Modulation of cortical oscillatory activities induced by varying single-pulse transcranial magnetic stimulation intensity over the left primary motor area: A combined EEG and TMS study

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Combined transcranial magnetic stimulation/electroencephalography (TMS/EEG) was used to study the activation and interaction of cortical regions to a variety of focused sub- and suprathreshold magnetic pulses over the left primary motor cortex (M1) in ten healthy subjects. Five single-pulse TMS conditions were performed based on the individual resting motor threshold (RMT): (1) 80%; (2) 100%; (3) 120%; (4) 130%; and (5) sham. Simple self-paced movements of the right first finger were also executed. We evaluated the reactions to magnetic stimulation and movement conditions using event-related power and event-related coherence transformations of \( \alpha \) and \( \beta \) rhythms. Event-related power reflected regional oscillatory activity of neural assemblies, while event-related coherence reflected the inter-regional functional coupling of oscillatory neural activity. The event-related power transformation revealed that the magnetic pulse modulated cortical oscillations within the first half second for both frequency ranges. For the \( \alpha \) rhythm, threshold TMS induced a small decrease in the amplitude of EEG oscillations over the stimulation site, while for both rhythms, a progressive synchronization was observed as the intensity of TMS was increased in both hemispheres. Movement onset produced a greater bilateral decrease of power compared with the effects of a magnetic pulse. The event-related coherence revealed that TMS enhanced the electrode connectivity of both hemispheres. Additionally, it was more enhanced within the first 500 ms following stimulation and was seen only for the \( \alpha \) frequency rhythm. The increase of functional connectivity between cortical areas was minor for magnetic stimulation conditions compared with that for finger movements. The single-pulse TMS over M1 partially modulated the motor cortex generators of oscillatory activity, while a simple active self-paced movement of the right first finger induced greater cortex activation and coupling between cortical regions. We propose that finger movements impose higher functional demands on the motor system compared to artificial magnetic stimulation. These findings are consistent with the possibility that the human motor system may be based on network-like oscillatory activity and might be modulated by brief electromagnetic sub- and suprathreshold pulses applied to M1, suggesting a phenomenon of resetting.

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Keywords: Motor system; Connectivity; Task-related power; Task-related coherence; EEG–TMS combination

Introduction

In the present study, we focused on brain modulation during internally, functionally generated and externally artificially induced cortex activations using combined electroencephalogram (EEG) and transcranial magnetic stimulation (TMS). TMS is a technique in which a pulsed magnetic field created by a focal coil positioned next to the scalp is used to locally depolarize neurons in brain cortex. In TMS, there is a complex interaction between the induced electric field and neuronal tissue. In fact, neuronal excitation can spread via intra- and interhemispheric association fibers to other cortical areas and across projection fibers to deeper subcortical structures. In the motor domain, the evoked responses from recorded muscles measured by a variety of different methods and using a range of TMS parameters are commonly used to indirectly quantify the excitability of the motor area (Amassian et al., 1989; Day et al., 1989; Pascual-Leone et al., 1994; Rothwell et al., 1989).

The combination of TMS and EEG provides the means to investigate how stimulation of superficial cortex results in electrophysiological responses, giving temporal information (with a resolution of the order of milliseconds) about the spread of activation from the stimulated cortical site (Ilmoniemi et al., 1997; Izumi et al., 1997; Komssi et al., 2002, 2004; Paus et al., 1998, 2001).

A prominent change in the EEG activity is the blocking of oscillatory activity, with a decrease in power in the \( \alpha \) and \( \beta \) frequency bands. This phenomenon of a decrease in power has been referred to as event-related desynchronization (ERD: \( \alpha \) and \( \beta \) rhythms, while event-related coherence revealed that TMS enhanced the electrode connectivity of both hemispheres. Additionally, it was more enhanced within the first 500 ms following stimulation and was seen only for the \( \alpha \) frequency rhythm. The increase of functional connectivity between cortical areas was minor for magnetic stimulation conditions compared with that for finger movements. The single-pulse TMS over M1 partially modulated the motor cortex generators of oscillatory activity, while a simple active self-paced movement of the right first finger induced greater cortex activation and coupling between cortical regions. We propose that finger movements impose higher functional demands on the motor system compared to artificial magnetic stimulation. These findings are consistent with the possibility that the human motor system may be based on network-like oscillatory activity and might be modulated by brief electromagnetic sub- and suprathreshold pulses applied to M1, suggesting a phenomenon of resetting.

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Pfurtscheller and Aranibar, 1977, 1979; Pfurtscheller, 1981, 1992) and has been used to describe the focal activation patterns over time associated with various sensory, motor, and cognitive tasks (e.g., Hari and Salmelin, 1997; Klimesch, 1996; Pfurtscheller and Lopes da Silva, 1999).

In the motor domain, movement preparation typically suppresses the cortical oscillations in both α and β rhythms starting about 1–2 s prior to the onset of a finger or hand movement (i.e. ERD) over contralateral sensorimotor areas, becoming bilateral when movement initiates (Leocani et al., 1997; Pfurtscheller and Berghold, 1989; Rappelsberger et al., 1994). Moreover, a brief “rebound” synchronization of neuronal activity of the β rhythm within and across different cortical regions can be observed hundreds of milliseconds after termination of voluntary movement (ERS: event-related synchronization, e.g., Pfurtscheller, 1981; Salmelin and Hari, 1994). It is assumed that ERD is an indicator of the activation of the primary sensorimotor cortex (Hari and Salmelin, 1997; Neuper and Pfurtscheller, 1996; Stanca et al., 2000).

It has been documented that ongoing oscillatory EEG activity can be modulated by magnetic stimulation delivered over the scalp (Paus et al., 2001). Single-pulse TMS induced a brief period of synchronized activity in the β range (15–30 Hz) in the vicinity of the stimulation site. It has been suggested that the TMS-induced oscillations likely reflect resetting of the oscillators (Paus et al., 2001).

Since the cortical motor areas operate in a network-like fashion (Gerloff et al., 1998), they modulate both the regional activity of individual areas and the degree of inter-regional communication (functional coupling). Functional coupling of motor areas can be assessed by computing the correlations between oscillatory activities of different brain regions. Frequency domain coherence has proven to be a useful index when applied to human EEG data (Andrew and Pfurtscheller, 1996; Classen et al., 1998; Rappelsberger et al., 1994; Thatcher, 1995). Rappelsberger et al. (1994) found an increase in coherence between central and frontal electrodes and a decrease in coherence between central and temporal electrodes during self-paced finger movement. Such event-related properties render coherence analysis a useful index of functional connectivity between different cortical areas, complementing power spectra (Andrew and Pfurtscheller, 1996). Decreases in ERD and increases in coherence during self-paced finger movement are therefore parallel, representing different parameters of the same phenomena.

Intracellular and EEG recordings in animals (Destexhe et al., 1999) have shown that modulation of the excitability of cortical pyramidal cells generates a powerful and coherent feedback to the thalamus, resulting in highly coherent oscillations similar to those measured during natural sleep. These experiments are compatible with a role for the cortex in triggering and synchronizing oscillations generated in the thalamus, through cortex–thalamus–cortex loops, thus providing a possible cellular mechanism to explain the genesis of large-scale coherent oscillations in the thalamocortical system. By stimulating the sensorimotor cortex using TMS, while recording spontaneous EEG activity, oscillations can be triggered and may also reset the ongoing rhythmic activity of a local pacemaker with a consequent synchronization of oscillations.

There is extensive evidence of movement-related modulations of cortical rhythms. Most studies with EEG have focused on the steady state changes in power and coherence associated with simple discrete events (Gerloff et al., 1998; Leocani et al., 1997; Manganotti et al., 1998). Manganotti et al. (1998) observed a power decrease accompanied by an increase in coherence over frontocentral areas during movement preparation and execution. They referred to such modulations of oscillatory activity as task-related power (TRPow) and task-related coherence (TRCoh). In the present study, we focused more on how the externally triggered event of TMS at different intensities activated the motor system and modulated cortical oscillations compared with subjects performing internally generated finger movements. Accordingly, we believe it is best to use the terms of event-related power (ERPow) and event-related coherence (ERCoh).

In order to characterize TMS- and movement-induced EEG rhythms, we investigated the connectivity and the degree of activation of cortical areas. The main aim of this study was to investigate the effects of different intensities of magnetic cortex stimulation on the EEG oscillatory activity in human healthy brain. EEG activity of the human brain has prominent oscillatory activity in the Alpha (8–12 Hz), Beta (13–30 Hz) and Gamma (30–50 Hz) frequency ranges.

First, we used the event-related desynchronization approach to determine the local patterns of oscillatory activity. Our approach was based on the spectral power analyses of EEG signals. Finally, we used coherence analysis by EEG or event-related coherence to study the functional coupling between distant cortical areas.

**Methods**

**Subjects**

Ten healthy volunteers (4 male, 6 female; age range 20–31 years) participated in the study. Eight subjects were right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). All subjects gave written informed consent for the study, in accordance with the declaration of Helsinki, which was approved by the Local Ethics Committee of the Department and Hospital.

**Experimental design**

Each subject underwent a 90 min session consisting of total of 6 experimental conditions counterbalanced across 6 blocks. Five 6-min conditions employing single-pulse TMS over the left primary motor cortex (M1) and containing 35 TMS trials were performed using a range of powers based on the individual rest motor threshold (RMT): (1) 80%; (2) 100%; (3) 120%; (4) 130%; and (5) sham TMS. Finally, an 8-min block of 80 self-paced movements of the first finger of the right hand was performed in order to compare the EEG oscillations related to movement to those elicited by TMS.

Subjects were seated in a comfortable armchair with their elbows flexed at 90°, hands pronated in a relaxed position, and eyes open. During all conditions, they were instructed to keep their eyes open, avoid blinking, and to look at a stationary fixed point in the center of a computer screen located at a distance of 1
m in front of them to prevent eye movement. In the TMS conditions, the computer triggered both the magnetic pulse and the insertion of a marker in a track of the multichannel EEG recording system.

Because event-related changes in ongoing EEG need time to develop and to recover, especially when α band rhythms are involved, the inter-trial interval was about 10 s for all experimental conditions.

Discharging the TMS coil is accompanied by a loud click and a knocking sensation on the scalp. The click elicits auditory-evoked potentials (AEP), namely the N1–P2 complex, with the maxima over the central and parietotemporal regions (Nikouline et al., 1999; Tiitinen et al., 1999). A loud 90 dB white noise was played through insert earphones to mask the coil-generated click. All subjects indicated that the white noise was sufficient to mask the auditory input.

TMS procedure

TMS was carried out with a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The magnetic stimulus had a biphasic waveform with a pulse width of about 300 μs. In this study, stimulus intensities were expressed as a percentage of the individual resting motor threshold. TMS was delivered through a figure-of-eight focal coil oriented so that the induced electric current flowed in a posterior–anterior direction over the left M1. The coil was placed tangentially compared with the scalp with the handle pointing backwards and laterally at a 45° angle away from the midline, approximately perpendicular to the line of the central sulcus. This orientation was chosen based on the finding that the lowest motor threshold is achieved when the induced electrical current in the brain flows approximately perpendicular to the line of the central sulcus (Brasil-Neto et al., 1992).

Motor evoked potentials (MEPs) were recorded from the right thenar eminence (TE) muscle with Ag/AgCl surface electrodes fixed on the skin with a belly-tendon montage. We determined the optimal position for activation of the right TE by moving the coil in 0.5 cm steps around the presumed motor hand area of the left motor cortex. The site where stimuli of slightly supra-threshold intensity consistently produced the largest MEPs with the steepest negative slope in the target muscle was marked as the ‘hot spot’. This was repeated to locate the right motor cortex hand area.

The resting motor threshold (RMT) intensity was approached from individual suprathreshold levels by reducing the stimulus intensity in 1% steps. It was defined as the lowest stimulus intensity that produced an MEP of at least 50 μV in 5 out of 10 subsequent trials (Rossini et al., 1994). The intensity of single-pulse TMS was set to 80%, 100%, 120%, and 130% of individual RMT, respectively.

The sham condition was performed with the coil tilted in order to avoid real stimulation of the motor cortex using a low intensity (80% of RMT).

Data acquisition

Continuous EEG was recorded with a 30-channel TMS-compatible system (Micromed, Treviso, Italy), with an anterior to Fz electrode as a reference and a posterior to Fz electrode used as the ground (Fig. 1).

Saturation of the EEG amplifiers by the TMS pulse occurs for a short temporal interval of about 15 ms when using a TMS-compatible amplifier. Overheating of electrodes located in the vicinity of the stimulating coil (Roth et al., 1992) was minimized by using TMS-compatible Ag/AgCl-coated electrodes (8-mm diameter, 0.5-mm thickness) with 2-mm slits to interrupt eddy currents. Electrode impedance was below 10 kΩ. The bandwidth of the amplifiers was between 0.01–512 Hz, and the signal was sampled at 1024 Hz.

The activities in the right TE muscle and in the right eye vertical electrooculogram (vEOG) were bipolarly recorded from surface electrodes using two EMG channels. The amplified and bandpass-filtered (50 Hz to 5 kHz) EMG signal was fed into a Basis Esaote Machine (Esaote Company, Florence, Italy) at a sampling rate of 5 kHz.

Data analysis

In order to characterize TMS-induced oscillations compared with finger movement, EEG data were analyzed with commercial software (NeuroScan Inc., Eaton, Ohio, USA) using two approaches: (i) event-related power and (ii) event-related coherence.

In TMS conditions, the first 20 ms following the magnetic pulse often contained large artifacts and for this reason the EEG trace analyses began at 30 ms after magnetic stimulation (Fig. 2).

For the 5 TMS conditions, waveforms were computed for three epochs: baseline (530 to 30 ms before TMS), first epoch (30 to 530 ms after TMS), and second epoch (531 to 1031 ms after TMS). In the case of the self-paced right first finger movements, the reference or baseline period was a few seconds before the onset of movement (3000 to 2500 ms). After
segmentation into non-overlapping epochs of 500 ms, EEG signals were filtered (1–30 Hz, slope 24 dB/octave). Each epoch was then inspected visually channel by channel to avoid artifacts. If the signal still contained muscle activity, EOG activity, or TMS artifacts, it was excluded from data analysis. Moreover, the 5 s prior to and after each trial of all experimental conditions containing movement activation or relaxation of the muscles were excluded to avoid using data that involved transients due to movement preparation, onset, or termination. Thus, we analyzed only steady-state tonic contraction and rest periods. A total mean of about 40 s of clean data were extracted from each TMS recording and 80 s were extracted for finger movement condition for each subject. These data lengths were necessary to achieve reliable spectral estimates.

### Event-related power

A discrete Fast Fourier Transform (FFT) of 3 non-overlapping epochs of 512 data points each was computed for all electrodes and then averaged across epochs under the same conditions. Power spectra were estimated for all frequency bins between 1 and 30 Hz (0.5 Hz bin width). Recordings were Hamming-windowed to control spectral leakage. Broad-band power changes were obtained by averaging the power values for α (8–12 Hz) and β (13–30 Hz) frequency ranges chosen for analysis (for criteria of selection of frequency ranges, see below).

In order to reduce the effects of inter-subject and inter-electrode variation in absolute spectral power values and to quantify the event-related relative changes of EEG power at an electrode \( x \) (ERP\(_{\text{Pow}_x} \)), an accepted event-related desynchronization/synchronization (ERD/ERS) procedure was used (Pfurtscheller and Aranibar, 1979; Pfurtscheller and Neuper, 1994), according to Eq. (1).

\[
\text{ERP}\text{Pow}_x = \frac{(\text{Pow}_x^{\text{activation}} - \text{Pow}_x^{\text{rest}})}{\text{Pow}_x^{\text{rest}}} \times 100
\]

The ERP\(_{\text{Pow}} \) (or ERD/ERS) transformation was defined as the percentage decrease/increase of instant power density at the ‘event’ compared to a ‘pre-event’ baseline. Therefore, event-related power decreases (‘cortical activation state’) are expressed as negative values, while event-related power increases (‘cortical idling state’) are expressed as positive values.

### Event-related coherence

Coherence was calculated by selecting a combination of C3 electrode (the nearest channel to the individual ‘hot-spot’) with all pairs from the FFT power spectrum. The coherence values were calculated for each frequency bin \( \lambda \) according to Eq. (2) using commercial software (Neuroscan).

\[
\text{Coh}_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}|^2}{(|f_{xx}(\lambda)| |f_{yy}(\lambda)|)}
\]

Eq. (2) is the extension of the Pearson’s correlation coefficient to complex number pairs. In this equation, \( f \) denotes the spectral estimate of two EEG signals, \( x \) and \( y \) for a given frequency bin (\( \lambda \)). The numerator contains the cross-spectrum for \( x \) and \( y \) (\( f_{xy} \)), the denominator the respective autospectra for \( x \) (\( f_{xx} \)) and \( y \) (\( f_{yy} \)). For the frequency \( \lambda \), the coherence value (Coh\(_{xy} \)) is obtained by squaring the magnitude of the complex correlation coefficient \( R \) and is a real number between 0 and 1. To obtain broad-band coherence values, Coh\(_{xy} \) (\( \lambda \)) was averaged over frequency bins in the chosen α (8–12 Hz) and β (13–30 Hz) frequency bands. Because coherence is the cross-correlation of two power spectra divided by the respective powers, it is already normalized by power within each subject. In order to reduce the effect of inter-subject and inter-electrode pair variations in absolute coherence values introduced by the reference electrodes (Fein et al., 1988; Rappelsberger and Petsche, 1988), event-related relative coherence (ERCoh\(_{xy} \)) was obtained by subtracting the resting value (Coh\(_{xy} \) \( \text{rest} \)) from the corresponding activation conditions (Coh\(_{xy} \) \( \text{activation} \)), according to Eq. (3).

\[
\text{ERCoh}_{xy} = \text{Coh}_{xy}^{\text{activation}} - \text{Coh}_{xy}^{\text{rest}}
\]

Therefore, coherence magnitude increments were expressed as positive values, and coherence decrements were expressed as negative values (Manganotti et al., 1998).

The measurement of power and coherence was determined across the entire range of α and β bands since they have been previously shown to be particularly sensitive to movement-related changes in cortical oscillatory activity in humans (Salmelin and
Hari, 1994; Tihonen et al., 1989). An alternative, perhaps more sensitive, method has been described by Doppelmayr et al. (1998) in which power is measured around the mean peak frequency evident in the α band in each subject. Nevertheless, measurements across predefined α bands have been used by many authors (Andrew and Pfurtscheller, 1997; Deiber et al., 2001; Manganotti et al., 1998; Mima et al., 2000a) and, as demonstrated in the results, were sensitive enough to reveal TMS-induced differences in coherence.

Statistical analysis

Event-related power

Spectral analysis with ERPow transformation was submitted to two repeated analysis of variance measurements (ANOVAs) for the α (8–12 Hz) and β (13–30 Hz) frequency ranges, respectively. Each ANOVA had three intra-subject factors; ‘epoch of time’ (first epoch, and second epoch after TMS or finger movement); ‘experimental condition’ (TMS at 80%, TMS at 100%, TMS at 120%, TMS at 130%, sham TMS, TMS at 130% of individual RMT, and self-paced right first finger movement); and ‘electrode’ (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4).

Event-related coherence

Spectral analysis with ERCoh transformation was between the C3 electrode (the nearest channel to the individual ‘hot-spot’) coupled with 8 electrodes (F3, Fz, F4, Cz, C4, P3, Pz, and P4). Each couple of electrode coherence was submitted to two repeated analysis of variance measurements (ANOVAs) for the α (8–12 Hz) and β (13–30 Hz) frequency ranges, respectively. Each ANOVA had two within-subjects factors; ‘epoch of time’ (first epoch and second epoch after TMS or finger movement); and ‘experimental condition’ (TMS at 80%, TMS at 100%, TMS at 120%, TMS at 130%, sham TMS, TMS at 130% of individual RMT, and self-paced right first finger movement).

In both, ERPow and ERCoh transformations, Bonferroni corrections were used for post-hoc paired t test comparisons. For all statistical tests, a P < 0.05 was considered significant.

Results

Event-related power

In general, the ANOVAs for event-related power transformation revealed that TMS induced oscillations in both the α (8–12 Hz) and β (13–30 Hz) frequency ranges. The oscillations began immediately after the pulse and were restricted to the first 500 ms after magnetic stimulation. Threshold single-pulse TMS induced a small decrease in amplitude of EEG oscillations in the α frequency band in the vicinity of the stimulation site, with a progressive synchronization with increasing TMS intensity for both rhythms. This trend was accentuated in premotor and parietal cortex ipsilateral to the stimulation side. The movement condition produced a greater bilateral decrease of power compared with TMS at 100% RMT. Overall, during the first epoch, both frequency bands showed a decrease in EEG oscillations (reduction of power) in the finger movement condition, in contrast to a particularly evident power increase for conditions with high intensity TMS.

Power changes in the Alpha band

Fig. 3 shows the grand average of ERPow for the α band (8–12 Hz) as a function of the three within-subjects factors: epoch of time, experimental condition, and electrode.

The ANOVA showed the following statistically significant main effects and interactions: epoch F(1,9) = 36.203 P < 0.001; experimental condition F(5,45) = 2.957 P < 0.05; electrode F(8,72) = 3.991 P < 0.001; epoch × experimental condition F(5,45) = 4.658 P < 0.01; electrode × epoch F(8,72) = 2.115 P < 0.05; experimental condition × electrode F(40,360) = 2.344 P < 0.001; and epoch × experimental condition × electrode with F(40,360) = 2.050 P < 0.001.

Post-hoc analyses of the three-way epoch × experimental condition × electrode interaction showed that there was a generalized synchronization in EEG oscillations in the first epoch compared with the second epoch. This effect of increased amplitude of cortical oscillations was ipsilateral to stimulation and suggests a short time effect of modulation of oscillatory activity induced by the TMS pulse. Comparing electrodes within the same experimental condition and the same epoch revealed a significant difference in the increase in EEG oscillations between Cz and Pz electrodes only at the first epoch and with TMS at 130% RMT (60.3 vs. 3.5%, respectively). This result reflects an effect of the magnetic field in modulation of synchronization of the oscillatory activities between the different cortical regions.

Considering the first epoch, distinguishing each electrode of the analyses, the post-hoc pairwise comparisons between the experimental conditions were significant. Thus, for the majority of electrodes, the task-related power results suggested that, in the α frequency range (8–12 Hz), internally generated finger movements are associated with higher regional activation and with a power decrease of the bilateral motor cortex, premotor cortex, and mesial frontocentral premotor cortex, compared with the TMS conditions. TMS pulses induced an amplitude increase in EEG oscillations with synchronization of cortical activity and an increase in stimulation intensity. More precisely, for the F3 electrode, there was a significant synchronization between the TMS 130% compared with sham TMS condition (48.1 vs. 3.6%). A similar difference between the two conditions was observed for the Fz electrode (44.3% vs. –0.2%). Moreover, within the same electrode, there was a significant amplitude decrease in EEG oscillations between the finger movement condition and the synchronization of all the TMS intensities (–26.3 vs. 23.9, 30.0, 30.1, 44.3%, respectively). For the C3 electrode, there was a significant synchronization of the EEG oscillatory activity for TMS at 130%, while finger movement produced a decrease in EEG power (31.2 vs. –15.6%). There was also significant synchronization between the TMS 130% condition compared with sub-threshold TMS condition (31.2 vs. 5.7%).

For the Cz electrode, there was a significant synchronization of the TMS 130% condition compared with TMS at 80% of RMT (60.3 vs. 5.0%) and a significant synchronization for TMS at 130% of RMT compared with a decrease in EEG oscillations of finger movement (60.3 vs. –15.7%). For the C4 electrode, there was a significant power decrease of the movement condition compared with the sham TMS condition (–20.0 vs. 1.6%). For the P3 electrode, there was a significant difference between the increase in EEG oscillations of TMS 130% and the decrease of power of TMS 120% conditions, respectively (36.0 vs. –12.5%). Additionally, there was a significant difference between the decrease in...
oscillations of the finger movement condition and the power of TMS at 130% RMT (−24.8 vs. 3.5%, respectively). Finally, for the P4 electrode, like electrode P3, there was a significant difference between the synchronization of TMS 130% and the reduction in EEG oscillations of TMS 120% conditions (36.1 vs. 13.5%, respectively) (see Fig. 3).

Power changes in Beta band

Fig. 4 shows the grand average event-related power changes for the β band (13–30 Hz) as a function of the three intra-subject factors, namely, the epoch of time, the experimental condition, and the electrode.

The ANOVAs executed for β (13–30 Hz) frequency ranges showed that the epoch × condition interaction with $F_{(5,45)} = 9.197$, $P < 0.001$ showed a statistically significant interaction. Post-hoc comparisons showed that, during the first epoch and for overall electrode placement, there was significant synchronization between the TMS at 130% RMT and sham TMS conditions (19.2 vs. 2.2%, respectively). There was also a significant synchronization of EEG oscillations for TMS at 130% RMT compared with the amplitude decrease in EEG oscillations in the finger movement condition (19.2 vs. −14.1%, respectively). Post-hoc comparisons between the two epochs for all electrodes for TMS at 120% RMT showed a significant difference between the increase of power at first epoch compared with second epoch (13.8 vs. −0.2). A similar trend was obtained for TMS at 130% RMT (19.2 vs. 6.2%, respectively). For finger movement, there was a significant difference between the amplitude decrease in EEG oscillations at the first epoch after the movement onset compared with the rebound synchronization of the second epoch (−14.1 vs. 8.6%, respectively) (Fig. 4).

Event-related coherence

In general, the ANOVA indicated that the changes in event-related coherence transformation were not globally present in any given electrode pair. Increases in task-related coherence were more prominent between motor and fronto-central areas for TMS conditions with the addition of left parietal and contralateral motor areas for finger movement. This increased density in the functional link was higher for the α band than for the β band. TMS at 130% RMT caused a significant increase in the connectivity between cortical regions with respect to sham TMS. On visual inspection, the right finger movement often
produced a greater increase in functional coherence between cortex areas compared with all TMS conditions and with a significant difference compared to sub-threshold TMS intensity conditions.

**Coherence changes in Alpha band**

Fig. 5 shows the average event-related coherence for the α band for each of 8 electrodes coupled with “C3” as a function of the experimental condition. Considering all the ANOVAs for averaged coherence between the 8 electrodes referenced to C3, only the main effect of experimental condition was statistically significant. For the C3–F3 pair of electrodes, the experimental condition factor was significant, with $F_{(5,45)} = 4.016$ ($P < 0.005$). Post-hoc comparisons demonstrated that the functional coupling between the two electrodes was greater for TMS at 130% RMT and finger movement compared with sham TMS (0.035, 0.111 vs. −0.027, respectively). A similar effect was seen for the C3–Fz coupling, with $F_{(5,45)} = 4.727$ ($P < 0.002$), with a significant coherence difference between the TMS 130% and finger movement conditions compared with the sham TMS condition (0.027, 0.075 vs. −0.032, respectively). A significant coherence difference between the TMS 80% and finger movement condition was observed for the C3–F4 coupling, with $F_{(5,45)} = 3.246$ ($P < 0.05$), (−0.004 vs. 0.079, respectively). The C3–Cz electrode coupling showed a significant difference between the sham TMS and both TMS 130% and finger movement ($F_{(5,45)} = 2.911$ ($P < 0.05$), −0.026 vs. 0.062, 0.116, respectively). For the C3–C4 electrode coupling, there was a significant difference between TMS 80% compared with finger movement condition ($F_{(5,45)} = 2.561$ ($P < 0.05$), 0.004 vs. 0.100, respectively). For the C3–P3 coupling, there was a significant difference between both TMS 80% and sham TMS conditions compared with finger movement condition ($F_{(5,45)} = 3.616$ ($P < 0.01$), −0.041, 0.001 vs. 0.085, respectively).

Taken together, these results show that, for the 8–12 Hz frequency band, only TMS at 130% RMT, like the finger movement condition, produced a significant increase in electrode coupling compared with the sham TMS condition. This trend was shown for the ipsilateral side of stimulation for the F3–C3, Fz–C3, and Cz–C3 pairs of electrodes. On the contrary, for P3–C3 couple of electrodes and TMS at 80% of individual RMT, a
significant decrease in ERCoh values was seen, in contrast to an increased density of functional links obtained in the finger movement condition (Fig. 5).

Coherence changes in the Beta band

Fig. 6 shows the average event-related coherence for the beta band for each of 8 electrodes coupled with “C3” as a function of the experimental condition. The ANOVA executed for the beta range and for C3–F3 electrode coupling indicated that only the epoch effect was significant with $F_{(1,9)} = 10.056 \ (P < 0.05)$. This suggests that in the overall experimental conditions the connectivity between the electrodes was different between the first compared with the second epoch of time after the event (0.001 vs. $-0.022$, respectively). A similar trend was seen for C3–Fz, and epoch factor with $F_{(1,9)} = 16.453 \ (P < 0.01)$, as it showed a significant coherence difference between the first compared with the second epoch (0.003 vs. $-0.011$, respectively). Again, for the C3–Cz couple, there was a significant interaction of epoch with condition, with $F_{(5,45)} = 3.134 \ (P < 0.05)$. The effect of TMS at 100% RMT was different for the first epoch compared with the second one (0.002 vs. $-0.010$, respectively). There was also a significant difference between the TMS at 130% RMT and the two epochs of time (0.011 vs. $-0.018$).

The results for the 13–30 Hz interval show that there was a significant decrease in electrode coupling in the second epoch of time after the TMS stimulation for the F3–C3, Fz–C3, and Cz–C3 pairs of electrodes (Fig. 6).

Discussion

The question we wished to address herein was whether TMS produces changes in cortical oscillatory activity not only at the site of TMS stimulation but also at distant sites connected synaptically.

We used measures of EEG power and coherence to observe the possible modulation of brain oscillations as a consequence of TMS stimulation. The main finding was the effect of the intensity of TMS on oscillatory activity, which to our knowledge has not been previously reported. Moreover, we compared
the effects of an externally triggered single-pulse TMS to the effects of an internally self-paced finger movement. Our results show that the electrical activity caused by the brief electromagnetic sub- and suprathreshold pulses applied to M1 induced short lasting oscillations in the β and α frequency ranges in the human brain, with the induced effects being related to the intensity of stimulation. Furthermore, single-pulse TMS and simple finger movements were associated with different patterns of functional coupling and regional activation of human cortical motor areas. In fact, the externally triggered single-pulse TMS induced an increase of power of regional oscillatory activity and less synchronization of inter-regional electrode coupling compared with a larger decrease of power and a greater functional coupling between cortical regions produced by the internally generated self-paced finger movement.

While motor event-related changes in oscillatory activity correspond to well known EEG and MEG (magnetoencephalogram) (Pfurtscheller and Lopes da Silva, 1999; Salmelin and Hari, 1994) findings, TMS-induced EEG oscillations to our knowledge have not been widely studied (Paus et al., 2001).

Oscillatory activity and movement

It has been shown by electrocorticography studies that movement preparation and execution are associated with changes in oscillatory neuronal activity in bilateral sensorimotor areas and are also reflected in a decrease of EEG oscillatory activity of the mu rhythm (Jasper and Penfield, 1949). Changes in the β band or in selected frequencies of the α band may represent activities closely related to the preparation and execution of movement, as measured by movement-related modulations in power (Pfurtscheller and Neuper, 1994; Salmelin and Hari, 1994; Toro et al., 1994a,b; Stancak and Pfurtscheller, 1996ac; Leocani et al., 1997) and coherence (Gerloff et al., 1998; Manganotti et al., 1998).

The different importance of α and β bands in the movement domain has been previously studied, and spontaneous oscillations in the β frequency range occurring at rest have been measured with EEG (Pfurtscheller, 1992) and MEG (Hari and Salmelin, 1997; Salmelin and Hari, 1994). Furthermore, β band oscillation synchronization between EEG/MEG signals and electromyogram (EMG) signals, particularly in the 15- to 30-Hz range, has
confirmed the functional importance of cortical $\beta$ rhythms in the motor efferent command (Brown et al., 1998; Conway et al., 1995; Hari and Salenius, 1999; Mima et al., 2000b; Salenius et al., 1997). Marsden et al. (2000) confirmed these observations in patients by recording electrical activity directly from the cortex. Changes in both frequency bands have been studied with spontaneous, self-paced, or externally triggered movements in the majority of reported studies. Only a few investigations have examined the effect of passive movement or peripheral stimulation on oscillatory cortical activity (Salmelin and Hari, 1994).

In our study, the EEG frequency domain analysis with event-related power transformation ($\alpha$ and $\beta$ bands) showed regional power decreases of the bilateral sensorimotor (primary motor and primary sensory) cortex (C3, C4 electrodes) and probably the lateral premotor cortex (area 6), as well as the SMA during right finger movements. Local decreases in oscillatory activity (event-related power decrease) are thought to reflect increased activity of extended neural assemblies in the cortex (Jasper and Penfield, 1949; Toro et al., 1994a;b; Stancak and Pfurtscheller, 1996a,b,c).

The extension of the activated task-related power area over the midline and towards electrode Fz can be most readily explained by the extension of the activated task-related power area over the main regions of interest during internally paced movements, in accordance with previous findings (Deiber et al., 1996; Gerloff et al., 1998).

Correlated activity in distant brain areas has been observed in relation to visuomotor performance in humans based on coherence (task-related coherence) analysis of raw EEG signals in the frequency domain. In the present study, event-related coherence was extended over the main regions of interest during internally paced finger movements, namely, the left and right central, mesial, frontocentral, and lateral premotor regions. The majority of previous results of motor task execution in humans have suggested that enhanced functional coupling of cortical regions reflects excitatory interaction, as indicated by increases in the inter-regional cross-correlation (Classen et al., 1998; Gerloff et al., 1998; Manganotti et al., 1998).

However, it is unclear whether the reciprocal interhemispheric inhibition across transcallosal cortico-cortical connections is always the mechanism involved in synchronizing inter-regional coherence (Jones, 1993). An alternative explanation invokes the relevance of enhancing the excitability of cortical pyramidal cells generating a more powerful and coherent feedback onto the thalamus that, as common pacemaker, synchronizes the cortical oscillations with the intervention of thalamocortical pathways (Destexhe et al., 1999; Steriade and Amzica, 1996). Stimulation of the sensorimotor cortex by TMS, a non-invasive technique, in humans allows for evaluation of this hypothesis based on observations in animal studies.

In the present study, self-paced finger movement produced the expected decrease in $\alpha$ and $\beta$ power over the central electrodes (i.e. decrease in amplitude of EEG oscillations). This was associated with a large increase of cortico-cortical coherence between ipsi- and contralateral central electrodes. The magnetic stimulation also produced an increase of power (i.e. increase in amplitude of EEG oscillations) in both $\alpha$ and $\beta$ bands associated with a lower synchronization of cortico-cortical electrode coupling restricted to the $\alpha$ rhythm compared with finger movement. We suggest that the relatively widespread increase of $\alpha$ and $\beta$ oscillations induced by TMS most likely reflects a phenomenon of ‘resetting’ more than an ‘idling’ state of the brain (Pfurtscheller et al., 1996). Resetting rhythms might be established in cortical networks or be driven by a common thalamic pacemaker (Destexhe et al., 1999; Steriade and Amzica, 1996). This effect is clearly short lasting because it occurs within the first 500 ms, while the self-paced movement produced a longer decrease in power. The effect seems strictly related to the TMS since the sham condition did not produce any effects on the oscillatory activity. The increase in power was present in both the $\alpha$ and $\beta$ bands probably because the higher oscillatory activity from 10 to 20 Hz is more sensitive to motor cortex activity.

Oscillatory activity and TMS

Different studies have investigated the effect of TMS on EEG recording mainly by looking at slow evoked activity by magnetic stimulation (Ilmoniemi et al., 1997, Komssi et al., 2004) and by click auditory stimulation (Tiitinen et al., 1999; Virtanen et al., 1999). In particular, TMS evoked potentials are characterized by short and long latency components between 15 to 185 ms distributed over the central and bilateral scalp. The EEG response amplitude has been shown to increase with increased stimulation intensity from 60% to 120% of MT (Komssi et al., 2004). Most authors considered these components to be sourced by motor areas that are artificially stimulated by magnetic stimulation. On the other hand, interaction between TMS and visual evoked potentials has been reported in other studies (Thut et al., 2003a,b) in which TMS can modify the amplitude of the evoked potentials associated with changes in behavioral performance. The effects of TMS on oscillatory activity have been investigated in only a limited number of studies (e.g., Paus et al., 2001). Synchronization of $\beta$ activity has been observed after single-pulse magnetic stimulation and associated with slow evoked potentials. The phenomenon has been linked to a form of resetting of the ongoing oscillatory activity produced by external magnetic stimulation of the brain (Paus et al., 2001). Animal investigations have demonstrated that electrical brain stimulation can trigger an oscillation and/or reset the ongoing rhythmic activity of a local pacemaker (Destexhe et al., 1999). Current models of interacting cortical and thalamic neurons indicate that modulation of the excitability of the cortex can affect spatiotemporal coherence with no changes in the thalamus. The highest levels of coherence are obtained by enhancing the excitability of cortical pyramidal cells. The underlying mechanism was ascribed to activity cortex–thalamus–cortex loops in which a more excitable cortical network generates a more powerful and coherent feedback onto the thalamus, resulting in highly coherent oscillations, similar to the properties measured during natural sleep (Destexhe et al., 1999). The non-invasive TMS stimulation of sensorimotor cortex in humans allows for evaluation of this hypothesis based on observations in animal studies.
The effect of TMS is strongest where the induced electric field is strongest, i.e. in the superficial cortical layers (Rothwell, 1991). Threshold and low TMS intensities produce both direct and indirect excitation of pyramidal neurons in the gray matter through transsynaptic volleys. High intensity magnetic stimulation is similar to electrical stimulation with a direct activation of axonal pathways (Amassian and Cracco, 1987; Day et al., 1989; Nakamura et al., 1996; Sakai et al., 1997). Therefore, the changes observed in the EEG activity at low intensity TMS are related to stimulation of the superficial layers of the cortex and probably to the source of oscillatory activity of the motor cortex. With the increase of stimulation intensity, the direct stimulation of the axonal pathways in deep gray matter structures could bypass the source of cortical oscillatory activity and activate deeper subcortical structures.

The synchronous activation of neurons of cortical and subcortical structures by artificial depolarization produced by TMS could be responsible for the short lasting synchronization of the oscillatory activity. It is very well known from animal studies that stimulation of subcortical structures (e.g., reticular system) in mesencephaly and pons induces a regional synchronization of the cortical oscillatory activity (Moruzzi and Magoun, 1949).

In summary, the effects of stimulation intensity in the present investigation suggest the involvement of different levels of modulation of oscillatory activity. Single-pulse TMS at low intensity stimulation might modify the coupling of motor cortex to other functional cortical areas through effects on both cortical motor neurons and interneurons (Di Lazzaro et al., 2000; Kujirai et al., 1993; Ziemann et al., 1996a,b). The effects of high intensity TMS on the motor cortex might be more indirect, involving remote aftereffects on subcortical structures. Such indirect subcortical or transcallosal effects might also account for the change in coupling between the motor cortex and the motor and premotor areas contralateral to the TMS.

Conclusion

The results of this study suggest that human cortical motor areas work in a network-like fashion, reflected in increases and decreases of the magnitude of regional oscillatory activity in addition to synchronization and desynchronization of oscillatory activity between distant regions. It is conceivable that TMS pulses affect this network by synchronization of the spontaneous activity of a population of neurons within the stimulated volume. Alternatively, the pulse may activate "idling" neurons that, owing to their membrane properties or intracortical connectivity, begin to oscillate, with the likelihood of activating these neurons being related to stimulus intensity. Irrespective of the underlying mechanisms, this study provides a demonstration of a new approach to investigate these and other cortical rhythms in both the healthy brain as well as in clinical conditions.

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References


