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EEG Modification Induced by Repetitive Transcranial Magnetic Stimulation

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Summary: Repetitive transcranial magnetic stimulation (rTMS) is a powerful, noninvasive tool for investigating cortical physiologic functions in the brain. However, EEG spectral analysis has not been investigated extensively in rTMS study. The authors investigated the influence of rTMS on the EEG power spectrum by stimulating the left frontal cortex in 32 healthy subjects. Stimulation parameters were a 10-Hz frequency, a 3-second duration, and a 100% motor threshold. The data showed that rTMS increased the peak frequency of EEG across the scalp within 2 minutes after stimulation, whereas the value decreased at 3 to 4 minutes. The mean absolute powers within 3 minutes after rTMS did not differ from those estimated before rTMS, but increased uniformly at 4 to 5 minutes. The spectra did not change after sham stimulation. These results indicate that rTMS can influence cortical activities significantly by increasing the frequency and amplitude of EEG, and is a useful tool for helping us understand brain functions. **Key Words:** EEG—Frequency components—Power spectrum—Magnetic stimulation.

Transcranial magnetic stimulation (TMS) allows noninvasive stimulation of the human brain. A large number of studies revealed that repetitive TMS (rTMS) can influence cortical functions, and the effect depends on the stimulation parameters (Classen et al., 1995; Kujirai et al., 1993; Wassermann et al., 1993). The relationship between rTMS and EEG activity has been addressed by others (Izumi et al., 1997; Jennum et al., 1994); however, whether rTMS is capable of changing EEG activity and how rTMS affects the activity remain unclear. Bridgers (1991) declared that exposure to TMS may not have persistent effects on EEG, but transient effects may occur. In an investigation of TMS over the right motor cortex with an intensity of 5% to 10% above the motor threshold, Rossini et al. (1991) demonstrated that EEG from the left central and occipital areas showed an increase in peak frequency by approximately 1 Hz, indicating that the neuronal networks revealed by EEG signals are affected by magnetic pulses. After improving their EEG recording technology by blocking signal input for 150 msec after TMS, Izumi et al. (1997) depicted a markedly slow wave, which occurred in 25% to 80% of records, with a duration ranging from 200 to 600 msec.

Recently, interest has focused on the delivery of repetitive magnetic stimulation. One of the reasons is that rTMS can disrupt brain functions for a relatively longer time than a single pulse, thus facilitating the detecting alteration of physiologic processes in the brain (Jahanshahi et al., 1997). Jahanshahi et al. (1997) delivered 100 trains of rTMS at 20 Hz in six healthy subjects over the left motor cortex, and no abnormalities were found on EEG after stimulation. However, several studies indicate that rTMS can induce epileptic seizures in healthy subjects (Pascual–Leone et al., 1993; Wassermann et al., 1996). Classen et al. (1995) reported a case of epileptic seizure induced by magnetic stimulation. First they delivered 30 stimuli at a 150% motor threshold over the motor cortex, and then continued with two stimuli at a

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90% motor threshold. An epileptic seizure occurred immediately after the transfer of the second stimulus. There was no EEG record during the study; hence, it is difficult to determine when the EEG abnormality started. In another study, Bridgers (1991) summarized that rTMS is generally safe, but not entirely free from unwanted effects, and further study to define those effects is needed.

Therefore, we assumed that rTMS could influence EEG activities and that such effects varied during different periods after the stimulation. To test this hypothesis, we calculated the power spectra of EEG signals and compared the spectra before and after rTMS. We were more interested in investigating how the spectra changed during the different periods. For this purpose, the left frontal cortex of healthy subjects was stimulated. A total of 5 minutes of EEG was collected after each train. The power spectra were estimated for each minute. Frequencies and amplitudes were compared statistically with those obtained before rTMS.

METHODS AND MATERIALS

Subjects

Thirty-two healthy men were selected and screened carefully before the study to rule out neurologic or psychological disorders. They were divided randomly into two groups: the rTMS group and the sham group. Twenty subjects were included in the rTMS group (mean age, 27 years; age range, 22–38 years), and 12 in the sham group (mean age, 27 years; age range, 24–40 years). All subjects were naive to the purposes and hypothesis of this study. This study was approved by the local ethics committee, and all subjects gave written informed consent. There were no side effects reported after the study.

Stimulation

For TMS, a high-frequency magnetic stimulator (Magstim Company Limited, Wales, UK) and a figure-of-eight-shaped coil were used in the current study. The stimuli were biphasic sine wave pulses, with a rise time of 60 μsec and a duration of 250 μsec for each pulse. The peak magnetic field was 2 T. The stimulus parameters followed the safety guidelines set out by Wassermann (1998). In each subject, two trains (10 Hz; 3 seconds per train; interval, 300 seconds) were delivered over the left prefrontal area at an intensity of 100% of the motor threshold of the right abductor pollicis brevis muscle. The coil was in a flat position and the handle was pointed toward the occiput. The stimulated position was 5 cm to the left of and 5 cm anterior to the vertex, and it was directly beneath the intersection of the two loops of the coil where the strongest magnetic field was induced.

The sham stimulation was designed carefully according to the study of Klein et al. (1999). First, all subjects were naive to rTMS treatment. None of them had received the stimulation before. They were blind to how we handled the coil and how we delivered the stimuli. They did not know whether the coil should touch their scalp, and did not know the sensation of rTMS before the experiment. Also, they did not know whether they would receive sham or real stimulation. Second, only one subject was stimulated at each time. This prevented the subjects from exchanging their feel of rTMS pulses. Accordingly, the subjects could not differentiate the sham and real rTMS. The coil was placed perpendicular to the scalp on the left frontal area without direct contact to minimize the energy flow into the skull. Thus, only the sound artifact was elicited. The stimulation parameters were the same as the real rTMS stimulation.

EEG Data

The subjects were seated comfortably in a semireclining armchair in a quiet room. To eliminate the influences on EEG, the subjects were asked to remain in a relaxed state, avoiding any movement or muscular contraction. They were instructed to close their eyes and avoid mental activities.

Fourteen electrodes were placed on the scalp according to the International 10-20 System (F_3, F_4, C_3, C_4, P_3, P_4, T_3, T_4, T_5, T_6, F_z, C_z, P_z, and O_z). The linked ear electrodes were used as a common reference. Approximately 5 minutes of EEG signals were recorded before the stimulation and after each train. EEG signals were amplified by a Neurofax 4421 (Nihon-Kohden Company, Tokyo, Japan) with a passband filter of 0.1 to 30 Hz. The signals were recorded on paper and stored simultaneously on high-fidelity magnetic tapes. Off-line, the signals were sampled from tapes at a sampling rate of 500 Hz in 16-bit resolution.

EEG signals were analyzed continuously with a time window of 4 seconds. In fact, the length of the window was 2,048 points. Therefore, every two consecutive segments contained 48 overlapping points. According to the stimulation, the segments were grouped into six periods: (1) before rTMS, (2) within 1 minute after rTMS, (3) 1 to 2 minutes after rTMS, (4) 2 to 3 minutes after rTMS, (5) 3 to 4 minutes after rTMS, and (6) 4 to 5 minutes after rTMS. EEG segments contaminated by artifacts were excluded from analysis. Approximately 10 segments were calculated in each period for each rTMS train.

TABLE 1. *The effects of factors on the power spectra among different frequency bands*

Estimated parameter	Effects	δ	θ	α	β	γ
Peak frequency	F_1	5.05†	0.39	9.74†	1.85*	6.64†
	F_2	3.93†	9.11†	57.9†	2.49*	7.41†
	$F_1 \times F_2$	0.56	0.23	0.87	0.34	0.72
Maximal absolute power	F_1	15.6†	11.2†	26.0†	5.73†	5.79†
	F_2	4.03†	14.9†	9.28†	1.73	9.08†
	$F_1 \times F_2$	0.23	0.24	0.31	0.38	0.94
Mean absolute power	F_1	16.7†	17.8†	27.9†	3.65†	8.78†
	F_2	4.66†	13.3†	6.35†	2.33*	12.8†
	$F_1 \times F_2$	0.26	0.18	0.11	0.59	0.92
Mean relative power	F_1	6.94†	10.2†	20.2†	14.2†	36.6†
	F_2	6.96†	25.3†	13.8†	1.25	15.0†
	$F_1 \times F_2$	0.34	0.12	0.30	0.53	0.63

The data are *F* values of analysis of variance.
* $0.01 < P < 0.05$.
† $P < 0.01$.
F_1, the effect of factor "channel"; F_2, the effect of factor "period"; $F_1 \times F_2$, the interaction effect of factors "channel" and "period."

Evaluated Parameters

EEG spectral analysis was performed with a conventional fast Fourier transformation algorithm. To observe the effects of stimulation, the spectrum was separated into five frequency bands: δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), and γ (30–40 Hz). Four parameters were estimated on the spectra: peak frequency, maximal absolute power, mean absolute power, and relative power.

The maximal absolute power was defined as the maximal value of power calculated by fast Fourier transformation. The value was estimated for each frequency band as well as for the whole frequency range (i.e., EEG). The peak frequency corresponded to the maximal absolute power. The mean absolute power was computed for each frequency band using the following formula: (the total power of investigated band)/(the data number within the band after fast Fourier transformation). Therefore, it stood for a mean value of the absolute power and was always smaller than its corresponding maximal absolute power. The relative power was expressed as a percentage, representing how many percent of the EEG power belonged to the investigated frequency band: (the total power of investigated band)/(the total power of EEG) × 100%. In this study, we were more interested in comparing the results among the periods after rTMS.

The Kolmogorov–Smirov test was applied to examine the normal distribution. Visual examinations using histograms were also performed on each dataset. Descriptive parameters (means and standard deviations) were calculated. Analysis of variance was performed on each frequency band in relation to two factors: "channel" × "period." Duncan's multiple range test was used for post hoc comparisons of individual variables. Significance was set at $P < 0.05$.

RESULTS

The Kolmogorov–Smirov test showed normal distributions on the estimated parameters ($P > 0.05$). For the sham stimulation, there were no significant differences detected by analysis of variance on the peak frequency, maximal absolute power, mean absolute power, and relative power in the six periods ($P > 0.05$). For the rTMS group, analysis of variance showed a strong effect for the period factor. The descriptive parameter of the *F* value in analysis of variance is summarized in Table 1. Interactions between the period and channel factors were not significant ($P > 0.05$), indicating that the effect of the period factor was not modified by electrode site (i.e., EEG signals from different electrode sites had similar changes).

Table 2 shows the peak frequency before and after rTMS. Comparing the values before rTMS, the peak frequency became faster in all channels within the first 2 minutes after the trains. The shift was significant in the frontal area, where the peak frequency was increased by 1.92 Hz at F_3 ($P < 0.01$), 1.58 Hz at F_4 ($P < 0.01$), and 1.72 Hz at F_z ($P < 0.01$). Signals recorded around the stimulated site showed similar results. For electrode C_3, the peak frequency increased by 1.34 Hz ($P < 0.05$); for T_3, by 1.585 Hz ($P < 0.01$); and for C_z, by 1.32 Hz ($P < 0.05$). Signals from electrodes far from the stimulated site also turned fast, but did not reach significance (except T_4). The values obtained at 2 to 3 minutes, 3 to 4 minutes, and 4 to 5 minutes after rTMS did not differ from those before rTMS ($P > 0.05$), indicating that the effect of rTMS weakened 2 minutes after the end of stimulation.

The mean absolute power of the α band among the electrodes was plotted in Fig. 1. The values estimated at

TABLE 2. *Peak frequency of EEG recorded at different electrode sites and during different periods*

Channel	Before rTMS	0–1 min after rTMS	1–2 min after rTMS	2–3 min after rTMS	3–4 min after rTMS	4–5 min after rTMS
F3	8.413 ± 1.384	10.33 ± 0.419†	10.26 ± 0.355†	8.900 ± 0.838	8.109 ± 1.722	8.784 ± 1.063
F4	8.570 ± 1.479	10.15 ± 0.565†	10.15 ± 0.488†	9.031 ± 0.837	8.589 ± 1.534	8.961 ± 0.904
C3	8.878 ± 1.336	10.22 ± 0.512*	10.18 ± 0.402*	9.243 ± 1.016	8.651 ± 1.598	9.105 ± 0.939
C4	9.228 ± 1.298	10.13 ± 0.598	10.14 ± 0.496	9.264 ± 0.911	8.721 ± 1.602	9.161 ± 1.094
P3	9.458 ± 1.434	10.22 ± 0.767	10.34 ± 0.375	9.653 ± 0.990	9.196 ± 1.790	9.658 ± 0.888
P4	9.549 ± 1.432	10.26 ± 0.817	10.25 ± 0.756	9.518 ± 0.892	9.220 ± 1.827	9.787 ± 0.856
T3	9.095 ± 1.169	10.68 ± 1.302†	10.60 ± 1.242†	9.534 ± 0.939	9.082 ± 1.741	9.239 ± 0.882
T4	9.369 ± 1.296	10.78 ± 1.774†	10.78 ± 2.091†	9.450 ± 0.787	8.930 ± 1.625	9.470 ± 0.482
T5	9.457 ± 1.599	10.32 ± 0.607	10.21 ± 0.440	9.760 ± 0.984	9.314 ± 1.539	9.721 ± 0.543
T6	9.443 ± 1.189	10.37 ± 0.518	10.38 ± 0.708	10.06 ± 1.931	9.447 ± 1.963	9.573 ± 0.738
Fz	8.509 ± 1.445	10.23 ± 0.475†	10.20 ± 0.442†	8.999 ± 0.864	8.514 ± 1.519	8.736 ± 1.203
Cz	8.834 ± 1.256	10.15 ± 0.589*	10.20 ± 0.444*	9.176 ± 1.001	8.548 ± 1.591	8.847 ± 1.078
Pz	9.418 ± 1.402	10.16 ± 0.675	10.25 ± 0.366	9.622 ± 1.072	9.017 ± 1.723	9.577 ± 0.908
Oz	9.701 ± 1.455	10.50 ± 0.428	10.39 ± 0.456	9.937 ± 0.901	9.749 ± 1.498	9.971 ± 0.636

Data are shown as mean ± standard deviation.
* $0.01 < P < 0.05$.
† $P < 0.01$ (compare with the results calculated before rTMS).
rTMS, repetitive transcranial magnetic stimulation.

3 to 4 minutes after rTMS were uniformly lower than those estimated in other periods, whereas the estimates at 4 to 5 minutes were the highest among all channels. The powers calculated before and within 3 minutes after rTMS could not be distinguished.

An EEG example obtained from a subject (age, 24 years old) is demonstrated in Fig. 2. Although 14 channels of EEG were recorded, only four channels were demonstrated. Power spectra are displayed at two electrode sites. The peak frequency increased after rTMS, which was most obvious during the first 2 minutes. Topograms of mean absolute power and relative power of the α band were seen on all channels.

DISCUSSION

Effect of rTMS

The current study revealed that rTMS can influence EEG activities significantly, increasing the peak frequency and powers. The effect was similar over the scalp, and decreased from the second minute after stimulation.

Previous studies showed that the changes in the EEG frequency and power might reflect functional alteration of brain activities (Siegel et al., 1982), and signals from normal subjects had some characteristics of nonlinear

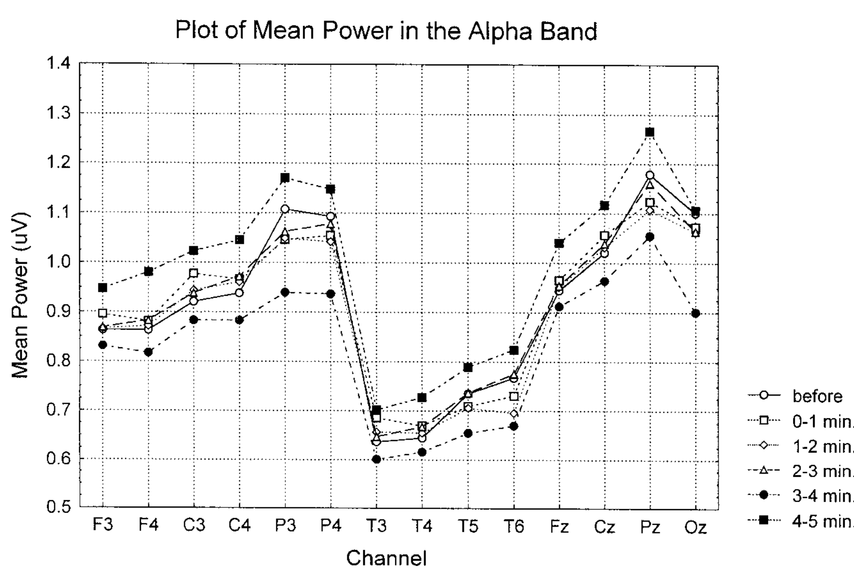

FIG. 1. Mean absolute power of the α band before and after repetitive transcranial magnetic stimulation (rTMS). The values obtained at 4 to 5 minutes after rTMS were uniformly higher than those calculated during other periods, whereas the minimal mean powers were yielded at 3 to 4 minutes. The values calculated before rTMS and within 3 minutes after rTMS could not be distinguished. The data were averaged for all subjects.

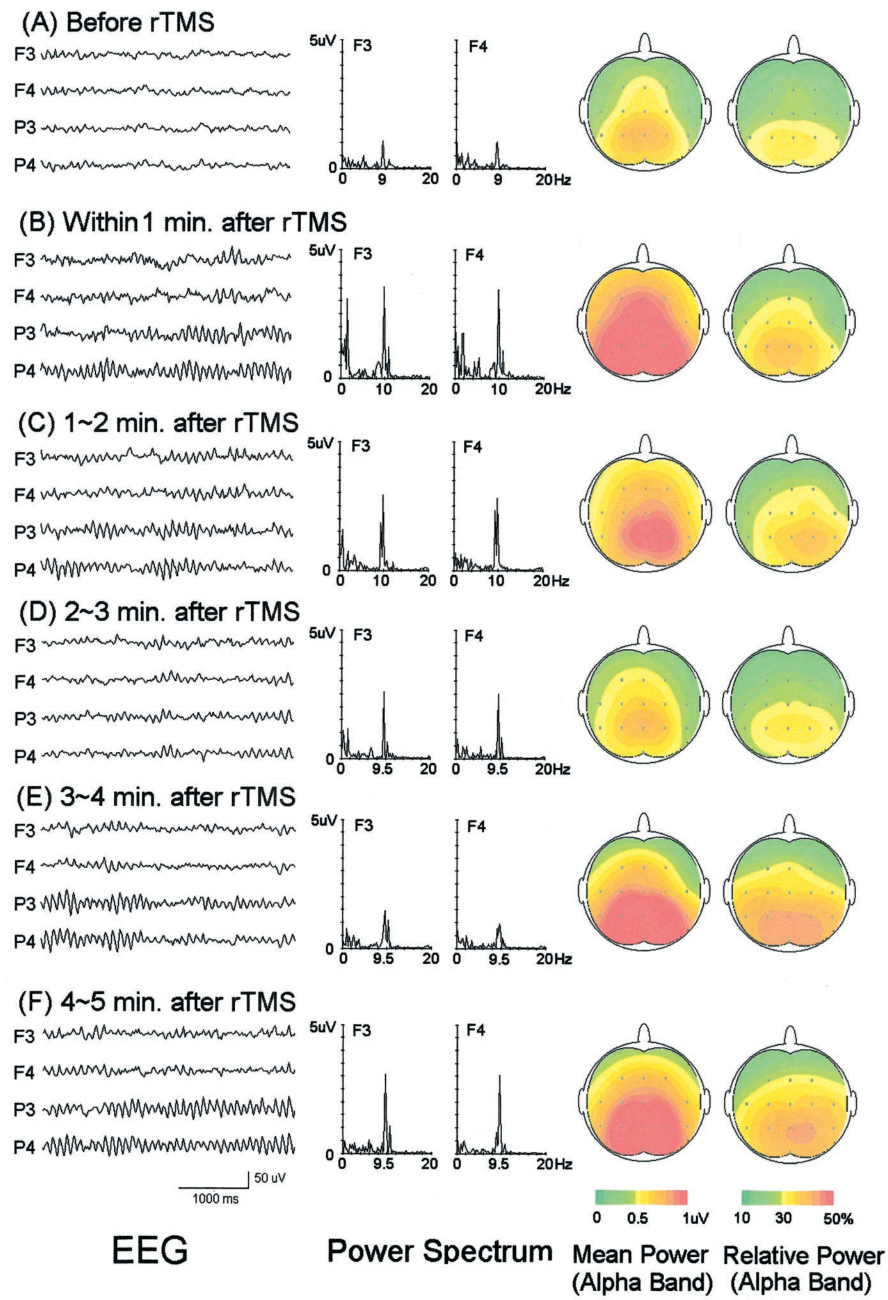

FIG. 2. EEG waves and power spectra calculated in a healthy subject. Fourteen channels of EEG signals were recorded and digitized, but only those recorded at the frontal and parietal areas are demonstrated. The power spectra displayed were estimated on the EEG obtained from the frontal area. The mean absolute power and relative power of all channels are shown in topograms. It should be noted that the values demonstrated in the topograms (**left**) are the mean power of the α band. Because of the average calculation, the values are lower than their corresponding maximal power.

dynamics (Jing and Takigawa, 2000b; Meyer–Lindenberg et al., 1998). Because the frequency of a nonlinear dynamic system can be altered by external influences, it is reasonable to consider that neuronal activities that show nonlinear properties may be affected by TMS pulses.

It is interesting that the changes in frequency and power were not simultaneous. First, the peak frequency increased immediately after rTMS and lasted for 2 minutes, but during this period, the changes in mean absolute power were not apparent. Second, at 2 to 5 minutes after rTMS, the peak frequency recovered to a level similar to that before rTMS. However, the mean absolute power obviously decreased at 3 to 4 minutes and increased at 4 to 5 minutes. These two observations suggest that EEG activity should receive attention during two periods: immediately after and 4 to 5 minutes after the stimulation. These findings were supported by the observations of Mottaghy et al. (1998), who indicated that the influence of rTMS lasted less than 2 minutes after they delivered a 20-Hz rTMS train over Wernicke's cortex in healthy subjects.

Our results showed an increase in EEG rhythm at all electrode sites. The variation at the left central area was more obvious than that at the right central area, indicating that the influence of rTMS was stronger for the stimulated site and its surrounding areas. The influence becomes weaker in the distant cortical areas. Recently, Izumi et al. (1997) demonstrated a slow activity of EEG signals at approximately 500 msec after TMS. Our data did not contradict theirs for several reasons:

1. We applied 10-Hz rTMS with an approximate 1.4-T intensity, in contrast to their single TMS with only a 0.44-T intensity.
2. We were interested in observing the EEG changes for 5 minutes after rTMS, in contrast to only a 2-second duration in their study.
3. In the EEG segments demonstrated in their report, there was no slow activity observed from 1 second after the stimulus; the mechanisms of rhythmic changes are different.

As they explained, the slow activity was ascribed to the sum of cutaneous sensory and auditory evoked potentials (Izumi et al., 1997). Our observations are consistent with the investigation by Rossini et al. (1991), who compared power spectra of the α and β bands after the stimulation of the motor cortex.The mechanisms of effects of rTMS on EEG activities remain unclear. In a similar experiment, using the same parameters, we found that directed coherences between cerebral sites changed significantly after rTMS (Jing and Takigawa, 2000a). In that study, we focused on two periods: 1 to 3 minutes and 3 to 5 minutes after the stimulation. The directed coherence from the frontal area to the parietal area was increased significantly in both hemispheres, especially during the first period. Additionally, the effect was much stronger for the α band, with the mean directed coherence from the stimulated site to other sites increased by 32%. It was interesting that the crossed interhemispheric frontoparietal coherence (i.e., from F_3 to P_4, from F_4 to P_3) also increased, although only the left frontal area was stimulated. A similar phenomenon was observed in the current study. The EEG power spectra changed not only at the left frontal area, but also at other cortical areas (e.g., F_4). This finding confirms the conclusion that the brain areas are not isolated from each other, regardless of whether the connections are direct (Jing and Takigawa, 2000a). For example, the nonspecific thalamic system and corpus callosum play important roles in transhemispheric signal transmission (Hamada and Wada, 1998), and the brainstem also contributes to the spread of signals (Kievit and Kuypers, 1975; Mcintyre and Goddard, 1973).The effect of rTMS on EEG frequency may be the result of a direct cortical effect. One mechanism is the neuronal interactions described by Pascual–Leone et al. (1993). The excitatory intracortical axons are collateral to pyramidal cells and inhibitory interneurons. The latter forms a feedback and projects to the pyramidal cells. Under normal circumstances, excitation and inhibition balance each other. rTMS upsets the balance by accumulating excitatory postsynaptic potentials temporarily, without compensation by inhibitory postsynaptic potentials because of the differences in the number of synapses and differences in the conduction along the myelinated monosynaptic excitatory collaterals (Pascual–Leone et al., 1993). This results in the spread of excitation and may even induce epileptic seizures (Classen et al., 1995). This mechanism explains the functional changes that occur during or immediately after the stimulation. However, our data revealed that the EEG frequency changes approximately tens of seconds after the rTMS and lasts for approximately 2 minutes, indicating that some other mechanisms occur in the brain. It is worth noting that similar observations have been reported by others (Fauth et al., 1992; Hömberg and Netz, 1989; Jing and Takigawa, 2000a; Kandler, 1990; Sakamoto et al., 1993). We considered that the delayed reaction may involve some complex metabolic processes or may be secondary to activation of some cerebral structures. For example, evidence from positron emission tomographic studies suggests that higher frequency stimulation (20 Hz) may increase brain glucose metabolism in a transsynaptic fashion, whereas lower frequency stimulation (1 Hz) may decrease it (Post et al., 1999; Siebner et al., 1999b), and such influence was correlated to the number of stimuli (Paus et al., 1997). Marked increase in the expression of c-fos in the different layers of the parietal cortex and hippocampus was reported recently in a chronic rTMS study (Hausmann et al., 2000), and a direct and fast connection between the cortex and brainstem was demonstrated by Meyer et al. (1997). Additionally, involvement of a multisynaptic subcortical network cannot be excluded (Siebner et al., 1999a). However, to explain the mechanism of EEG modification, one needs to perform detailed studies in the future.The limitation of our study was that only 5 minutes of EEG was recorded after each train, but our results showed that the power increased during 4 to 5 minutes, although the frequency recovered at that moment. We recognize this problem and suggest recording EEG signals for a much longer time in future studies.

Stimulation Parameters

The rTMS parameters used in the current study should be considered when extending the current results. Previous studies revealed that effects of rTMS depend on several factors: (1) intensity of stimulus, (2) frequency of stimulus, (3) duration of train, and (4) intertrain interval. These four factors are not completely independent from each other. Combinations of different values form a complex pattern. Many studies have investigated the effect of rTMS with different parameters on the functions of cerebral cortex (Chen et al., 1997; Pascual–Leone et al., 1993; Wassermann, 1998). Based on that research, it is concluded that stimulation at high intensity may cause the spread of excitation, and short intertrain interval rTMS may carry the risk of exciting the cortex, even resulting in epileptic seizures.

Other parameters that may influence the results are (1) direction of induced current flow in the brain (i.e., clockwise or counterclockwise) (Trompetto et al., 1999), (2) orientation of the coil's handle (e.g., lateromedial direction and posteroanterior direction) (Di-Lazzaro et al., 1998; Kaneko et al., 1996), and (3) the shape of the coil (Classen et al., 1995).

Considering that a number of factors may influence the effects of rTMS, it is necessary to reiterate that the modifications of EEG activities observed in the current study are based on rTMS at a frequency of 10 Hz, with a 3-second duration, and at 100% of the motor threshold.

Although the frequency and amplitude of EEG signals increased after rTMS, there were no epileptiform discharges observed in any subjects. Because of its ability to influence the activity of the cerebral cortex, rTMS is a useful tool to facilitate understanding of the mechanisms of cortical physiologic functions.

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