

## SHORT COMMUNICATION

# Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency

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**Keywords:** alpha, EEG, mental rotation, oscillations, rTMS

### Abstract

We applied rapid-rate repetitive transcranial magnetic stimulation (rTMS) at individual alpha frequency (IAF) to **improve cognitive performance by influencing the dynamics of alpha desynchronization**. Previous research indicates that a large upper alpha power in a reference interval preceding a task is related to both large suppression of upper alpha power during the task and good performance. Here, we tested the hypothesis that rTMS at individual upper alpha frequency (IAF + 1 Hz) can enhance alpha power in the reference interval, and can thus improve task performance. Repetitive TMS was delivered to the mesial frontal (Fz) and right parietal (P6) cortex, and as sham condition with 90°-tilted coil (P6 position). The behavioural effect was assessed in a mental rotation task. Further control conditions were rTMS at a lower IAF (IAF – 3 Hz) and at 20 Hz. **The results indicate that rTMS at IAF + 1 Hz can enhance task performance and, concomitantly, the extent of task-related alpha desynchronization. This provides further evidence for the functional relevance of oscillatory neuronal activity in the alpha band for the implementation of cognitive performance.**

### Introduction

Associations between cognitive performance and endogenous modulations of oscillatory neuronal activity in the individual alpha frequency (IAF) range have been established in a number of studies (see Klimesch, 1999). If these associations are functionally relevant (rather than mere epiphenomena), then it should be possible to influence cortical oscillations and thereby modulate behavioural performance. Here we tested the hypothesis that repetitive transcranial magnetic stimulation (rTMS) can induce predictable changes in oscillatory cortical activity and improve performance in a mental rotation task.

Transcranial magnetic stimulation (TMS) has been used in various ways to interfere with cortical function. It has the potential to disrupt cortical functions in a target region of interest (for a recent review see Hallet, 2000). This ability to create a temporary ‘virtual brain lesion’ allows to study the causal role of the affected region for complex motor (Gerloff *et al.*, 1997) and cognitive processes (for a review see Jahanshahi & Rothwell, 2000). As an example, TMS applied over V5 can interfere selectively with the perception of motion of a stimulus without impairing its recognition (for a review see, e.g. Walsh & Cowey, 1998).

Transcranial magnetic stimulation has also been used to improve brain function (for a recent review see Triggs & Kirshner, 2001). Thereby, one important parameter is the frequency of repeatedly delivered single TMS pulses (rTMS). At frequencies of 5 Hz and higher, rTMS transiently enhances cortical excitability (Pascual-Leone *et al.*, 1994),

whereas slow rTMS at a frequency of about 1 Hz induces a transient suppression of excitability (Chen *et al.*, 1997a). 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 & Pascual-Leone, 1998; Mottaghy *et al.*, 1999; Triggs *et al.*, 1999; Evers *et al.*, 2001; Sparing *et al.*, 2001) or in short periods during processing of a task (Boroojerdi *et al.*, 2001), enhanced performance can be observed. Facilitating effects have also been reported when single pulse TMS is used with a long interstimulus interval (500 ms or more) before task onset (Töpper *et al.*, 1998).

In the present study, **we applied rTMS at IAF** to enhance cognitive performance. The rationale of the experimental procedure is derived from three basic findings about the human electroencephalogram (EEG) alpha rhythm (for an extensive review of the following findings cf. Klimesch, 1999). First, interindividual differences in **mean or peak alpha frequency** are large (7–13 Hz; mean for young adults is about 10 Hz) and are related to memory performance and the speed of information processes. Second, the extent of alpha reactivity [as measured, e.g. by event-related desynchronization (ERD); cf. ref. Pfurtscheller & Aranibar, 1977] depends on the amplitude of alpha oscillations during a resting or reference period that precedes task performance. In a series of studies, we have shown that cognitive performance is related to the extent of ERD, which in turn depends on the extent of power in a resting or test interval. Subjects with large alpha power tend to exhibit a pronounced ERD and both measures are associated with good

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Received 16 September 2002, revised 17 December 2002, accepted 20 December 2002

cognitive performance in a variety of different tasks (Neubauer *et al.*, 1995). Thus, large resting (or reference) alpha power and a large ERD are associated with good cognitive performance. Third, these findings are frequency sensitive. They can be observed in a narrow upper alpha band (width of 2 Hz) but only if frequency boundaries are adjusted to IAF (e.g. for a subject with fast IAF of 12 Hz, the upper alpha band is 12–14 Hz).

On the basis of these findings, our conclusion was that a period of pronounced (upper) alpha activity – preceding task performance – is associated both with a large ERD (alpha suppression or reactivity) and good performance. Thus, the logic underlying the present experiment was to apply rTMS at individual upper alpha frequency (IAF + 1 Hz) in a period preceding task performance. Because the human alpha rhythm (as measured by scalp EEG) shows a clear association with visual information processing demands, we used a mental rotation task and applied rTMS at IAF + 1 Hz over a right parietal (P6) and a frontal site (Fz). These sites were selected because functional magnetic resonance imaging studies have shown repeatedly that the superior-parietal lobule (BA 7) – particularly in the right hemisphere – plays a significant role in mental rotation (e.g. Richter *et al.*, 2000; Thomsen *et al.*, 2000). There is also evidence that the lateral premotor and supplementary motor area (lateral and medial BA 6) is involved (Richter *et al.*, 2000). Control conditions were rTMS at IAF – 3 Hz (lower alpha, individually adjusted) and at 20 Hz (beta frequency, not adjusted individually). We expected that compared with the control conditions, subjects would show improved mental rotation performance, increased upper alpha power during a reference period (preceding the task) and increased ERD (larger suppression) during task performance in the experimental condition (rTMS at IAF + 1 over the right parietal cortex).

It is interesting to note that almost all studies reporting facilitating effects (ignoring those exploiting the potential of disinhibition) applied rTMS at a frequency that either equals mean alpha frequency (which is about 10 Hz) (Hamilton & Pascual-Leone, 1998; Wassermann *et al.*, 1999), harmonics of alpha at 20 Hz (Mottaghy *et al.*, 1999; Triggs *et al.*, 1999; Sparing *et al.*, 2001) or subharmonics like 5 Hz (Boroojerdi *et al.*, 2001). Thus, the facilitating effects of these studies may have been already been, at least in part, because of the influence of IAF.

## Materials and methods

### Subjects

Experiments were carried out at the Department of Neurology, University of Tübingen Medical School. They were performed in accordance to standard safety guidelines (Chen *et al.*, 1997b) and the Code of Ethics of the World Medical Association and were approved by the Institutional Review Board of the University of Tuebingen. In Experiment 1, a sample of 16 subjects (six healthy males with a mean age of 26.7 years, range 22–29 years and ten females with a mean age of 23.1 years, range 18–30 years) was used. Because one female subject did not tolerate rTMS, 15 subjects remained for data analysis. In Experiment 2, a different sample of six subjects (three healthy males with a mean age of 27.3 years, range 24–29 years and three females with a mean age of 24.7 years, range 20–30 years) was used. All subjects were right handed, had normal or corrected to normal vision and were paid for participation. They participated after giving written informed consent.

### Stimulus presentation and cognitive tasks

Stimuli were line drawings of cubes that were modified versions of the subtest mental rotation of the IST-70 (a standard German intelligence test). The cubes had different symbols on each side. On each trial a set of six cubes (three in an upper and three in a lower row) were presented on a computer monitor. The target cube always appeared in the middle position of the first row and was marked by a surrounding square. Subjects had to decide which of the other five cubes matched the mentally rotated target. They were instructed to perform the task as fast and accurately as possible. The six cubes remained on the screen until the subject responded by pressing one of five buttons. A single trial started with a warning signal (i.e. the visual presentation of the letters 'TMS') for 1000 ms. Then, the train of 24 TMS pulses was delivered starting at the offset of the warning signal. Immediately after the last TMS pulse, the cubes were presented. The next trial started 11 600 ms after the subject responded.

The set of six cubes were presented in nine blocks, each consisting of eight trials. Analogous to the IST-70, the target cube differed for a series of sets (trials) whereas the five test cubes remained the same. For construction of the trials, we used a sample of nine series with eight sets. In each of the eight sets the target cube was different, but the other five cubes remained the same. The sequence of blocks was randomized between subjects. Dependent variables were reaction time and percentage correct answers calculated separately for each block of trials.

### rTMS protocol

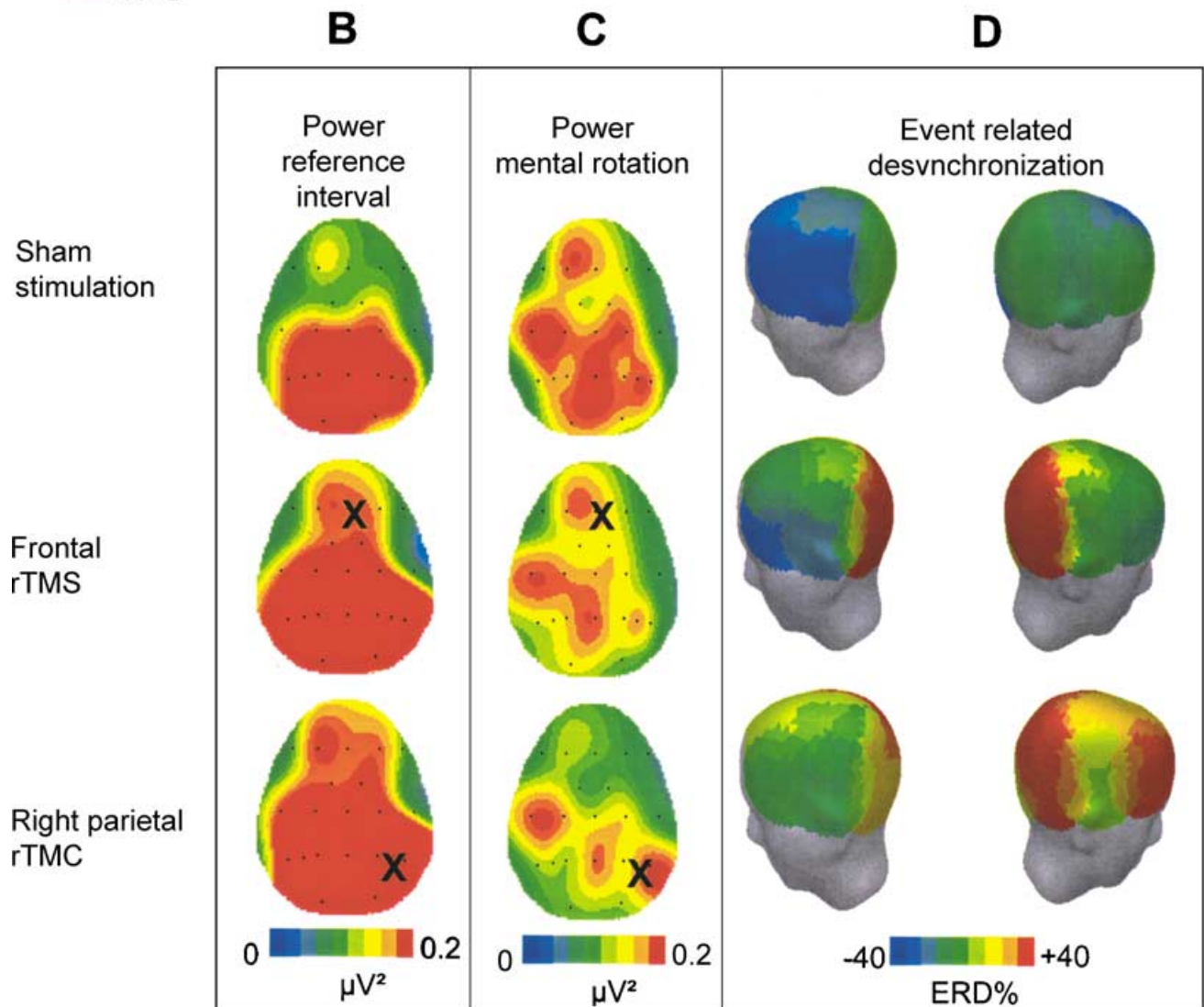
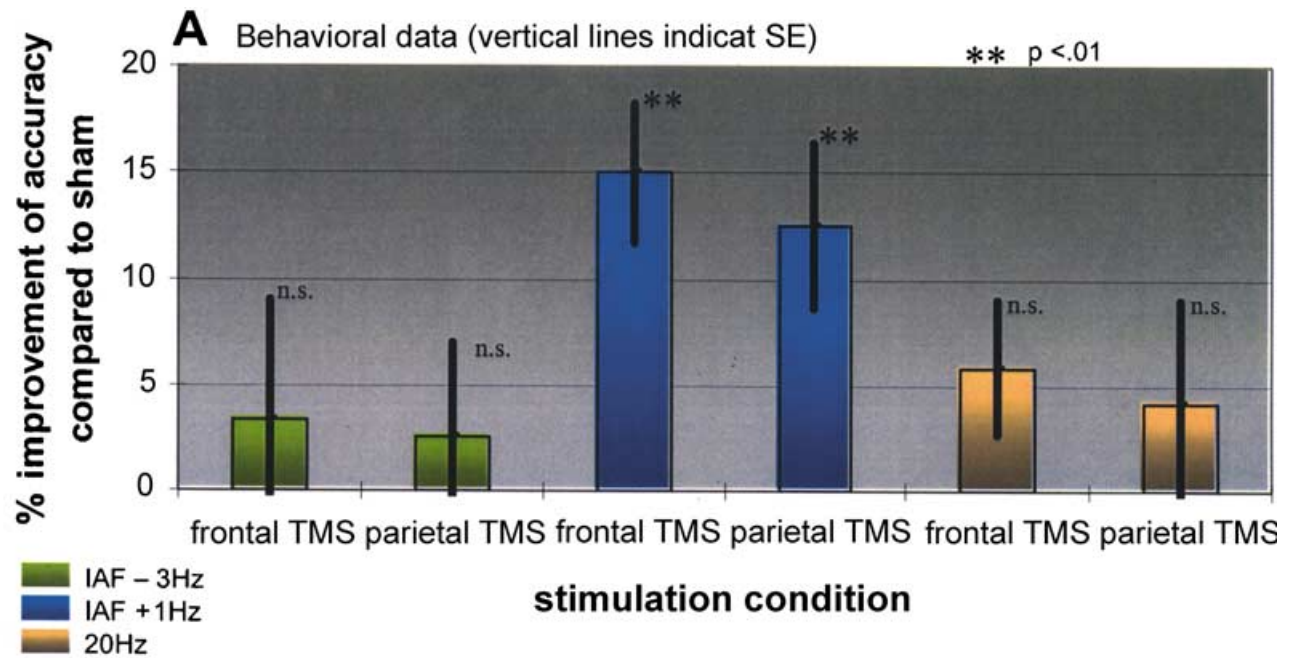
A MagStim Rapid stimulator (MagStim, Whitland, UK) with a 70-mm figure-8 coil was used. Locations for rTMS stimulation were determined according to the international 10–20 system. In the experimental condition, rTMS was applied at P6 (above the intraparietal sulcus), at Fz and rotated by 90° over P6 for sham. This experimental manipulation is termed the stimulation condition. The output strength of the rTMS was set to 110% of the subjects' motor threshold, defined as the intensity needed for eliciting motor evoked potentials of at least 50  $\mu$ V recorded at the thumb of the left hand in 50% (5/10) of single pulses delivered to the contralateral motor cortex. The electromyogram was recorded from two bipolar Ag–AgCl electrodes over the left abductor pollicis brevis muscle (band pass, 5–200 Hz; sample rate, 1000 Hz). Mean intensity for rTMS was 57.3% of maximal stimulator output. Sham served as the control condition in which the sensory effects of rTMS were simulated to some extent without interfering with cortical processes. Subjects could not be aware of whether a stimulation condition was real or not because conditions were applied in a randomized way, subjects could not see the coil and were not informed about the existence of placebo stimulation.

In order to keep the total 'energy' applied to the cortex by rTMS constant for the different frequencies (see below), a fixed number of 24 pulses was delivered in each condition. Thus, the duration of pulse trains varied between 1.2 to ~4.8 s (depending on IAF and condition). No rTMS was given during execution of the task.

### Experiments 1 and 2

Both experiments started with the recording of the EEG to determine IAF. Experiment 1 served to assess cognitive performance and Experiment 2 to monitor changes in ERD and absolute band power (for the reference and test interval). In Experiment 1 the three stimulation

FIG. 1. (A) Task performance increases after repetitive transcranial magnetic stimulation (rTMS) (A). The rTMS induced improvement of accuracy of mental rotation is significant for individual alpha frequency (IAF) + 1 Hz only. The influence of rTMS at individual upper alpha frequency (IAF + 1 Hz) on the EEG is depicted in the lower panel. The results for the reference interval (a time period preceding rTMS), the test interval (time period during task performance) and event-related desynchronization (ERD) are shown in B, C and D, respectively. Note the rTMS-induced increase in power during reference and decrease during test.



conditions (Fz, P6, sham) were combined with three stimulation frequencies resulting in nine blocks of experimental conditions. Stimulation frequencies were IAF + 1 Hz, IAF – 3 Hz, and 20 Hz. The nine blocks of trials were assigned randomly to each of the nine experimental conditions. In order to increase the number of trials for the analysis of the EEG, only stimulation frequency at IAF + 1 Hz was used, but three blocks of trials were presented under each of the three stimulation conditions in Experiment 2. In Experiment 1, the electrodes were removed before delivering rTMS. In Experiment 2, the electrodes remained on the subject's scalp throughout the entire session. The IAF was determined for right parietal sites on the basis of power spectra (obtained from a 3-min resting period with eyes closed, preceding the performance of the experiment) as the peak frequency within 7 and 14 Hz (IAF  $\pm$  SD, measured at rest was  $9.7 \pm 1.57$  Hz).

### EEG recording

EEG signals were amplified by a Neuroscan 32 channel amplifier system (Neuroscan, El Paso, TX, USA). They were recorded referentially against a common linked earlobe reference (impedance  $<3$  k $\Omega$ ) from 21 Ag–AgCl electrodes according to the international 10–20 system. Sampling rate was 250 Hz, upper frequency limit was 40 Hz. The electro-oculogram (EOG) was recorded from two additional electrodes. Data were converted to a digital format via a 32-channel A/D converter. Sampling rate was 250 Hz.

### EEG data analysis for Experiment 2

Absolute band power (for the reference and test interval) and ERD were calculated in individually determined frequency bands. The reference interval consisted of a period of 3 s starting 5 s before the onset of the warning signal, and the test interval consisted of the first 3 s following presentation onset of the cubes. In these time windows epochs of 1024 ms were used for averaging. Thus for each stimulation condition and subject 72 ( $3 \times 24$ ) epochs remained for analysis. All of the epochs in each condition were carefully checked individually for artifacts (eye blinks, horizontal and vertical eye movements, muscle artifacts, etc.) by visual inspection. Epochs that were associated even with small changes in the horizontal or vertical EOG-channel within the reference and test interval (see below) were rejected. The average number of artifact-free trials for the three stimulation conditions (Fz, Pz and sham) were 30.8, 30.4, and 35.1, respectively. During the rTMS train the EEG amplifier was blocked.

The ERD is the percentage change in test power with respect to a reference interval (Pfurtscheller & Aranibar, 1977):

$$\text{ERD} = 100 \times [(\text{reference} - \text{test power})/\text{reference power}]$$

Frequency bands were determined individually for each subject  $i$ , by using individual alpha frequency IAF( $i$ ) as a cut-off point between the lower and upper alpha band. Four EEG frequency bands were analysed: Theta, IAF( $i$ ) – 6 Hz to IAF( $i$ ) – 4 Hz; lower-1 alpha, IAF( $i$ ) – 4 Hz to IAF( $i$ ) – 2 Hz; lower-2 alpha, IAF( $i$ ) – 2 Hz to IAF( $i$ ); and upper alpha, IAF( $i$ ) to IAF( $i$ ) + 2 Hz. Mean alpha frequency at rest was  $10.25 \pm 1.05$  Hz.

### Statistical analysis

We have focused on the comparison between stimulation at Fz, P6 and sham. One-way ANOVAs with the factor stimulation condition (Fz, Pz, sham) were used to analyse the behavioural data (percentage of correct responses and reaction time) of Experiment 1. Separate ANOVAs were carried out for each dependent variable and stimulation frequency. For Experiment 2, we performed two-way ANOVAs with the factors

stimulation condition (Fz, Pz, sham) and recording site (the entire set of 21 electrode sites) to analyse ERD in the four EEG bands. The Greenhouse Geisser correction was applied. Significance level was set at 5%. For Experiment 2, again separate ANOVAs were carried out for each dependent variable (ERD, reference and test power).

## Results

### Behavioural data

Performance (percentage correct responses) increased significantly only after rTMS at IAF + 1 Hz as indicated by the significant factor stimulation condition ( $F_{2,28} = 8.86$ ,  $P < 0.01$ ; cf. Fig. 1). *Post hoc* Scheffé tests indicate significant differences between stimulation at Fz and sham ( $P < 0.01$ ) as well as P6 and sham ( $P < 0.01$ ) but not between P6 and Fz. No significant changes in performance were induced with stimulation frequencies at IAF – 3 Hz, or 20 Hz. No significant effects were found for reaction time in any condition.

### EEG data: ERD

From the four EEG bands analysed, only the upper alpha and lower-2 alpha band showed significant results. Compared with sham, rTMS at IAF + 1 Hz, induced a significant increase in lower-2 and upper alpha desynchronization (ERD) during mental rotation. For the ERD in the lower-2 alpha band, the only significant effect was found for factor stimulation condition ( $F_{2,10} = 5.68$ ,  $P < 0.05$ ). Scheffé tests revealed a significantly larger ERD only at P6 ( $P < 0.05$ ) compared to sham. For the upper alpha band factor stimulation condition ( $F_{2,10} = 8.82$ ,  $P < 0.05$ ) reached significance. Again, no other variance sources were significant. Scheffé tests show a significant increase between rTMS at Fz and sham ( $P < 0.05$ ) as well as P6 and sham ( $P < 0.01$ ). No significant difference was found between P6 and Fz. Figure 1D indicates that the increase in upper alpha ERD during rTMS stimulation is a result of both decreased poststimulus power (Fig. 1C) and increased reference power (Fig. 1B). For ERD/ERS in the remaining two EEG bands (lower-1 alpha and theta) none of the variance sources reached significance.

### EEG data: band power in reference and test interval

For band power values in the reference and test interval, only one significant effect of factor stimulation condition was found ( $F_{2,10} = 5.44$ ,  $P < 0.05$ ). This was obtained for the lower-2 alpha band during the test interval. Scheffé tests revealed a significantly lower band power after stimulation at P6 as compared with Fz ( $P < 0.05$ ). Factor recording site reached significance in all but two cases (lower-2 alpha, reference and upper alpha, test interval). In none of the cases did the interaction between the two factors reach significance. Because factor 'recording site' reflects the usual pattern of topographical differences, these findings will not be considered in the following.

## Discussion and conclusions

As predicted, rTMS delivered at the subjects' IAF at Fz and P6 lead to a significant improvement in mental rotation performance when compared with sham. This most likely because of the fact that both frontal and parietal sites play an important role in mental rotation (Richter *et al.*, 2000; Thomsen *et al.*, 2000).

The influence of rTMS at IAF on EEG parameters mimicked exactly that situation which we know is typical for good performance: increased reference power, decreased test power and, consequently, a large ERD. It is important to note that the influence of rTMS was not restricted to the time period immediately following the delivery of pulses (i.e. to the test interval) but could be observed also in the



reference interval that followed the last rTMS stimulation after an inter-trial interval of about 30 s (depending on the reaction time). Most interestingly, the direction of change in power is different in the reference and test interval. In the same way as we know from EEG studies, good performance was related to increased alpha band power in a reference, but decreased band power during a test period (for an extensive review see Klimesch, 1999). Thus, we conclude that rTMS at IAF improves performance by way of those factors that are known to be of importance under normal conditions.

The physiological nature of those mechanisms underlying the rTMS-related improvements are not known. It could be assumed that during rTMS cortical networks are put in a state of 'resonance', in a similar way as was observed for photic driving (Silberstein, 1995; Hermann, 2001). However, little is known about the dynamic changes in spontaneous electrocortical activity during and immediately after rTMS.

The present findings suggest that the relationship between the dynamics of alpha desynchronization and cognitive performance is not correlative but causal in nature. Consequently, rTMS at IAF might even be useful as a therapeutic tool for patients with cortical dysfunctions. The timing of the rTMS application relative to the task will be critical and future research is necessary to clarify this aspect.

## Acknowledgements

This research was supported by the Austrian 'Fonds zur Förderung der wissenschaftlichen Forschung', Project P-13047 to W.K. C.G. was supported by the Deutsche Forschungsgemeinschaft (grant SFB 550/C5).

## Abbreviations

ANOVA, analysis of variance; EEG, electroencephalogram; EOG, electro-oculogram; ERD, event-related desynchronization; IAF, individual alpha frequency; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

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