

Modulation of Cortical Oscillatory Activity During Transcranial Magnetic Stimulation

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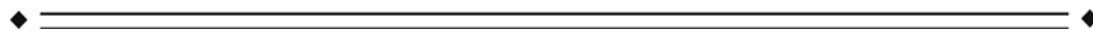
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Abstract: Transcranial magnetic stimulation (TMS) can transiently modulate cortical excitability, with a net effect depending on the stimulation frequency (≤ 1 Hz inhibition vs. ≥ 5 Hz facilitation, at least for the motor cortex). This possibility has generated interest in experiments aiming to improve deficits in clinical settings, as well as deficits in the cognitive domain. The aim of the present study was to investigate the on-line effects of low frequency (1 Hz) TMS on the EEG oscillatory activity in the healthy human brain, focusing particularly on the outcome of these modulatory effects in relation to the duration of the TMS stimulation. To this end, we used the event-related desynchronization/synchronization (ERD/ERS) approach to determine the patterns of oscillatory activity during two consecutive trains of sham and real TMS. Each train of stimulation was delivered to the left primary motor cortex (MI) of healthy subjects over a period of 10 min, while EEG rhythms were simultaneously recorded. Results indicated that TMS induced an increase in the power of brain rhythms that was related to the period of the stimulation, i.e. the synchronization of the α band increased with the duration of the stimulation, and this increase was inversely correlated with motor-evoked potentials (MEPs) amplitude. In conclusion, low frequency TMS over primary motor cortex induces a synchronization of the background oscillatory activity on the stimulated region. This induced modulation in brain oscillations seems to increase coherently with the duration of stimulation, suggesting that TMS effects may involve short-term modification of the neural circuitry sustaining MEPs characteristics. *Hum Brain Mapp* 00:000–000, 2007. © 2007 Wiley-Liss, Inc.

Key words: rTMS; electroencephalography; event-related desynchronization/synchronization; ERD/ERS; TMS/EEG coregistration; motor-evoked potentials; MEP



INTRODUCTION

Transcranial magnetic stimulation (TMS) is an electrophysiological technique, which allows the investigation of the functional state of the human cerebral cortex (Heller and Van Hulsteyn, 1992). By means of a pulsed magnetic field created by a round or eight-shaped coil positioned next to the scalp, electric currents are induced in the brain and these, in turn, produce transynaptic depolarization of neurons located in the superficial cortical layers (Heller and Van Hulsteyn, 1992). When delivered over the pri-

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115 mary motor cortex (M1) with adequate intensity, magnetic
 116 stimuli induce neural efferent volleys along the corticospinal
 117 pathway and trigger electromyographic responses,—
 118 named motor-evoked potentials (MEPs)—which can be
 119 recorded from the muscles contralateral to the site of stimu-
 120 lation (Barker et al., 1985). Amplitudes and latencies of
 121 MEPs are parameters, which allow the evaluation of the
 122 functional state of the corticospinal pathway, thus provid-
 123 ing valuable information about the functioning of motor
 124 pathways in both physiological and pathological condi-
 125 tions (Barker et al., 1986; Rossini and Rossi, 1998). In gen-
 126 eral, motor responses induced by TMS are the result of a
 127 combination of excitatory/inhibitory events occurring at
 128 different neural levels along the motor pathway and the
 129 relative contribution of these events is far from being
 130 entirely clarified.

131 Technical advances in the early 1990s introduced a novel
 132 type of TMS able to deliver trains of repetitive stimuli
 133 (rTMS) opening new research directions. Since rTMS has
 134 been introduced, it has become evident that the effects of
 135 cortical stimulation may outlast the specific stimulation pe-
 136 riod, and this possibility has generated interest in experi-
 137 ments aiming to improve deficits in the cognitive domain
 138 (Cotelli et al., 2006) as well as in clinical applications in
 139 the field of neuropsychiatry (e.g. treatment of depression)
 140 and for treating movement disorders (George et al., 1999;
 141 Miniussi et al., 2005; Wassermann and Lisanby, 2001).
 142 Above all, the possibility of inducing long-lasting changes
 143 in cortical excitability might explain the beneficial results
 144 obtained in depressed patients (Siebner and Rothwell,
 145 2003), suggesting that TMS may induce modulations, or
 146 even a rearrangement, of synaptic efficiency within a given
 147 network. Nevertheless, the mechanisms underlying these
 148 changes in cortical function remain unclear.

149 It has been shown that several parameters, such as fre-
 150 quency, duration, and intensity of stimulation, influence
 151 the effects of TMS on cortical excitability. A low frequency
 152 stimulation (stimulus rates of 1 Hz or less) of the primary
 153 motor cortex is reported to lead to a transient decrease in
 154 corticospinal excitability (Chen et al., 1997), while higher
 155 frequencies (stimulus rates of more than 5 Hz) may pro-
 156 mote a short-term increase in cortical excitability (Berar-
 157 delli et al., 1998; Di Lazzaro et al., 2002; Maeda et al., 2000;
 158 Pascual-Leone et al., 1998; Peinemann et al., 2000).

159 With regard to the duration of suprathreshold TMS
 160 effects, Pascual-Leone et al. (1994b) demonstrated a 3–
 161 4 min period of increased excitability after 10 pulses of
 162 20 Hz rTMS. Berardelli et al. (1998) observed an increase
 163 in corticospinal excitability up to 900 ms after one train of
 164 5 Hz rTMS and an increase in cerebral blood flow was
 165 observed at 10 min after 1 Hz stimulation to the motor cor-
 166 tex (Fox et al., 1997). All these studies suggest that the
 167 modulatory effects of rTMS on corticospinal excitability
 168 can vary from milliseconds to minutes, depending on fre-
 169 quency, stimulus intensity, intertrial interval, and duration
 170 of the rTMS. Nevertheless, stimulating the cerebral cortex
 171 has played an important role in therapeutic applications of

172 rTMS. Therefore, the possibility to verify on line its inhibi-
 173 tory or facilitatory effects on bioelectrical activities of the
 174 stimulated cortex, as well as of cortical areas well outside
 175 the motor cortex, is of great interest to research and clinical
 176 application. Studying the modulations of ongoing oscil-
 177 latory EEG activity by rTMS may be a key to verifying
 178 such effects. In general, voluntary movements are accom-
 179 panied by a modulation in the α and β power bands,
 180 which is characterized by a decrement (event-related
 181 desynchronization or ERD) starting about 1–3 s before the
 182 onset of a self-paced finger or hand movement over con-
 183 tralateral sensorimotor areas and becoming bilateral when
 184 the movement begins; an increment (event-related syn-
 185 chronization or ERS) occurring earlier for the β than for
 186 the α band can be observed after the movement execution
 187 (Derambure et al., 1993; Leocani et al., 1997; Manganotti
 188 et al., 1998; Pfurtscheller and Berghold, 1989; Pfurtscheller
 189 and Lopes da Silva, 1999; Stancak and Pfurtscheller, 1996).
 190 There is a general agreement that decreases in EEG power
 191 reflect oscillatory aspects of cortical activation (i.e. arousal)
 192 while increases of EEG power have been associated with
 193 predominantly inhibitory activities (Chen et al., 1998;
 194 Hummel et al., 2002; Pfurtscheller et al., 1996).

195 Even though it has been previously demonstrated that
 196 TMS can modulate the ongoing oscillatory EEG activity,
 197 only a limited number of studies have investigated this
 198 topic. Recently, Strens et al. (2002) have evaluated the
 199 effects of rTMS in the α band after a train of 1,500 low fre-
 200 quency (1 Hz) stimuli delivered over the primary motor
 201 cortex at a subthreshold intensity. Recordings were taken
 202 prior to, immediately after, 25 min after, and 50 min after
 203 rTMS. Power decreased by 6% during the active compared
 204 to the rest state, but there was no apparent difference
 205 between the different active periods. Moreover, changes
 206 occurred on the hemisphere ipsilateral but not in the one
 207 contralateral to the stimulation.

208 In a coregistration EEG-TMS study, Paus et al. (2001)
 209 reported that single-pulse TMS induced a highly synchro-
 210 nous oscillation in the β range (15–30 Hz) that lasted for
 211 several hundred milliseconds. Moreover, they observed
 212 that the probability of potentiating such rhythmicity was
 213 linked to the intensity of stimulation: the only two subjects
 214 with a minimal oscillatory response were those with the
 215 lowest stimulation intensity. Fuggetta et al. (2005) showed
 216 that the magnetic stimulation applied to M1 produced a
 217 synchronization both in α and in β rhythms, which
 218 increased linearly with TMS intensity. In addition, this
 219 effect was clearly short-lasting because it occurred within
 220 the first 500 ms after the magnetic stimulation. The TMS-
 221 induced oscillations observed in Paus et al. (2001) and
 222 Fuggetta et al. (2005) have been more linked to the reset-
 223 ting of the ongoing oscillatory activity (produced by exter-
 224 nal magnetic stimulation of the brain) than to an idling
 225 state of the brain (Pfurtscheller et al., 1996). Resetting ac-
 226 tivity might be established in cortical networks or might
 227 be driven by a common thalamic pacemaker (Destexhe
 228 et al., 1999; Steriade and Amzica, 1996).

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229 In the present study, we investigated for the first time
 230 the immediate effects of TMS on the ongoing EEG oscillatory
 231 activity in the healthy human brain, with particular
 232 focus on the relationship of such variations to the duration
 233 of the stimulating procedure. In practice, we divided
 234 10 min of continuous real low frequency TMS into three
 235 consecutive periods and compared the cortical response
 236 from the first block of stimulation (from 0 to 3.33 min) to
 237 the second (from 3.34 to 6.66 min) and to the third (from
 238 6.67 to 10 min) block of stimulation, using the ERD/ERS
 239 approach to determine the patterns of oscillatory activity
 240 during these three stimulation periods.

241 One of the basic features of ERD/ERS measurements is
 242 that the EEG power of an interval of interest (active period)
 243 is displayed relative to (i.e. as a percentage of) the
 244 power of the same EEG leads recorded during a reference
 245 period. In this study, the power in α and β frequency
 246 bands computed in the 480 ms following a low frequency
 247 rTMS (1 Hz) was compared with two different reference
 248 periods: a standard reference period 480 ms preceding
 249 each single pulse of the magnetic stimulation (standard
 250 reference) and a sham reference that was collected 480 ms
 251 following each single pulse of sham magnetic stimulation
 252 (sham reference) collected in a 10 min session just before
 253 real TMS. The standard reference was chosen according to
 254 the common procedure of using the few seconds before
 255 the event of interest (i.e. TMS pulse) as reference period,
 256 while the sham reference was chosen to better address the
 257 modulation of cortical oscillatory activity over time as well
 258 as the eventual effect of the acoustic event represented by
 259 the stimulator's noise. In fact, if modulations of cortical oscillatory
 260 activity induced by rTMS persist over time, this effect should
 261 affect both the interval preceding and following each magnetic
 262 stimulation pulse in a train of pulses. Thus, small changes
 263 should be detected by comparing the pre- and post-TMS pulse
 264 periods, but larger changes should emerge when comparing the
 265 EEG power induced by real TMS with that induced by sham TMS.

MATERIALS AND METHODS

Procedure and Subjects

272 Six healthy right-handed volunteers (three males and
 273 three females, mean age 34 years) were enrolled after giving
 274 written informed consent. None had history of neurological
 275 disorder or head injury. All experimental protocols had
 276 been approved by the local Ethics Committee.

Real and Sham TMS Was Applied Over the Left MI Simultaneously With EEG Data Collection

281 Each subject underwent an experiment consisting of two
 282 10-min sessions, a sham TMS and a real TMS session respectively,
 283 separated by some minutes stimulus-free interval to allow
 284 replacement of the coil (from sham coil used in the first
 285 session to real coil used in the second session).

286 For each session of stimulation, a train of 600 magnetic
 287 stimuli were delivered at 110% resting motor threshold with
 288 1 Hz repetition rate. Subjects wore ear plugs and were seated
 289 in a comfortable armchair in an electrically-insulated and
 290 sound-proof room with their hands pronated in a relaxed
 291 position and eyes open.

Stimulation

292 TMS was carried out by a Magstim SuperRapid magnetic
 293 stimulator connected to four booster modules and a standard
 294 figure-of-eight shaped coil with an outer winding diameter
 295 of 70 mm (Magstim Company, Whitland, UK) that generates
 296 2.2 T as a maximum output. In the present protocol individual
 297 biphasic stimuli were employed. The coil was placed
 298 tangentially to the scalp with the handle pointing backwards
 299 and laterally at about a 45° angle away from the midline.
 300 The current flow of the initial ring phase of the biphasic
 301 pulse in the TMS coil induces a current flowing from
 302 posterior to anterior in the underlying motor cortex. To
 303 establish the motor "hot spot" and the resting motor
 304 threshold, the coil was moved in steps of 0.5 cm in the
 305 fronto-central region of the scalp. The optimal position
 306 ("hot spot") was functionally defined as the point where
 307 a specific TMS pulse induced a maximum evoked motor
 308 response from the abductor pollicis brevis (APB) muscle
 309 of the right hand. At this point, to assist in the position
 310 of the TMS over the subject's head, the coil was stabilized
 311 in the same position, with respect to the site of stimulation,
 312 by means of a mechanical support that consisted of a
 313 holding arm (Magic arm Manfrotto, with two large clamps)
 314 and a heavy duty tripod. Once the coil was immobilized,
 315 the resting motor threshold was determined as the lowest
 316 stimulus intensity, which produced in the APB muscle
 317 at least five MEPs of 50 μ V out of 10 consecutive
 318 stimuli (Rossini et al., 1994).

319 For the sham-TMS condition, the Magstim Placebo Coil
 320 System was used. This is a device specially designed to
 321 replicate the standard figure-of-eight coil; it produces
 322 discharge noise without stimulating cortical tissue, since
 323 its magnetic field output is about ten-times lower compared
 324 to that delivered by the standard coil. The experimental
 325 set-up was therefore similar in both the sham and real
 326 TMS sessions.

EEG Recordings

327 TMS-compatible EEG equipment (BrainAmp 32MRplus,
 328 BrainProducts GmbH, Munich, Germany) was used for
 329 recording TMS-evoked potentials from the scalp. The EEG
 330 activity was continuously acquired from 19 scalp sites
 331 using electrodes mounted on an elastic cap, positioned
 332 according to the 10–20 International system. Additional
 333 electrodes were used as ground and reference. The ground
 334 electrode was placed in the midoccipital position (OZ).
 335 The left and right mastoid served as reference for all
 336 electrodes. A continuous recording mode without any
 337 sample

and hold circuits was chosen. The design of new amplifiers allows appropriate selection of amplifier sensitivity and operational range that is adapted to the TMS stimulus magnitude (Bonato et al., 2006). This obviates the need to wait for the signal to recover after the TMS pulse.

The signal was digitized at a sampling rate of 2.5 kHz, using a 16 bit A/D-Converter with 0.1 μV/bit sensitivity. Data were recorded with a band-pass filter of 0.1–500 Hz. To minimize overheating of the electrodes located in the vicinity of the stimulating coil, magnetic field-compatible Ag/AgCl-coated electrodes were used. Skin/electrode impedance was measured with the dedicated BrainVision module and was confirmed to be ≤5 kΩ.

Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG). The voltage difference between two electrodes located to the left and right of the external canthi recorded horizontal eye movements. The voltage difference between reference electrodes and electrodes located beneath the right eye recorded vertical eye movements and blinks.

EMG activity and MEPs from the right APB were recorded via surface electrodes in belly-tendon montage; the signal was band-pass filtered at 50–1,000 Hz with all the other parameters as for the EEG signal.

EEG Analysis

To characterize the cortical oscillatory activity, EEG data were analyzed offline with a commercial software (Scan 4.3, Compumedics Neuroscan). Since the first few milliseconds following the TMS pulse contained large and transient signals probably due to currents induced by the magnetic field, the EEG trace analyses began at 20 ms after magnetic stimulation. Epochs of 480 ms were obtained for the active period—from 20 to 500 ms after the real TMS—, for the standard reference—from –500 to –20 ms preceding the real TMS—, and for the sham reference—from 20 to 500 ms after the sham TMS pulse. For each type of period, the total 600 epochs were divided into three blocks of stimulation, each containing 200 trials (first: 1–200 magnetic stimuli; second: 201–400 magnetic stimuli; third: 401–600 magnetic stimuli). All the epochs were visually inspected and those with excessively noisy EEG (i.e. due to EMG contamination) or eye-movement artifacts (blinks or saccades) were rejected from the analyses. Overall, the number of accepted epochs for each block ranged between 65 and 194. For each subject and for each epoch/sweep, the power spectra was estimated for the α (8–12 Hz) and β (12–30 Hz) frequency bands by means of the Fast Fourier transform (Hamming window; frequency resolution = 2,000 Hz). The mean band power was then obtained by averaging the power values of the sweeps for each block of stimulation. To quantify the EEG power changes induced by TMS, event-related ERD/ERS were computed in accordance with the standard formula: [(band power in active period) – (band power in reference period)/(band power in reference period) × 100] (Pfurtscheller and Lopes

da Silva, 1999). Two different ERD/ERS were computed depending on the 480 ms reference period used (standard reference, sham reference).

The ERD/ERS transformation is 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.

For each of the two frequency bands of interest (α 8–12 Hz; β 13–30 Hz), four factors were tested within subjects, using ANOVAs: *reference period* (standard reference vs. sham reference), *stimulation block* (first, second, third), *region* [frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4)], and *side* [right (F4, C4, P4), midline (Fz, Cz, Pz), left (F3, C3, P3)]. The Huynh–Feldt ε correction factor was applied where appropriate to compensate for possible effects of nonsphericity in the measurements compared. The correction factor reduces the degree of freedom of the usual F-test; only the corrected probability values are reported. We used Statistica Data Analysis Software (Statsoft) to perform all the statistical analyses. In all conditions, the normal distribution was tested applying the Kolmogorov–Smirnov test (for all $P > 0.2$). Post-hoc tests were performed to investigate significant effects, by means of *t* tests, using the Bonferroni correction as appropriate in the case of multiple comparisons.

MEP Analysis

The MEPs recorded from the right APB were computed as the absolute amplitude between the two largest peaks of opposite polarity after 20 ms from the TMS pulse. MEPs amplitude was measured peak-to-peak from the initial down-going deflection to the following up-going one (Fig. 3). Mean MEP peak-to-peak amplitudes (mV) were normalized and calculated for each block of stimulation. To verify whether there was any correspondence between the modulatory effects of TMS on the amplitude of the MEPs and the modulatory effects of TMS on the event-related synchronization, a Pearson's correlation ($P < 0.05$) coefficient was calculated between the changes in the MEPs and the changes in the event-related synchronization over C3 and P3 through the three blocks of stimulation.

RESULTS

Subjects did not report any adverse side effects during the course of the experiment. Mean motor threshold was 62%, ranging from 58 to 65%, therefore the mean stimulation intensity was 68% of the maximum output of the stimulator.

In both the frequency bands, rTMS induced a general increase in EEG power oscillations (ERS), which reached larger amplitudes in the α compared to the β band independently of the baseline.

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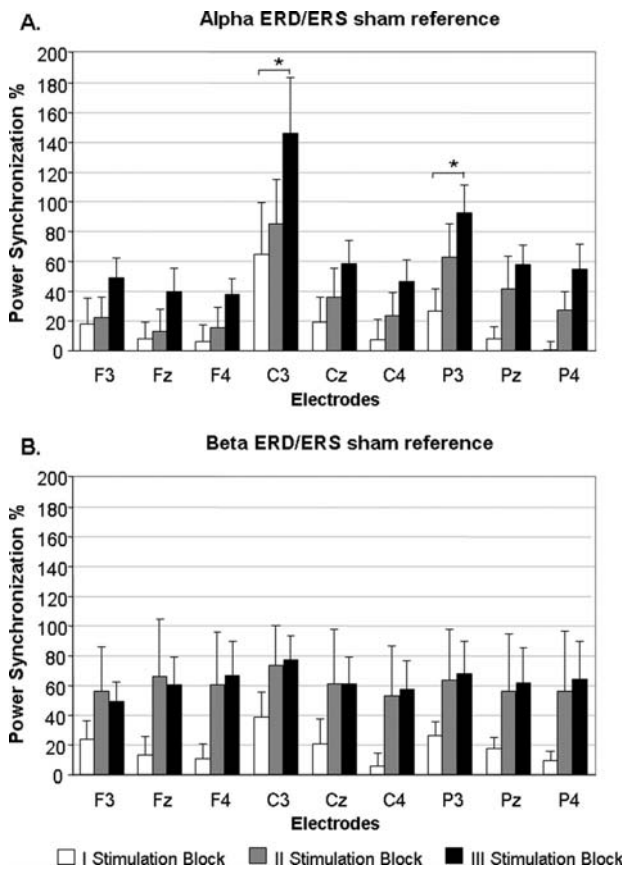


Figure 1.

Average data of the event-related power modulations induced by 1 Hz rTMS for the α frequency band (Panel A) and for the β frequency band (Panel B) using the sham TMS reference. The data are shown as a function of three successive stimulation blocks: first in white—from trial I to 200; second in gray—from trial 201 to 400; third in black—from trial 401 to 600. On the x-axis the analyzed recording electrodes are reported. Bars correspond to the standard error of mean.

α Band

The statistical analysis performed on the α frequency band revealed a significant effect of *region* [$F(2, 10) = 4.40, P = 0.042$]. Planned *t* tests proved that the synchronization over the central electrodes (mean = 52.69%; \pm SD = 24.90) was larger compared to that recorded over the frontal electrodes (mean = 17.97%; \pm SD = 13.02) ($P = 0.042$), while no difference emerged between central and parietal electrodes ($P = 0.44$). A significant effect of *side* [$F(2, 10) = 10.55, P = 0.01$] also emerged, indicating that the left hemisphere (ipsilateral to the TMS stimulation) showed a larger synchronization amplitude (mean = 56.48%; \pm SD = 24.48) compared to the right hemisphere (mean = 21.37%; \pm SD = 13.80) ($P = 0.004$) and to the midline (mean = 29.09%;

\pm SD = 16.23) ($P = 0.02$). There was no difference between the right side and the midline ($P = 1.0$). Finally, a four-way interaction [*reference period* \times *stimulation block* \times *region* \times *side*: $F(8, 40) = 2.76, P = 0.01$] showed a difference in the synchronization amplitude power between the first and the third stimulation blocks on C3 (mean = 64.62%; \pm SD = 43.95 vs. mean = 146.10%; \pm SD = 46.19) and P3 (mean = 26.78%; \pm SD = 16.11 vs. mean = 92.79%; \pm SD = 23.09) electrodes particularly when the sham TMS reference was used (Figs. 1A and 2). As a matter of fact, the post hoc analysis revealed significant differences between the two blocks directly for C3 ($P < 0.001$) and P3 ($P < 0.001$) electrodes with respect to the sham TMS reference. The same comparison using the standard reference showed a significant difference between the first and the third stimulation blocks on P3 ($P = 0.048$), but not on C3 ($P = 1.0$) electrodes. This result was indicative of an increasing modulatory effect related to the duration of the stimulation that was also partly reference-specific.

β Band

The statistical analysis performed on the β frequency band showed a significant two-way interaction [*region* \times *side*: $F(4, 20) = 4.17, P = 0.01$] indicating that the synchronization power was larger over the C3 electrode (ipsilateral to the TMS stimulation) compared to all the frontal electrodes (all $P < 0.013$), to the contralateral C4 ($P < 0.001$) and to the parietal Pz and P4 electrodes (all $P < 0.005$). There was a trend for this difference to be larger when the sham TMS reference was considered with respect to the standard reference [*reference period* \times *region* \times *side*: $F(4, 20) = 2.72, P = 0.058$] (Fig. 1B). Moreover, the main factor of *reference period* approached significance [$F(1, 5) = 6.13, P = 0.056$], revealing an interesting trend whereby real TMS induced a larger synchronization power relative to the sham TMS reference (mean = 47.01%; \pm SD = 26.93) than to the standard (i.e., pre real TMS pulse) reference (mean = 8.79%; \pm SD = 10.75).

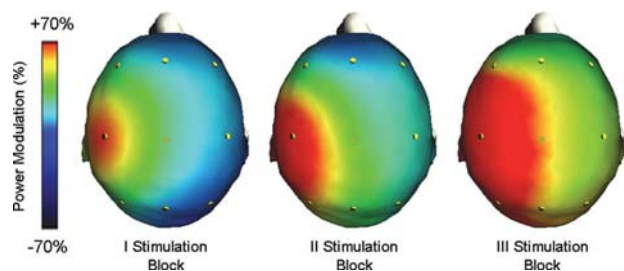


Figure 2.

Scalp distribution maps of the average ERD/ERS induced by the real rTMS for the α frequency band, with sham as reference, represented separately for the three stimulation blocks. Red color represents maximum relative synchronization.

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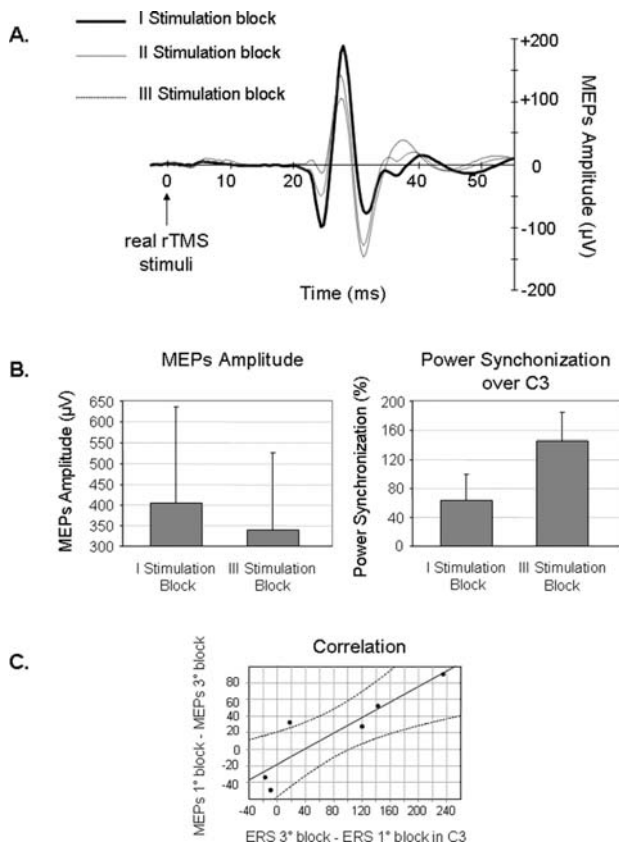


Figure 3.

Panel **A**: Motor-evoked potential recorded from the right APB; grand averaged data elicited during real TMS of the left MI in three successive stimulation blocks: the first: 1–200 magnetic stimuli (solid line), the second: 201–400 magnetic stimuli (thin line), and the third: 401–600 magnetic stimuli (dashed line). Panel **B**: Mean amplitude of the motor-evoked potential (on the left) and of the power synchronization recorded over the electrode C3 (on the right) elicited during the first and the third blocks of stimulation. Bars correspond to the standard error of mean. Panel **C**: The scatterplot shows the significant correlation between the changes in the amplitude of the MEPs, i.e. a decrease, on the y-axis and the changes in the power synchronization recorded over the electrode C3, i.e. an increase, on the x-axis, between the first and the third stimulation blocks. The dotted lines represent 95% confidence limits.

MEPs

F3 As can be seen in Figure 3A, the mean amplitude of the MEPs decreased in the second and third blocks of stimulation in comparison to the first block. Nevertheless this difference did not approach a significant value in statistical analysis ($P = n.s.$; first block 404.14 µV vs. third block 338.57 µV). Since a difference between the first and the third stimulation blocks emerged in the analysis of α band synchronization over C3 and P3 electrodes when the ERS

was computed using the sham TMS reference (*reference period* \times *stimulation block* \times *region* \times *side*), a correlation analysis was performed between the changes of the MEPs and of the ERS in the three intervals (α band; sham TMS reference). The decrease in the MEPs amplitude correlated with the increase of the power synchronization over the C3 electrode (Fig. 3B). As a matter of fact, a significant correlation emerged between the difference in the amplitude of the MEPs between the first and the third stimulation blocks and the difference in the power synchronization recorded over the electrode C3 between the two blocks ($r = 0.88, P = 0.02$) (Fig. 3C). A correlation approaching significance was also observed between the first and the second stimulation blocks ($r = 0.79, P = 0.063$). No correlation was found between the decrease of the MEPs and the increase of the synchronization amplitude over the P3 electrode.

DISCUSSION

The present study was designed to explore EEG power modulations induced by low frequency rTMS in the α and β frequency bands. According to previous studies (Fuggetta et al., 2005; Paus et al., 2001), a widespread synchronization of α and β activity has been observed after magnetic stimulation. In self-paced movements, the power synchronization typically emerges after the onset of the movement and it has been linked to an idling (Pfurtscheller et al., 1996) or “nil-working” state (Mulholland, 1995) or to an inhibitory control of neuronal activity (Hummel et al., 2002; Pfurtscheller and Andrew, 1999; Suffczynski et al., 1999), while desynchronization is present during self-paced movement and is correlated with the activation of motor areas (Pfurtscheller, 1992). Since in the present study subjects were in a relaxed state and had no process to control, it is most likely that the synchronization observed after the cortical stimulation reflects resetting of the oscillators, as previously suggested (Fuggetta et al., 2005; Paus et al., 2001). Nevertheless, it has recently been suggested that α ERS may stem principally from rhythmic fluctuations of inhibitory neurons (Klimesch et al., 2007), and therefore it may play an active role in the inhibitory control of cortical processing as evidence against the idling hypothesis.

There was a slight difference in the power modulation patterns between α and β bands. In general, a larger synchronization was reached in the α rhythm than in the β rhythm. Furthermore, in the α band, larger amplitude was observed over the stimulated hemisphere than to the contralateral one, while in the β band only the central parietal region showed a focal difference. This result is in line with findings, which state that the effect of TMS is strongest where the induced electric field is strongest (Rothwell, 1991), in this case in the left motor area. The larger involvement of the posterior regions relative to the central stimulated area in β , and partly also in the α band, could be explained by the close connections between motor and

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685 somatosensory regions, the so called sensory-motor area.
 686 The use of suprathreshold intensity induced muscle
 687 twitches that could modulate central processing via sensory
 688 afferents. It has been shown that increase of β
 689 rhythm, contralateral to the stimulated hand, can be found
 690 in sensorimotor areas following peripheral somatosensory
 691 stimulation (for a review, see Neuper et al., 2006); this observation
 692 would support our results, accounting for the β
 693 rhythm synchronization. However, these studies also suggest
 694 an associated desynchronization of the α rhythm
 695 (Neuper et al., 2006) and this is inconsistent with our
 696 results. Therefore, the effect due to the afferent input
 697 (muscle twitches) could account for synchronization of the
 698 β , but not of the α rhythm. α rhythm includes what is
 699 called the μ rhythm (10 Hz), that tends to be associated
 700 with motor activity, and several experiments suggest that
 701 the synchronization of the μ rhythm is associated with
 702 cortical inhibition of the motor cortex (Pfurtscheller et al.,
 703 1996). Finally, the coil position or its orientation could also
 704 account for these differences in the patterns of α and β
 705 bands (Amassian et al., 1989; Pascual-Leone et al., 1994a;
 706 Ruohonen et al., 1996).

707 In contrast with our results a previous study by Strens
 708 et al. (2002) found a decrease of α power immediately after
 709 subthreshold 1 Hz rTMS. This study differs from ours
 710 since we did use an on-line recording and the stimulation
 711 intensity was 110% of the individual motor threshold.
 712 Such differences in the experimental setting can account
 713 for different results. In fact other studies (Fuggetta et al.,
 714 2005; Paus et al., 2001) suggest that the intensity of stimulation
 715 determines the increase of power induced by TMS
 716 and that these effects are short lasting.

717 To characterize a possible strengthening of the effects
 718 induced by the TMS on cortical activity, we compared
 719 EEG power modulations, as well as MEPs amplitude, in
 720 three consecutive periods during a train of stimulation. An
 721 increase in the power synchronization from the first to the
 722 third block of stimulation appeared only in the α band
 723 and inversely correlated with the MEPs amplitude. This
 724 result suggests that the increasing modulatory effect of
 725 rTMS on EEG activity over the course of the stimulation
 726 may relate to the amount of energy transferred to the
 727 brain. Changes in the α band may represent activities
 728 related to source generators in motor areas as measured
 729 by movement-related EEG signal power and coherence
 730 modulation (Gerloff et al., 1998; Leocani et al., 1997; Manganotti
 731 et al., 1998; Pfurtscheller et al., 1994; Salmelin and
 732 Hari, 1994; Toro et al., 1994). In addition, the α band has
 733 been documented to be more reactive than broad β band
 734 to movement programming and execution (Manganotti
 735 et al., 1998) and to single pulse TMS (Fuggetta et al., 2005).
 736 More significant differences were observed between the
 737 first, second and third blocks of stimulation when the real
 738 TMS condition was compared with the sham baseline than
 739 when it was compared with the pre-TMS baseline. The
 740 TMS likely affected cortical activity over the entire session
 741 of stimulation by increasing the band power synchroniza-

742 tion both in the active (post-TMS pulse) and in the refer-
 743 ence period (pre-TMS pulse). Consequently, the ratio
 744 between them remained the same and did not reveal evi-
 745 dent power modulations related to TMS duration. On the
 746 contrary, the sham magnetic stimulation did not produce
 747 any power alterations, therefore representing the ideal refer-
 748 ence period. This interpretation is supported by the
 749 study of Fuggetta and colleagues (2005) in which they
 750 demonstrated that the sham condition did not produce
 751 any effect on the oscillatory EEG activity.

752 Several considerations should be made in relation to the
 753 use of the sham condition and possible potential con-
 754 founds. The first is related to the order of the sham condi-
 755 tion in the present experiment (i.e. sham always preceded
 756 to real stimulation) and the second is that indeed sham
 757 stimulation by itself is not an ideal control condition in the
 758 sense that it does not reproduce the "skin sensation" that
 759 one gets with real TMS. As regards the first point, the
 760 choice of this order raises the possibility that the increase
 761 in α power throughout the 10-min session could be a
 762 result of changes in subjects' arousal during the real stimu-
 763 lation. Nevertheless, the choice of this experimental proce-
 764 dure was based on the fact that it was not possible to
 765 counterbalance the sham and real sessions since the possi-
 766 bility of a lasting effect after TMS may have influenced a
 767 subsequent sham recording. Moreover, the specificity of
 768 the results, that were localized and lateralized, cannot
 769 account for the explanation of a general arousal effect. In
 770 the same vein, an increase of synchronization should also
 771 have been present over the first 10 min in the sham condi-
 772 tion, since subjects were in a relaxed state and had no pro-
 773 cess to control skin sensation or twitches induced by TMS;
 774 nevertheless, no differences were present between the first
 775 and the last block in the sham condition.

776 As regards the second point, a different control condi-
 777 tion, like real TMS on occipital cortex, might have been a
 778 superior approach instead of sham. Nevertheless, to try to
 779 ensure that changes in "performance" are specifically at-
 780 tributable to the effects that TMS induces upon the brain,
 781 it was necessary to have a control condition free from
 782 influences of specific TMS effects, since the stimulation of
 783 other areas as control condition could have produced an
 784 unbalanced baseline condition inducing modifications of
 785 the general brain response.

786 The main finding of the present experiment is the correla-
 787 tion between the progressive decrease of MEPs ampli-
 788 tude and the simultaneous increase in EEG synchroniza-
 789 tion, which in itself provides additional information on
 790 plasticity in the human brain. It has been known for some
 791 time that MEPs amplitude tends to decrease progressively
 792 during recurrent TMS at a slow repetition-rate; this phe-
 793 nomenon has been ascribed to self-defending mechanisms
 794 against the impact of stimulation delivered from the out-
 795 side within the intra-cortical circuitry (Rossini et al., 1991).
 796 However this explanation is unlikely from a phylogenetic
 797 point of view since there are no reasons that such a mech-
 798 anism could be useful. A more probable explanation is

799 that such modulation can be ascribed to the activation of a
800 form of neuronal gain-control, suggesting an active inhibi-
801 tory mechanism for the control of cortical processing, con-
802 gruent also with the idea that α ERS may stem principally
803 from rhythmic fluctuations of inhibitory neurons.

804 Recently it has been documented that low frequency
805 TMS (≤ 1 Hz) given at subthreshold ($\leq 95\%$ resting thresh-
806 old) or suprathreshold ($\geq 110\%$ resting threshold) intensity
807 produce a transient decrease in corticomotor excitability
808 that lasts seconds to minutes (Chen et al., 1997; Maeda
809 et al., 2000; Muellbacher et al., 2000; Touge et al., 2001). In
810 addition, low frequency (1 Hz) rTMS over the motor cortex
811 produced an increase in ipsilateral cortico-cortical coher-
812 ence immediately after the rTMS (Strens et al., 2002). It has
813 been suggested that rTMS is able to excite cortical inter-
814 neurones, thereby acting transynaptically on pyramidal
815 cells. Subthreshold low frequency rTMS has also been
816 shown to decrease regional cerebral blood flow, consistent
817 with the idea of TMS-induced activation of local inhibitory
818 mechanisms (Paus et al., 1998; Speer et al., 2000). Moreover,
819 using evoked potentials, it has been shown that 1 Hz rTMS
820 of human primary motor cortex changes cortical excitability
821 at the site of stimulation as well as in ipsilateral somatosen-
822 sory cortex, probably via cortico-cortical pathways between
823 motor and sensory cortex (Enomoto et al., 2001). Thus, in
824 agreement with previous publications, we can hypothesize
825 that rTMS produces changes in cortical inhibitory mecha-
826 nisms responsible for the development of cortical oscilla-
827 tions and increased connectivity (Contreras et al., 1997;
828 Paulus et al., 1999; Rubin and Terman, 2000). The decrease
829 in MEPs amplitude during 1 Hz TMS stimulation is consis-
830 tent with the potentiation of inhibitory mechanisms
831 related to this kind of stimulation. On the other hand, the
832 reduction in MEPs amplitudes can be related to a reduction
833 in synaptic efficacy under the stimulated site; in this case,
834 there is less postsynaptic efficacy for a fixed excitatory
835 input driven by the magnetic pulse and therefore less pre-
836 motor neuron (i.e. pyramidal cells) activity, resulting in a
837 reduced motor response (Lee et al., 2003).

838 Although the magnitude of this effect was clear, so far
839 we can only say that rTMS produces changes in cortical
840 excitability at the site of stimulation as well as in corre-
841 lated areas. Some data indicate that the effects of cortical
842 stimulation may not only induce a modification of cortical
843 excitability at the site of stimulation, but there is also the
844 possibility of a subcortical contribution to its effects. A few
845 studies have analyzed possible activation of subcortical
846 areas or changes of neuroactive substances after TMS in
847 humans, showing modulation at distant levels (Strafella
848 et al., 2001, 2003; but see Shaul et al., 2003 in human neu-
849 roblastoma cells; Szuba et al., 2001 in thyroid hormone;
850 Zangen and Hyodo, 2002 in neurotransmitter). Indeed, the
851 possibility to disentangle focal from distant effects induced
852 by TMS upon different structures of the central nervous
853 system may have valuable implications, and combining
854 EEG recording with TMS is a fascinating way to study
855 these aspects.

856 In summary, slow rTMS over primary motor cortex 856
857 induces a synchronization of α and β bands that preferen- 857
858 tially affects the stimulated hemisphere. This power modu- 858
859 lation seems to increase over time in relation to the dura- 859
860 tion of real stimulation and correlates with MEPs reduc- 860
861 tion, suggesting that TMS may affect the mechanisms 861
862 regulating short-term synaptic efficacy of the intracortical 862
863 circuitries, inducing decrease of cortical excitability or 863
864 increase of inhibition expressed as increase in cerebral syn- 864
865 chronization. Future studies on the healthy brain during 865
866 and after different motor tasks, as well as in pathophysio- 866
867 logical conditions dealing with brain excitability, will add 867
868 new information to these interesting aspects of brain neu- 868
869 rophysiology. 869
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