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Chapter 34

Effects of repetitive transcranial magnetic stimulation (rTMS) on slow cortical potentials (SCP)

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1. Introduction

Negative slow cortical potential shifts are thought to reflect depolarization of the apical dendrites of layer I cortical pyramidal cells, and hence to indicate cortical excitability (Rockstroh et al., 1993). Studies testing reaction time (Rockstroh et al., 1982) and mental arithmetic (Lutzenberger et al., 1982) have shown performance enhancement following biofeedback trained increases in negativity. Studies in epileptic patients have shown that a learned decrease in cortical negativity reduces seizure rate and severity when employed during early aura (Rockstroh et al., 1993; Kotchoubey et al., 2001). Birbaumer et al. (1999) have proposed that a brain-computer interface (Thought Translation Device; see Hinterberger, 1999), controlled by self-regulation of slow cortical potentials (SCP) can contribute to communication of completely paralyzed patients. Following operant learning principles, a shaping procedure enables the patients to select letters in a Language Support Program by producing SCP amplitude changes (Birbaumer et al., 1999). However, one of the main barriers to the efficacy of neurofeedback training is that some subjects (about 30%) have not been able to gain sufficient control over their SCP even after extended training. Accordingly, we are searching for a possibility to support self-regulation of SCP and hence to facilitate the learning process. A promising approach seems to lie in the application of repetitive transcranial magnetic stimulation (rTMS). Repetitive TMS uses trains of magnetic pulses to induce an electrical field in the neural tissue below the coil (Walsh and Rushworth, 1999; Hallett, 2000). Thereby, one important parameter is the frequency of repeatedly

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delivered TMS pulses. Several studies report an inhibitory effect of low-frequency (1 Hz or less) rTMS (Chen et al., 1997a; Boroojerdi et al., 2000) while high-frequency (5 Hz and more) rTMS has been shown to lead to an increase of cortical excitability (Pascual-Leone et al., 1994; Mottaghy et al., 1999). Another important factor is the temporal relationship between task performance and magnetic stimulation. Application of fast rTMS (at a frequency of 5 Hz or higher) during task performance (or the presentation of the task relevant stimulus) usually has detrimental effects on cognitive processes (Grafman et al., 1994; Wassermann et al., 1999). If, however, fast rTMS is delivered in a period preceding a task (Hamilton and Pascual-Leone, 1998) or in short periods during processing of a task (Boroojerdi et al., 2001), enhanced performance can be observed. In the current study we investigated if rTMS contributes to voluntarily induced modulation of SCP. Since negative SCP shifts were shown to reflect an increase, and positive SCP shifts a decrease in the excitability of the underlying cortical networks (Birbaumer et al., 1992), we hypothesized that high-frequency rTMS would enhance negative SCP shifts, whereas low-frequency rTMS would enhance positive SCP.

2. Methods

2.1. Subjects

Ten right-handed healthy volunteers (9 men, aged between 20 and 33 years) gave their informed consent according to the standards of the local ethics committee and were trained for four sessions (within 2 weeks) to self-regulate their SCP amplitude using the Thought Translation Device (Hinterberger, 1999; Kübler et al., 1999).

2.2. EEG recording

The electroencephalogram (EEG) was recorded from the following positions against both mastoids: Cz, FC3, CP3, FC4, CP4. The vertical electrooculogram (vEOG) and respiration (respiratory sensor) were recorded additionally and the EEG was corrected on-line for vEOG artifacts. Low-conductivity small Ag-AgCl electrodes prevented possible TMS induced heating artifacts (Ilmoniemi et al., 1997). An eight-channel EEG amplifier (EEG 8, Contact Precision Instrument) was used with a time constant of 16 s and a low pass filter of 40 Hz. Data were sampled at 256 Hz.

2.3. Experimental procedure

Participants sat in a comfortable chair viewing the neurofeedback monitor. Training included 11 blocks on each of the four sessions, each block comprised 34 feedback trials. A Medtronic-Dantec Magnetic Stimulator (Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses with a focal figure-of-eight magnetic coil (MC-B70). At the beginning of each session the individual resting motor threshold (MT) was registered from the right abductor pollicis brevis muscle (APB). MT was defined as the minimal intensity of stimulation capable of inducing MEPs greater than 50 μV peak-to-peak amplitude in at least five out of 10 consecutive trials.

Figure 1 shows the chosen rTMS parameters for the activation (a) and the inhibition (b) condition.

In the activation condition subjects received 15 Hz rTMS for 2 s preceding each feedback trial. After a 500 ms pause (in order to let the EEG amplifier recover from the TMS artifact) a baseline (BL) was recorded. A feedback phase followed lasting 3.5 s, in which visual feedback of SCP was provided as a cursor movement on a PC screen. The cursor moved up and down proportionally to the current SCP amplitude compared to the previously recorded baseline (the algorithm is described in Kübler et al., 2001). In each trial participants had to move the cursor towards the top (by producing a negative shift of their SCP) or towards the bottom of the feedback screen (by producing a positive SCP shift). The required direction was randomised over trials and was indicated by highlighting a corresponding rectangle at the top or bottom of the screen. If the subject was successful, a reinforcement stimulus (a smiling face) appeared for 500 ms on the feedback screen.

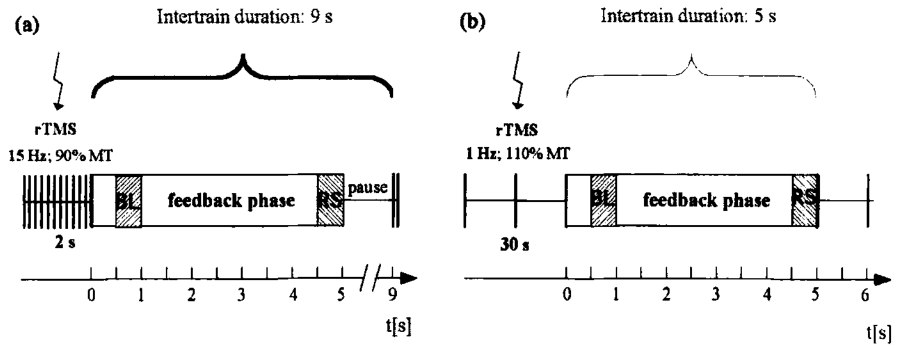

Fig. 1. Scheme of the experimental paradigm with the excitatory (a) and inhibitory (b) condition. (a) In the excitatory condition subjects received 15 Hz repetitive transcranial magnetic stimulation (rTMS) with a duration of 2 s and an intensity of 90% of the resting motor threshold (MT) preceding each feedback trial. (b) In the inhibitory condition subjects received 1 Hz rTMS with a duration of 30 s and an intensity of 110% of the resting motor threshold (MT). Note that in both conditions a fixed number of 30 pulses were applied before each feedback trial. After rTMS application a pause of 500 ms was added in order to let the EEG amplifier recover from the TMS induced artifact. The following 500 ms served as actual baseline (BL) for the SCP-feedback calculation. During the feedback phase, in which visual feedback of SCP was provided as a cursor movement on a PC screen, subjects had to move the cursor towards the top (by producing a negative SCP shift) or towards the bottom of the screen (by producing a positive SCP shift). If the subject was successful, a reinforcement stimulus (RS; a smiling face) appeared for 500 ms on the screen.

In order to increase the safety of the subjects during high-frequency stimulation, a pause of 4 s was added, so that the next rTMS train never started earlier than 9 s after the previous stimulation. Furthermore, the stimulation intensity was set at 90% of the MT (cf. Chen et al., 1997b; Jalinous, 2001). In the inhibition condition (Fig. 1(b)) subjects received 1 Hz rTMS for 30 s preceding each feedback trial. In both the activation and inhibition condition subjects received a fixed number of 30 pulses before each feedback trial. In order to maximise the inhibitory effect of the 1 Hz stimulation, rTMS was delivered at an intensity of 110% of the MT (cf. Fritzgerald et al., 2002). RTMS was delivered centro-frontally over the supplementary motor area (SMA) for two reasons. First, fMRI data show that self-regulated negative SCP shifts are associated with activation of the SMA (Birbaumer et al., 2001); and second, SCP amplitudes are highest over the centro-frontal region of the cortex (Birbaumer et al., 1990). The TMS coil was positioned tangentially to the skull on FCz, according to the international 10-20 system of electrode placement, with the handle parallel to the sagittal axis, and with the center of the figure-eight over the site to be stimulated. The junction region of the double squared coil straddled the midline. This coil orientation is assumed to be most effective for stimulating the SMA (Deecke et al., 1990; Cunnington et al., 1996; Verwey et al., 2002). FCz is the scalp position in between Cz and Fz, 10% of the distance between the inion and the nasion (i.e. about 4 cm) anterior of Cz. During sham stimulation the magnetic coil was also positioned on the SMA, but in a 90° angle to the scalp in order to prevent the magnetic field reaching the brain tissue (Loo et al., 2000; Verwey et al., 2002).

The experimental design contained the following conditions: (1) feedback without rTMS; (2) feedback immediately after high-frequency rTMS (15 Hz for 2 s with an intensity of 90% of the resting motor threshold); (3) feedback after low-frequency rTMS (1 Hz for 30 s with an intensity of 110% of the resting motor threshold); (4) feedback after high-frequency sham stimulation (15 Hz for 2 s) and (5) feedback after low-frequency sham stimulation (1 Hz for 30 s). The order of these conditions was counterbalanced across the training sessions.

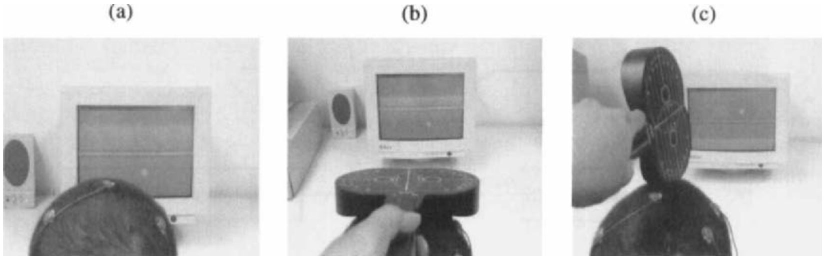

Fig. 2. Experimental conditions. Neurofeedback of SCP (a) without rTMS, (b) after high- (15 Hz) or low-frequency (1 Hz) rTMS, (c) after high- (15 Hz) or low-frequency (1 Hz) sham stimulation.

3. Results

To investigate differential effects of high- and low-frequency rTMS on SCP shifts, trials were separated according to the task requirement (positive vs. negative shifts). A multifactorial repeated measures ANOVA with correct response as dependent variable, the applied frequency (1 Hz vs. 15 Hz) and the experimental condition (real TMS, sham TMS, without TMS) as fixed factors and the task as repeated measures revealed a significant task effect [$F_{(1,235)} = 78.70$; $p < 0.001$]. Post hoc *t*-test showed that subjects were in general better able to produce negative SCP shifts than positive ones ($p < 0.001$; cf. Fig. 3). Both frequency [$F_{(1,235)} = 3.16$; $p = 0.90$] and experimental condition main effects [$F_{(2,235)} = 1.17$; $p = 0.31$] were (independent of the task requirement) not significant, however the interaction between frequency, experimental condition and task was in accordance with our hypotheses significant [$F_{(2,235)} = 15.62$; $p < 0.001$], indicating a differential effect of the stimulation conditions on required positive and negative SCP shifts, respectively.

Duncan post hoc tests revealed a significant increase of positive SCP shifts ($p < 0.01$) and a significant decrease of negative SCP shifts ($p < 0.05$) after 1 Hz rTMS compared to *all* other conditions. 15 Hz rTMS, in turn, caused numerically the highest amount of negative SCP shifts and the lowest amount of positive SCP shifts, however this effect was not consistently significant compared to the other stimulation conditions. 15 Hz rTMS led to a significant increase of negative SCP shifts compared to 1 Hz rTMs ($p < 0.001$), sham 1 Hz rTMS ($p < 0.01$) and to sham 15 Hz rTMS ($p < 0.05$), however there was no significant difference to the condition without stimulation ($p = 0.20$). After 15 Hz rTMS positive SCP shifts were significantly fewer than negative ones ($p < 0.001$). Positive SCP shifts after 15 Hz rTMS were also significantly reduced compared to sham 1 Hz ($p < 0.05$), but there was no significant difference compared to the other two control conditions (sham 1 Hz and without stimulation). Among the control conditions sham 1 Hz rTMS didn't lead to a significant increase of positive SCP shifts compared to the condition without stimulation ($p = 0.05$) and sham 15 Hz rTMS didn't lead to a significant increase of negative SCP shifts compared to the condition without stimulation ($p = 0.16$). Figures 3 and 4 summarize the main results: low-frequency (1 Hz) rTMS enhanced positive SCP but reduced negative SCP in comparison to *all* other conditions, whereas high-frequency (15 Hz) rTMS enhanced negative SCP and reduced positive SCP only partially compared to the other conditions. A modulating effect of high- and low-frequency rTMS on SCP shifts could be found, whereby the inhibitory effect of low-frequency stimulation seems to be more consistent than the excitatory effect of high-frequency stimulation.

4. Discussion

We have reported here, for the first time, the modulating effect of high- and low-frequency rTMS

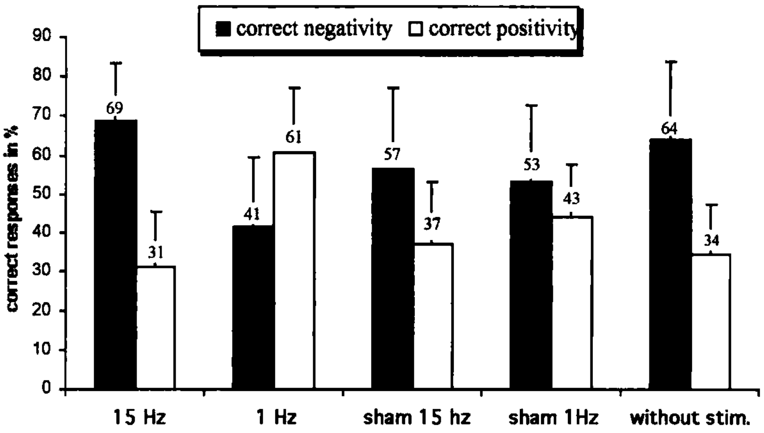

Fig. 3. Percentage of correct responses according to the stimulation condition. Error bars indicate the standard deviation.

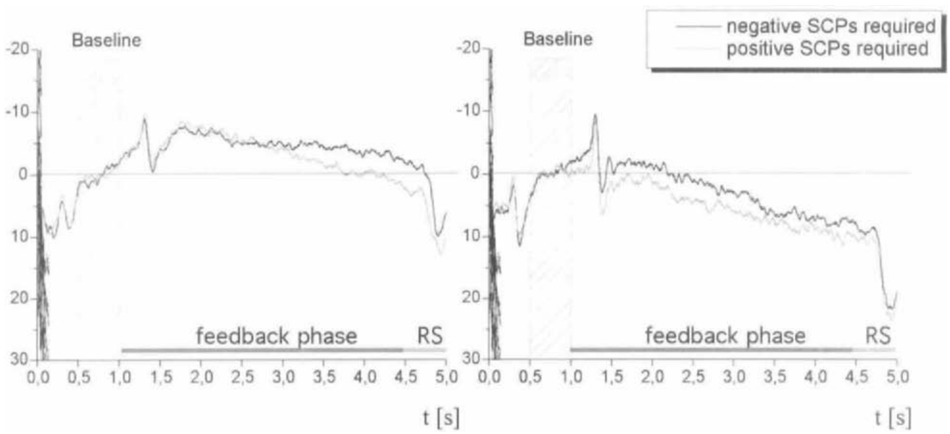

Fig. 4 Averaged SCP curves for 5 s (a) after 15 Hz rTMS and (b) after 1 Hz rTMS. A differential modulating effect can be observed: 15 Hz rTMS enhanced negative SCP shifts but reduced positive SCP shifts, whereas 1 Hz rTMS enhanced positive SCP shifts and reduced negative SCP shifts. The end of the feedback phase elicited a positive evoked potential with a latency of 300 ms. RS = reinforcement stimulus (a smiling face).

on SCP shifts as used in our brain-computer interface. The observed effects are in line with findings of several researchers, who describe facilitating effects of high-frequency and inhibiting effects of low-frequency rTMS (e.g. Mottaghy et al., 1999; Boroojerdi et al., 2000). The finding that the assumed inhibitory effect of low-frequency stimulation leads to more consistent results than the facilitating effect of high-frequency stimulation has already been reported by different research groups (cf. Grafman, 2002; Lappin and Ebmeier, 2002). Besides the question of the temporal relationship between the onset of the task and magnetic stimulation, a further escrow issue may lie in the fact that every attempt to enhance the effectiveness of high-frequency rTMS (by applying higher intensities or longer stimulation trains) can potentially be at the expense of the subjects safeness. Interestingly, Mottaghy et al. (1999) assume that there might be a cut-off point, where the facilitating effect of rTMS with higher intensities disappears and might even change into disruption of cognitive processes. However, according to Gerloff et al. (1997) it may be conceivable that the applied intensities in our study, especially during high-frequency stimulation, are too low in order to stimulate the SMA. Thus, future studies will have to clarify which changes of TMS parameters (intensity, frequency and stimulation site) will optimise the modulating effect on SCP. In a follow-up study we are going to investigate if the modulating effect of rTMS on SCP can be used to facilitate the learning process of self-regulating SCP shifts. It would mean a new hope for non-learners among patients with locked-in syndrome to support self-regulation of SCP and hence to re-establish communication through a Brain-Computer Interface. The presented combination of rTMS and neurofeedback may provide a new, exceptionally potent non-invasive tool for supporting neurofeedback training and for investigating cortical areas which are involved in self-regulation of EEG parameters.

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