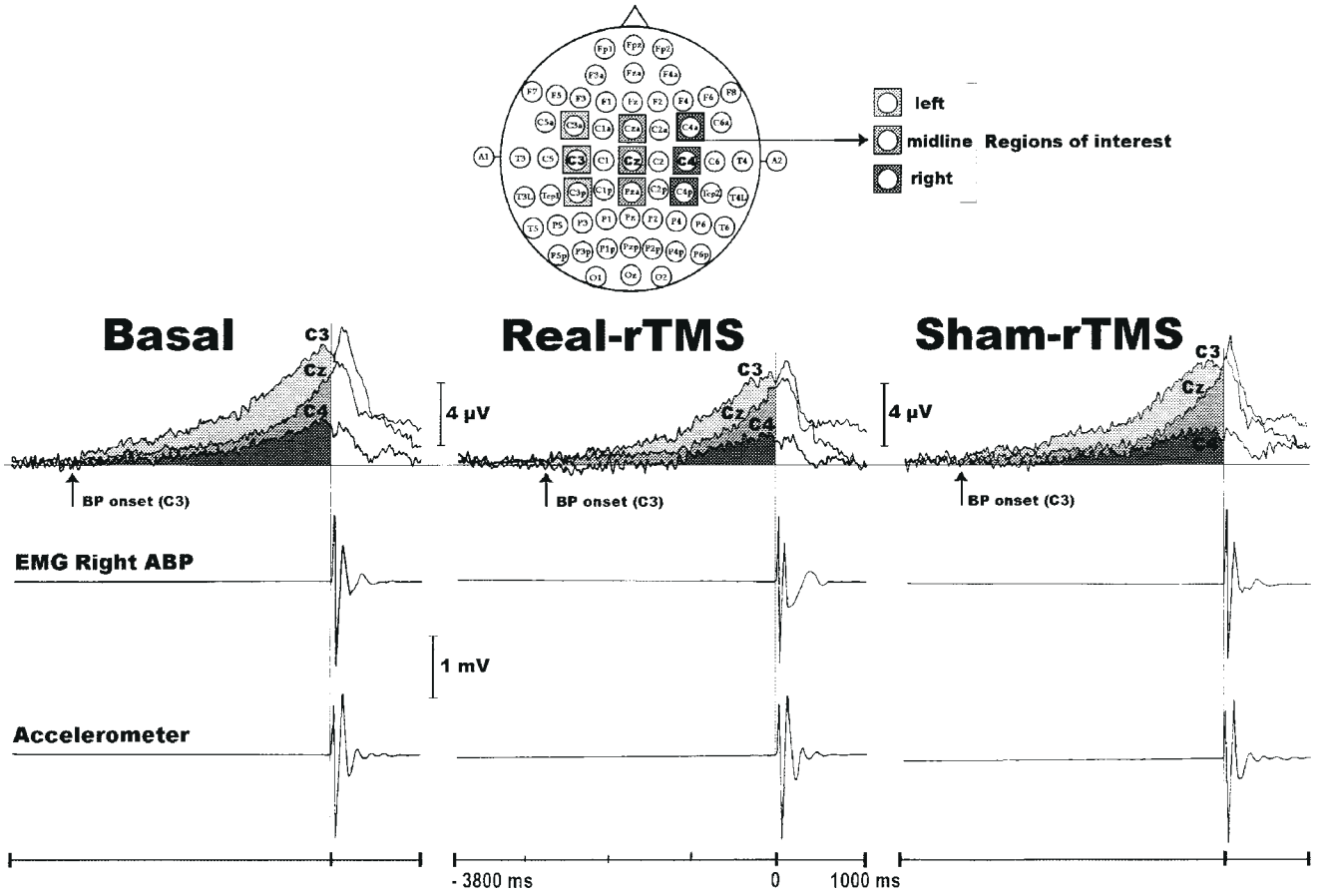

Figure 2. Top: scheme of the electrode positioning. Grey circles indicate the scalp sites, from which original sample traces shown below are taken (C3, Cz, C4). Each BP is the average of 85 movement-related trials. EMG: electromyogram of the right abductor pollicis brevis muscle (ABP) and accelerometer of the thumb. Note the amplitude reduction of the negative phase preceding the movement onset in all the represented electrodes after real rTMS of the left M1 (middle traces) and the shortening of the BP onset time.

Before the basal condition, immediately after the protocols 1 and 2, a finger-tapping test (= number of thumb oppositions to the other finger's tip in 15 s) was used to evaluate whether 1 Hz TMS induced changes in major motor performance. During the tapping test accelerometric recordings were not carried out. The number of tappings was monitored independently by two examiners.

In protocol 3, subjects were asked to produce 900 thumb movements at 1 Hz. The appropriate frequency for voluntary movements was paced by a metronome. Thus, the velocity, rate and total number of the movements (900) was similar to that in protocol 1; the peak-to-peak accelerometric amplitude of these voluntary movements was about twice the size of that of the TMS-linked twitches. This protocol was run with two of the investigated subjects, on a different day from that of the experiment. The basal BP recording was performed before and immediately after the 900 1 Hz thumb twitches, mimicking those evoked by the real rTMS. Protocol 3 was performed to investigate whether changes in movement-related cerebral activity were specifically induced by the active rTMS or were simply due to the 900 movements performed.

In one of the three subjects in which the protocol 1 was performed first (cf. Fig. 1), the entire procedure was repeated 3 days later, with the order of protocols 1 and 2 inverted.

EEG Recording Procedure and Data Analysis

Using a 64-channel EEG system (Neuroscan), brain electrical potentials were recorded in continuous mode from 61 scalp positions distributed equally over both hemispheres (cf. Fig. 2) referenced to a Cz electrode. The EMG, the accelerometer and an electro-oculogram were recorded as well. Bandpass filters were set to DC-100 Hz with a sampling rate of 500 Hz. The ground electrode was on the forehead. Two of the examiners made the following analysis blindly: a trigger signal was inserted manually at the beginning of the EMG, after reviewing all individual trials; only trials with a very sharp onset rising up from total muscular relaxation were selected for further analysis. A total of 75–90 artefact-free trials were used for each experimental condition. Since the study was designed to investigate rTMS-related changes in the cortical activity preceding movements, rather than behavioural effects on movement kinematics, only trials with the same EMG (= onset rising up from muscular 'silence', with the first EMG burst of >70 μV followed by a congruent accelerometric displacement) and the same accelerometric pattern (= same initial direction and peak-to-peak amplitude not exceeding 20% of the mean amplitude value of movements taken to compute the basal BP waveform) were selected for the three conditions. The analysis time window was set from 3500 ms before to 1000 ms after the EMG onset. The first 500 ms served as baseline. Artefact-free trials were averaged, bandpass-filtered between 0 and 35 Hz and re-referenced to common average reference.

In each subject, amplitude values (taken as the maximal negativity of the NS before movement onset) recorded from the nine central electrodes (C3a, C3, C3p, CZa, CZ, Pza, C4a, C4, C4p) during basal condition were *z*-transformed within-subjects. In such a way, a *z*-score of 0 indicates the subject's mean activity, while a *z*-score of +1 (or –1) indicates an activity 1 SD above (or below) the subject's mean. Basal mean and SD were then used to standardize amplitudes recorded during the other conditions (post-rTMS and sham). For each condition and recording electrode, 95% confidence intervals were calculated. Finally, an analysis of variance (ANOVA) for repeated measures was applied, with condition and electrode location as within-subject factors, to verify the main effect of the real rTMS as well as the homogeneity of its effect on the different scalp sites. The significance level was set at 0.05.

Results

The entire procedure was well tolerated by all subjects and no significant side effects were noted. Individual thresholds of stimulation ranged between 58 and 70% of the maximal stimulator output. One of the subjects complained of a slight headache lasting ~10 min after protocol 1, confined to the stimulated hemiscalp. No spread of excitation at the cortical level was detected by analysing online the absence of MEPs from the deltoid muscle. In keeping with previous studies using near-threshold 1 Hz rTMS, no consistent increase or decrease of the MEP amplitude during the stimulation period was observed (Pascual-Leone *et al.*, 1994b; Chen *et al.*, 1997), although a trend to an MEP amplitude reduction after a few seconds of stimulation has also been described previously (Wasserman *et al.*, 1996). In order to save time between the end of stimulation and BP execution, the cortical excitability to single transcranial stimuli after real or sham rTMS was not measured.

The number of tappings obtained in the basal condition was 33 ± 4.3. In line with previous observations and comparable parameters of rTMS (Chen *et al.*, 1997), it did not differ significantly from the values obtained immediately after protocol 1 (34.5 ± 3.9) or after protocol 2 (32.5 ± 5.2), suggesting no changes in major motor performance.

According to the experimental design, subjects performed movements at irregular intervals between 8 and 20 s. The real and the sham rTMS did not influence subjects to cluster their self-generated sequence of movements toward shorter or longer intervals. The total number of movements collected to obtain the BP did not differ across conditions (i.e. trials discarded due to artefacts or movements performed with different characteristics did not exceed 10% in each condition).

Figure 2 shows the original data set for one representative subject in the three experimental conditions. Figure 3 shows the individual behaviour of amplitude changes of the NS in the nine selected central electrodes during the different experimental conditions. In all subjects, the real rTMS induced an amplitude decrement which ranged from ~10 to ~60% of the basal value (mean ~30%). In all subjects but one, these values returned close to basal ones after the sham stimulation (see later). Figure 4 shows the spatial distribution of the maximum negativity over the nine central electrodes for the three different experimental conditions.

As shown in Figure 5 and confirmed by ANOVA, amplitude values showed significant differences between electrodes (F = 3.6; df = 8, 32; $P < 0.001$), due to the physiologically higher amount of activity recorded on central (Cz and PzA) and contralateral (C3) electrodes, together with the low activity recorded at C4a (anterior to C4), ipsilateral to the moved finger.

When conditions (real and sham rTMS) were added in the ANOVA, a significant effect was found (F = 4.9; df = 2,8; P = 0.041), due to the decrement post-real rTMS and recovery after sham stimulation. No interaction between condition and electrodes was observed (F = 0.9; df = 16, 24; P = 0.546), suggesting a generalized effect of the active rTMS consistently across scalp locations. These effects took place irrespective of the degree of the basal neural activity accompanying movements. The z-score amplitude means after sham stimulation returned close to basal activity, although with greater variability (Fig. 5).

In four out of five subjects, the BP onset times were shorter in the post-real rTMS condition than in the basal and sham conditions. The mean latency of the BP in basal condition was –2572 ± 101 and –2560 ± 452 ms after the sham stimulation. There was a trend towards a shorter BP onset time after protocol 1 (–2321 ± 296 ms). However, if pooled, these differences were not significant, due to the relatively high variability of BP onset times.

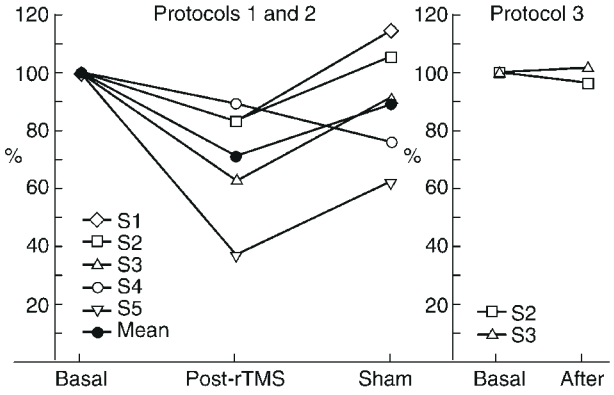

Figure 3. Left side: mean and individual percentual changes of the maximal negative amplitude of the negative slope of the BP of the five subjects (S1–S5) in the three experimental conditions of protocols 1 and 2. The black symbols indicate the mean value of the five subjects. The reduction in the post-real rTMS condition with respect to the basal and sham rTMS conditions is consistent in all subjects. Right side: individual percentual changes of the maximal negative amplitude of the negative slope of the BP in the two subjects in which the BP was repeated after metronome-paced voluntary thumb movements (protocol 3). The amplitude variability is <6%.

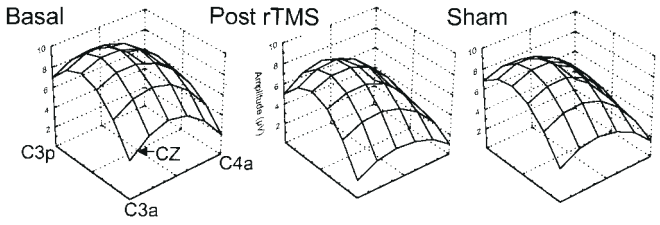

Figure 4. Spatial distribution of the maximum negativity over the nine central electrodes for the three different experimental conditions: basal, post-real rTMS and post-sham stimulation. Amplitude data of the maximal negativity preceding the EMG onset of the movement are shown as pooled subjects. The vertex electrode (CZ) is indicated by an arrow; C3a and C4a correspond to pre-central electrodes, C3p to a post-central position. The remaining electrodes (not labelled in the figure) correspond to each intersection on the x–y plane. Note the generalized amplitude reduction induced after the rTMS and the similar amplitude values between basal and sham.

In one of the subjects (S3) the experiment was repeated 3 days later and with an inverted order of protocols 2 and 1. Both the post-real rTMS reduction (35 versus 40%) and the normalization of the amplitude values after the sham stimulation were reproducible, without significant changes in the tapping test.

As shown in Figure 3, the amplitude of the NS of the subject S4 after the sham stimulation (which was performed as a first condition after the basal BP) was lower than that after the real rTMS, which was performed as the third condition. Thus, these findings suggest that a carry-over effect of the real rTMS on to the next application (sham rTMS) was unlikely to occur. This seems to be further supported by the counterbalancing of the conditions between subjects.

In order to study the specificity of the effect of the active rTMS, two subjects underwent a further BP recording before and after a sequence of 900 voluntary right thumb movements at 1 Hz, mimicking those elicited during rTMS (protocol 3; cf. Fig. 1). In both subjects, no significant differences were found either in

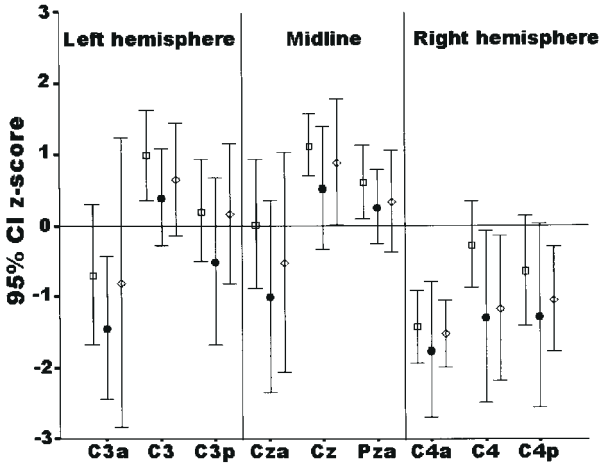

Figure 5. *z*-Scores of the maximal NS amplitude values of the nine central electrodes in the three conditions: basal (blank squares), post-TMS (black circles) and post-sham stimulation (blank rhombus). Movements were right thumb abductions. The horizontal line represents the mean *z*-score. There is a physiologically high activity on the central [Cz and PzA (posterior to Cz)] and contralateral (C3) electrodes, together with a low activity recorded at C4a, ipsilaterally to the moved finger. The inhibitory effect produced by the real rTMS, and the recovery close to basal values after the sham stimulation, are consistent across electrodes, irrespective of their initial degree of activation (= higher *z*-scores). Statistical evaluations are in the text.

BP onset times or in the maximal NS amplitude over the contralateral, midline and ipsilateral precentral electrodes (Fig. 3).

Discussion

Repetitive TMS has provided a unique opportunity to interfere non-invasively with complex human cortical functions [for a review see (Pascual-Leone *et al.*, 1998)]. However, the neurophysiological mechanisms linking the modulation of the cortical activity related to movements and rTMS are as yet poorly understood. Earlier studies on the effects of rTMS on EEG activity were carried out on subjects at rest and did not reveal significant changes after long (Wassermann *et al.*, 1996) or brief trains of stimuli (Pascual-Leone *et al.*, 1991; Rossini *et al.*, 1991). More recently, taking advantage of high-resolution EEG and a sample -and-hold circuit which eliminated the stimulus artefact from the brain signal, Ilmoniemi *et al.* demonstrated that single magnetic shocks induced immediate and sequential activation of the motor cortex, ipsilateral premotor and contralateral sensorimotor areas in relaxed healthy subjects not performing motor tasks (Illmoniemi *et al.*, 1997).

Results of the present study show that even movement-related preparatory brain activity can be modulated by rTMS without inducing modification of the overt motor performance (at least that represented by the tapping test), as already found (Chen *et al.*, 1997). However, since accelerometric parameters were not recorded during tapping performance, tiny kinematic changes in producing each tap after rTMS cannot be ruled out. The observed changes (NS amplitude reduction and tendency to shorter BP onsets) are specific for the real rTMS (protocol 1) and are likely to be cortically induced, since sham stimulation (protocol 2) and prolonged voluntary thumb twitches (protocol 3) both failed to reproduce them. In other words, it is unlikely that movements *per se*, either elicited by rTMS or voluntarily executed, would have produced changes in movement-related activity at the cortical level.

The selectivity of stimulation of M1 is ensured by the low TMS intensity producing twitches only in hand muscles and by the use of a focal coil. Under these circumstances, the induced field in the brain involves little or no subcortical structures at all (i.e. basal ganglia). If the coil is held tangentially to the scalp and near-threshold stimulation intensities are used, the currents induced in the brain flow almost parallel to the cortical surface (Roth *et al.*, 1991), resulting in a preferential activation of horizontally oriented neural networks, which are mainly cortico-cortical interneurons (Amassian *et al.*, 1990).

That the BP amplitude may be influenced by the physical and cognitive aspects of the forthcoming movement (Lang *et al.*, 1984; Kristeva-Feige *et al.*, 1997) is well known. In the attempt to minimize the influence of the subject's attentional and fatigue state on the BP amplitude, the experimental conditions were counterbalanced. The choice of similar movements, before and after active or sham rTMS, was essential to investigate changes only in the brain activity preceding the type of movement under investigation. In other words, the inclusion of self-paced movements performed with different kinematic characteristics, although behaviourally relevant, *per se* would have biased the resulting BP waveform.

The BP can be considered a measure of the overall excitatory and inhibitory synaptic activity required for the sequential planning and execution of voluntary movements: the initial part of the BP reflects the preparatory activity of the SMA (Shibasaki and Ikeda, 1996; Ball *et al.*, 1999; Cui *et al.*, 1999), while the NS is related mainly to M1 activity (Neshige *et al.*, 1988; Kristeva-Feige *et al.*, 1994, 1996; Urbano *et al.*, 1996; Cui *et al.*, 1999). Therefore, the reduced NS after rTMS might reflect a lower activity of the cortical areas taking part in the voluntary movement preparation and execution. Previous investigations have shown a lowering of the excitability threshold to a test MEP in the stimulated motor cortex after 15 min of 1 Hz rTMS (Chen *et al.*, 1997). Berardelli *et al.* (Berardelli *et al.*, 1999) have shown that the duration of the silent period induced by single transcranial stimuli in healthy subjects is increased after rTMS at 3 Hz. Siebner *et al.* (Siebner *et al.*, 1999a) used a paired-pulse TMS technique, a widely employed paradigm to estimate transsynaptic inhibitory interneural circuits at the cortical level (Kujirai *et al.*, 1993), and demonstrated that 1 Hz rTMS of M1 is able to restore the defective intracortical inhibition found in dystonic patients. Finally, these electrophysiological findings fit nicely with a recent metabolic study in which Paus *et al.* demonstrated a reduction of cerebral blood flow after rTMS, the amplitude of the effect being linked to the frequency-dependent amount of delivered stimuli (Paus *et al.*, 1998). Therefore, rTMS of M1 at 1 Hz may facilitate inhibitory interneuronal activity at the cortical level, although other sites (subcortical, spinal) at which inhibitory modulation might take place cannot be ruled out.

Notably, the NS amplitude was lower not only over the stimulated motor area but also over the midline and over the unstimulated contralateral central areas (Figs 4 and 5). This is in line with the observation of a crossed reduction of motor cortex excitability – as measured by the flattening of the MEP recruitment curve – following 1 Hz rTMS (Wassermann *et al.*, 1998), in parallel with a decrement of cerebral blood flow in the vicinity of and at a distance from the stimulating site (Fox *et al.*, 1997).

Due to the unchanged overt motor performance in the tapping test, the functional meaning of the amplitude reduction of the NS and the shortening of the BP onset after protocol 1 is still not clear. However, it suggests that a smaller amount and a shorter time of cortical activation were needed to perform the same movement after 15 min of 1 Hz rTMS of M1. This might

reflect the faster activation of smaller and/or more efficient neural networks of primary and non-primary motor areas, in a sort of an 'economy mode' of activation (including the same cortical motor areas as in the basal condition) for producing the same movement. Single unit recordings in primates indicate that the initial movement direction can be considered, together with the force, as not only the most represented motor control information within motor areas, but also the very first output signal during movement (Schwartz, 1992; Fu *et al.*, 1995). Therefore, it might be speculated that 15 min of 1 Hz rTMS of M1 (= 900 evoked thumb twitches in the same direction) would have produced a sort of 'externally forced training' for that movement, so that a preferential motor circuit would have been used by the brain to produce it. This mechanism might share some similarities with a recent experiment by Classen *et al.* (Classen *et al.*, 1998), where focal TMS induced isolated and directionally consistent thumb movements. Then movements were voluntarily performed in a different direction for several minutes. After this training, TMS-driven thumb twitches transiently changed toward the newly practiced direction, suggesting that short-term use-dependent adaptational changes took place in the cortical network encoding kinematic aspects of thumb movements.

It remains to be determined whether the observed rTMS-induced changes on movement-related cortical activity are specific for the cortical neural network controlling thumb movements, a question not addressed in this study due to the length of the experiment, which precluded the investigation of the movement-related cerebral activity for other muscles. However, the possibility of rTMS interfering with mechanisms subserving motor cortical organization is attractive and deserves further study in the light of the growing interest of this technique in the field of movement disorders.

Notes

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