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Differential effects of low-frequency rTMS at the occipital pole on visual-induced alpha desynchronization and visual-evoked potentials

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Abstract

Visual-induced alpha desynchronization (VID) and visual-evoked potentials (VEPs) characterize occipital activation in response to visual stimulation but their exact relationship is unclear. Here, we tested the hypothesis that VID and VEPs reflect different aspects of cortical activation. For this purpose, we determined whether VID and VEPs are differentially modulated by low-frequency repetitive transcranial magnetic stimulation (rTMS) over the occipital pole. Scalp EEG responses to visual stimuli (flashed either to the left or to the right visual field) were recorded for 8 min in six healthy subjects (1) before, (2) immediately following, and (3) 20 min after left occipital rTMS (1 Hz, 10 min). The parameters aimed to reduce cortical excitability beyond the end of the TMS train. In addition, simple reaction times to visual stimulation were recorded (left or right hand in separate blocks). In all subjects, VID was significantly and prominently reduced by rTMS ($P = 0.0001$). In contrast, rTMS failed to modulate early VEP components (P1/N1). A moderate effect was found on a late VEP component close to manual response onset ($P = 0.014$) but this effect was in the opposite direction to the VID change. All changes were restricted to the targeted left occipital cortex. The effects were present only after right visual field stimulation when a right hand response was required, were associated with a behavioral effect, and had washed out 20 min after rTMS. We conclude that VID and early VEPs represent different aspects of cortical activation. The findings that rTMS did not change early VEPs and selectively affected VID and late VEPs in conditions where the visual input must be transferred intrahemispherically for visuomotor integration (right visual field/right hand) are suggestive of rTMS interference with higher-order visual functions beyond visual input. This is consistent with the idea that alpha desynchronization serves an integrative role through a corticocortical "gating function."

Keywords: EEG; TMS; Event-related desynchronization; Alpha rhythm; Visual-evoked potentials; Occipital cortex; Visuomotor integration

Introduction

There are several changes in ongoing EEG/MEG activity that signal activation of cortical regions. Two prominent changes are the blocking of oscillatory activity in the alpha frequency band (event-related alpha desynchronization) and the development of evoked potentials/magnetic fields. Both measures have been used to describe the task-specific, focal activation patterns over time associated with various sensory, motor, and cognitive tasks (e.g., Hari et al., 1997; Klimesch, 1996; Michel et al., 2001; Pfurtscheller and Lopes da Silva, 1999; Williamson et al., 1997). For example, event-related alpha desynchronization occurs over the visual areas in response to visual stimulation (visual-induced desynchronization, VID) and over motor areas preceding a movement (movement-induced desynchronization, MID). Averaging EEG signals time locked to the same visual stimuli or movements discerns the visual-evoked or movement-related potentials (VEPs/MRPs) over the respective visual and motor areas.

Because alpha suppression and evoked potentials show

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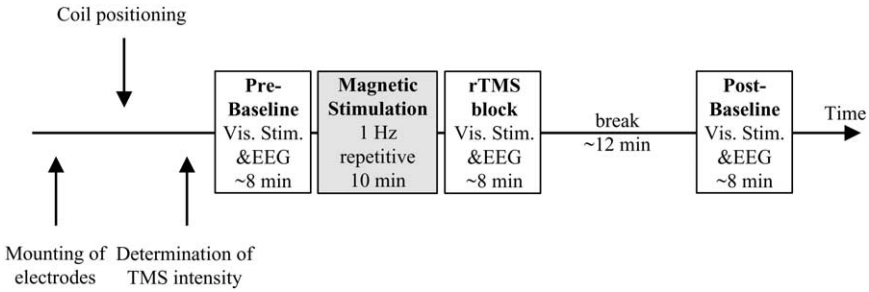

Fig. 1. Pre–post design. 1-Hz rTMS was applied for 10 min (n = 600 stimuli) over the left occipital pole (rTMS session, gray panel), off-line to visual stimulation. EEG responses to visual stimuli were recorded in three experimental blocks (white panels) (1) preceding (prebaseline block), (2) immediately following (rTMS block), and (3) 20 minutes after the rTMS session (postbaseline block). In each block, unimanual reaction times to the visual stimuli were recorded in addition to EEG. The site and intensity of magnetic stimulation were defined prior to the experiment using functional and anatomical coil positioning procedures (see text for details).

similar spatiotemporal characteristics in response to the same visual or motor tasks, the question has been raised whether these two measures are governed by the same neurophysiological mechanism. Direct comparisons of MID and MRPs evoked by motor tasks have suggested partial independence regarding magnitude and spatial distribution within motor areas (Babiloni et al., 1999; Toro et al., 1994). Comparisons of movement-related desynchronization and movement-related magnetic fields measured with MEG have yielded similar results (Feige et al., 1996). This suggests that MID and MRPs reflect different aspects of cortical activation, despite similarities in origin and timing. Less is known about the relationship between event-related alpha desynchronization and potentials over the occipital cortex (VID vs. VEPs).

To address this question, we applied repetitive transcranial magnetic simulation (rTMS) to the occipital pole at stimulation parameters shown to reduce visual (Boroojerdi et al., 2000a) and motor cortex excitability (e.g., Chen et al., 1997a; Muellbacher et al., 2000; Romero et al., 2002; Touge et al., 2001) and investigated whether, and in what way, such magnetic stimulation affects VID and VEPs. We expected that rTMS at the occipital pole is likely to modulate EEG correlates of occipital activation, given that frontal rTMS has recently been shown to modulate event-related potentials reflecting motor and cognitive functions (Evers et al., 2001; Jing et al., 2001; Rossi et al., 2000) as well as oscillatory activity in spontaneous EEG (Jing and Takigawa, 2000; Okamura et al., 2001; Schutter et al., 2001). We furthermore expected that magnetic stimulation of visual areas at the occipital pole increases the chance of interference with both VID and VEPs, given that VID and early VEPs (P1/N1 complex) share some common generators in striate cortex (Brodmann area 17) and/or adjacent extrastriate areas (Brodmann area 18) (for VID, see Hari et al., 1997; Rougeul-Buser and Buser, 1997; for VEPs, see Bonmassar et al., 2001; DiRusso et al., 2001). Here, we tested the hypothesis that different aspects of cortical activation are reflected in these two measures. Differential effects of rTMS on VID and VEPs would point toward partial independence with respect to underlying neurophysiology. Similar effects may suggest that VID and VEPs are correlates of one and the same aspect of cortical activation.

While there is at present no study on whether, and in what way, occipital TMS affects EEG correlates of occipital activation such as VID and VEPs, functional disruption of visual processes by occipital TMS is well documented for single-pulse (Amassian et al., 1998) and repetitive TMS designs (Kosslyn et al., 1999). In the present study, visual stimuli were presented in the left or right visual fields (LVF/RVF) before and after rTMS over the left occipital pole. We expected rTMS effects to occur mainly over the targeted left occipital cortex and in response to RVF stimulation, given that RVF stimuli are directly projected to the left visual areas. In addition to EEG, we also recorded reaction times to visual stimulation (left or right hand in separate experimental blocks) to monitor potential behavioral effects.

Materials and methods

Subjects

Six healthy, right-handed subjects (one woman, five men), aged 27–35 years (mean, 31 years), participated in this study. All had normal or corrected to normal vision and no history of neurological or psychiatric disorders. Written informed consent was obtained from all subjects prior to participation in the study that had been approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center. None of the subjects was naïve to TMS, having previously participated in other TMS experiments.

Procedure

The procedure is illustrated in Fig. 1. After the scalp electrodes had been mounted and before the experiments began, the position and intensity of TMS were carefully determined for each subject separately using functional and

anatomical coil positioning procedures (see later, "Transcranial magnetic stimulation"). EEG responses to visual stimuli were then recorded for ~8 min in three experimental blocks (1) before (prebaseline block), (2) immediately following (rTMS block), and (3) 20 min after occipital rTMS (postbaseline block). rTMS was applied at stimulus parameters (1 Hz, 10 min, 110% phosphene threshold) shown to reduce cortical excitability for several minutes beyond the duration of the TMS train (e.g., Boroojerdi et al., 2000a). Prebaseline served to establish a control. Postbaseline served to assess whether changes are transient, that is, to exclude that EEG differences between prebaseline and rTMS blocks are confounded by linear changes in EEG over time (e.g., caused by changes in arousal). In addition to EEG, we also recorded simple reaction times to visual stimulation in the prebaseline, rTMS, and postbaseline blocks. Subjects were tested twice on two separate days, on one day giving manual responses with the right and on the other day with the left index finger. The procedure was identical for the 2 days. The order of left and right hand conditions was counterbalanced across subjects.

Visual stimulation and task

Visual stimuli consisted of black dots (visual angle, 0.5°; distance from subjects' eyes, 1 m) presented against a gray background in a dimly lit room. Dots were displayed for 60 ms every 1.5–2.5 s in randomized order either to the lower left or to the lower right quadrant (3° below, 4° to the left or right of a fixation cross). A lower visual field position was chosen because TMS to occipital cortex induces phosphenes and visual field defects predominantly in the lower visual fields (Kammer, 1999; Kastner et al., 1998; Ray et al., 1998). We presented 130 stimuli per visual field in each experimental block. Each block lasted approximately 8.5 min. During visual presentation, subjects were asked to fixate the cross and to avoid eye movements including eye blinks and saccades. In addition, subjects were instructed to place one index finger on a response button and to briskly press the button as fast as possible in response to any visual stimulus, that is, independent of stimulus location. Visual stimuli were presented and response data collected using a 16-in. Apple monitor (Apple Computers, Cuppertino, CA) and the PsyScope button box (New Micros, Dallas, TX) driven by a Power Mac computer (Model 9600/200, Apple Computers), running PsyScope (Cohen et al., 1993).

Transcranial magnetic stimulation

TMS was applied with a 70-mm figure-of-eight coil on the left occipital pole. A Magstim super rapid transcranial magnetic stimulator (Magstim Company, Dyfed, UK) was used. We attempted to maximize TMS effects using a functional coil positioning procedure. This consisted of targeting an occipital spot close to the midline where single TMS pulses evoked phosphenes that overlapped in space with the RVF stimulus position. Phosphenes show spatial overlap with scotomas (perceptual suppression) and can thus serve as a guide for optimal alignment of coil and visual stimulus position to maximize TMS effects on visual functions (Kammer, 1999). Functional coil positioning consisted of two steps. In a first step, the coil was moved on the scalp until the blindfolded subjects reported seeing phosphenes near the RVF stimulus position (between four and five o'clock on a visually imagined analogue clock). For fine-tuning, the blindfold was removed in the completely darkened room and subjects were shown three very small white dots (visual angle, 0.05°) presented against the black computer screen. The white dots marked the positions of fixation cross and visual stimuli (LVF and RVF) that were presented during the experimental blocks. Subjects were asked to fixate the central dot corresponding to the fixation cross and to report after each single pulse the location of the induced phosphene relative to the RVF dot. If necessary, the coil was repositioned until the evoked phosphene overlapped in space with the RVF stimulus marker. At the end of fine-tuning, subjects were asked to draw the phosphene on paper (shape, spatial extent, and location relative to the three dots; see Fig. 2C).

In addition, we determined the anatomical sites of magnetic stimulation on each subject's MR image by optical tracking using a frameless stereotaxic system (Brainsight, Rogue Research, Montreal, Quebec, Canada) (for a more detailed description see Paus, 1999). The site of magnetic stimulation, as determined with functional positioning matched in all subjects the anatomical target region of the occipital pole (pericalcarine structures; see Fig. 2B).

Intensity of rTMS was set to 110% of individual phosphene threshold at the stimulation site. Phosphene threshold was determined in the blindfolded subject and defined as the minimal intensity of the stimulator output that was capable of evoking phosphenes in at least three of six consecutive trials.

Functional coil positioning and determination of TMS intensity lasted approximately 5 min each. No subject was thus blindfolded for more than 10 min. Blindfolding was kept below 10 min, because light deprivation may change visual cortex excitability after 45 min (Boroojerdi et al., 2000b). After blindfolding and before visual stimulation began, subjects were given some time for readaptation to light. In addition, subjects were explicitly instructed to keep their eyes open during all following parts of the experiment including the rTMS session and the break. With the eyes open, no subject perceived phosphenes at the stimulation intensity used for rTMS (110%, suprathreshold under blindfold conditions). With one exception (S5), the coil was oriented with the handle pointing upward inducing currents in the rostrocaudal direction. In S5, the coil had to be rotated counterclockwise by 90° to induce phosphenes (induced current flowing in lateromesial direction).

EEG recordings and averaging

EEG was recorded continuously from 29 standard locations according to the international 10–10 electrode system (Fp1, Fpz, Fp2, AF7, AF3, AFz, AF4, AF8, FT7, FC3, FCz, FC4, FT8, C3, Cz, C4, TP7, CP3, CPz, CP4, TP8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2). Nonpolarizable, plastic-body electrodes coated with silver epoxy were used (Ives et al., 1998). This is important to prevent overheating of the EEG electrodes during exposure to TMS, which could lead to scalp burning (Pascual-Leone et al., 1990; Roth et al., 1992). Signals were recorded using a bipolar montage and were recalculated off-line against the average reference. Eye movements were monitored by two additional bipolar horizontal and vertical EOG derivations. Impedance was kept below 10 kΩ. Data were sampled at 200 Hz (0.1–100 Hz bandpass filtered) using a standard acquisition system (NeuroScan, Herndon, VA). Single sweeps were carefully scanned for artifacts including eye movements and blinks. Sweeps contaminated by artifacts were removed prior to analysis. The remaining artifact-free trials were further scanned on the basis of reaction time (RT) data. Trials with RTs lower than 100 ms (stimulus anticipation) or deviating more than 3 SD from the mean RT of a given condition (mean ± 3 SD) were also discarded. Per condition, approximately 80 trials were included in the cross-subject averages (~50 trials discarded; rejection ratio, artifacts\RTs ~ 3\1).

VID

Changes in alpha band power were computed according to the event-related desynchronization/synchronization method (Pfurtscheller and Lopes da Silva, 1999). Band power changes were defined as the percentage of decrease or increase in band power during a test interval (0 to 1024 ms after stimulus) compared to a reference interval (−1024 to 0 ms before stimulus). The bandpass filter was set to 8–12 Hz (48 dB/octave rolloff, trim left and right of 100 ms). To prevent masking of an alpha band power decrease (alpha suppression) by a phase-locked alpha power increase due to the VEPs' lower frequency components, non-phase-locked power changes were calculated by applying the intertrial variance method (calculation of point-by-point variance across trials; Kalcher and Pfurtscheller, 1995). Data were smoothed by averaging time samples over 50 ms. Scan 4.1 software was used for computations (NeuroScan Inc).

VEPs

Visual-evoked potentials were computed for 600-ms epochs aligned to visual stimulus onset (−100 to 500 ms). The baseline was corrected for each channel by subtracting the mean amplitude value of the prestimulus interval (−100 to 0 ms).

Data analysis

EEG analyses were performed on the amplitude values of VID or VEPs and included spatial screening for significant effects (map analysis) and analysis of VID and VEPs over selected electrodes (trace analysis). For map analysis, amplitude values of each electrode were compared time frame by time frame between conditions using paired *t* tests. Significant *t* values were averaged over the entire poststimulus interval for each electrode separately, before being mapped on the electrode array. For trace analyses, between-condition comparisons were performed on the maximum or minimum peak values corresponding to a given VEP component or the minimum peak of VID using overall analysis of variance (ANOVA). Latencies of maximum or minimum values were also subjected to overall ANOVAs as were reaction time data (cutoffs for slow and fast reaction times as defined previously; see "EEG recordings and analysis"). 2 × 2 × 2 × 2 ANOVAs with within-subject factors Electrode (Left electrode vs. Right electrode), Visual field (LVF vs. RVF), Hand (Left vs. Right), and Baseline (Pre- vs. Postbaseline) were applied to characterize baseline patterns. 2 × 2 × 2 ANOVAs with factors Visual field (LVF vs. RVF), Hand (Left vs. Right), and rTMS (rTMS vs. Baseline) were used to assess rTMS effects. In addition, Pearson correlation analyses were performed to explore the relationship between rTMS effects on VID, VEP, and behavior.

To provide information on the possible functional locus of occipital rTMS effects, we characterized VID and VEP amplitudes with respect to their dependency on visual stimulus and manual response features over time. Note that our design with four visual field/hand pairings (LVF/L hand, LVF/R hand, RVF/L hand, RVF/R hand) dissociates the spatial location of the visual stimulus from the side of the motor response. Accordingly, it allows us to search for EEG responses that covary in amplitude with visual stimulus position independently of manual response side (stimulus-dependent activity) or vice versa (movement-dependent activity). Assessing the temporal evolution of such stimulus- and movement-dependent activity provides some clues on timing of perceptual and motor stages of information processing and, in visuomotor tasks, on time periods of temporal overlap, the latter reflecting possible correlates of sensory–motor integration (e.g., Wascher and Wauschkuhn, 1996; Wascher et al., 1999). Stimulus dependency over time was derived by averaging VID and VEP traces over corresponding visual field conditions (RVF/R hand, RVF/L hand vs. LVF/R hand, LVF/L hand) and computing subtraction plots between these two visual field averages (Mean amplitudes$_{(\text{RVF conditions})}$ − Mean amplitudes$_{(\text{LVF conditions})}$). To obtain a measure for movement dependency over time, we reordered the same data set with respect to hand (RVF/R hand, LVF/R hand vs. RVF/L hand, LVF/L hand) and averaged traces over corresponding hand conditions before computing subtraction plots between these averages (Mean amplitudes$_{(\text{R hand conditions})}$ − Mean amplitudes$_{(\text{L hand conditions})}$).

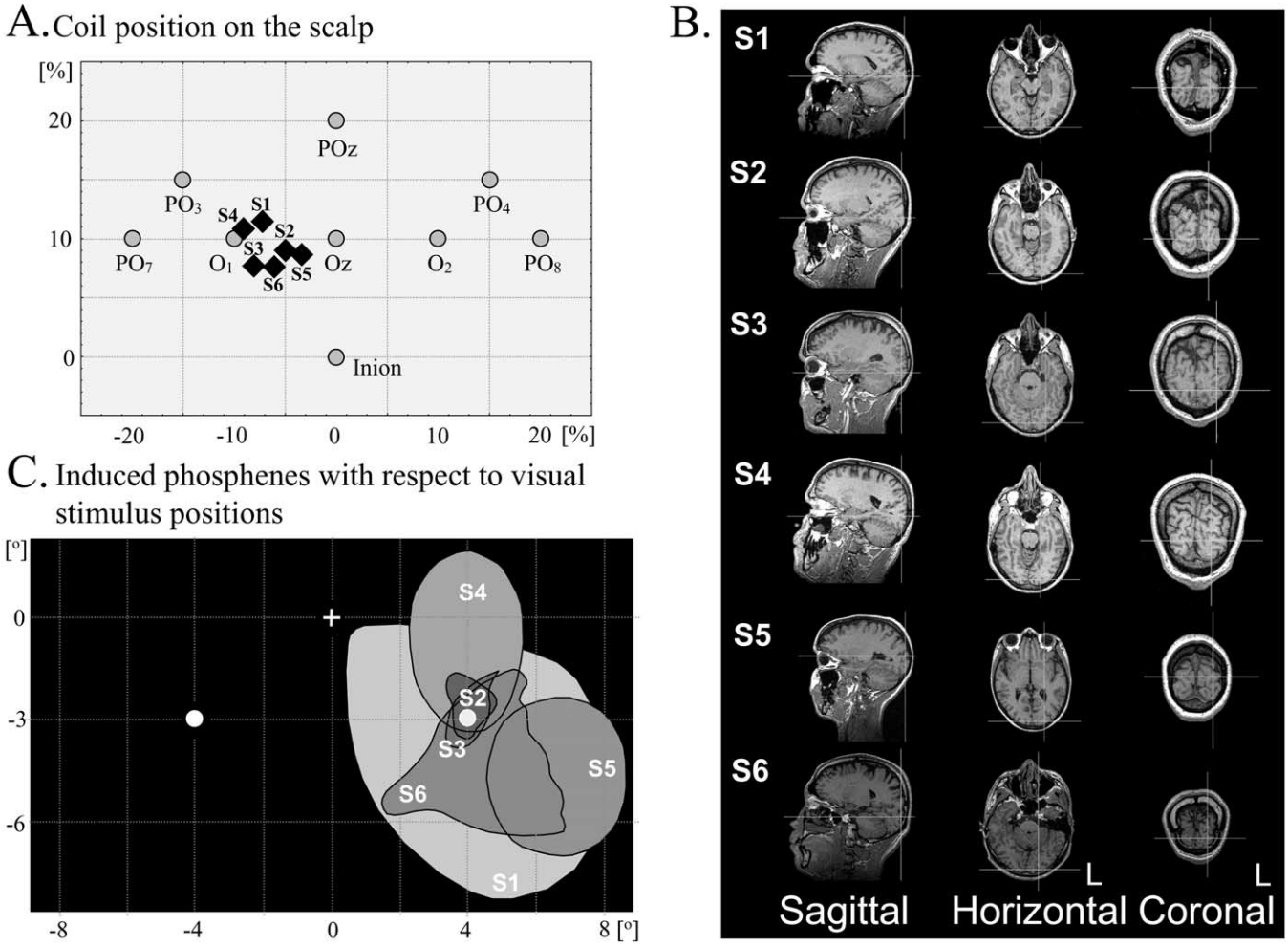

Fig. 2. Coil position and induced phosphenes. (A) Location of the coil center relative to occipital electrode positions of the international 10-10 EEG system. Coil locations are represented for each subject separately (S1–S6). (B) Magnetic stimulation site relative to each subject's MR image. TMS sites, extrapolated using a frameless stereotaxic system, are highlighted by cross-hairs. (C) Induced phosphenes as drawn by each subject superimposed on visual stimuli and fixation cross. Phosphenes were induced in the blindfolded subjects by single TMS pulses for optimization of coil positions prior to the experiment. Phosphenes overlap with scotomas (visual suppression) and thus can serve for functional coil positioning to maximize TMS effects on visual functions. Note the overlap of phosphenes with the RVF stimulus. Note also that, as a consequence, one expects rTMS effects to occur mainly in response to RVF stimulation. Data for right hand blocks are presented. There was no difference, neither quantitatively (coil position) nor qualitatively (phosphenes), from the left hand blocks (see Results).

Subtraction plots were calculated for baseline and rTMS blocks separately and compared for electrodes and time periods of interest (area under curve) using ANOVAs.

Results

TMS: coil position, induced phosphenes, and intensity

The center of the coil was located 1 to 2.5 cm to the left of the Inion (x axis) and 2.8 to 4.9 cm above the Inion (y axis). There was no significant difference regarding coil positioning between the right hand blocks (mean ± SE in cm, $x = -1.9 \pm 0.3$, $y = 3.4 \pm 0.2$) and the left hand blocks ($x = -1.6 \pm 0.3$, $y = 3.7 \pm 0.3$) recorded on 2 different days. With respect to the international 10–10 EEG coordinate system, the coil center was placed between O1 and Oz, on average closer to O1 (Fig. 2A, right hand blocks/left hand blocks, $x = -6.5 \pm 0.9\%/-5.7 \pm 0.9\%$, $y = 9.2 \pm 0.7\%/10.1 \pm 1.1\%$, $x = 0/y = 0$, Inion). Anatomically, TMS sites were located over pericalcarine structures (inferior part of cuneus, inferior occipital gyrus) of the left occipital pole (Fig. 2B). Single pulses at these locations evoked, in the blindfolded subjects, phosphenes in the contralateral, lower visual field (Fig. 2C). The phosphenes overlapped with the RVF stimulus position for all subjects except one (S5).

The mean output intensity of the stimulator (expressed in percentage of maximum output) was not significantly different between the two recording days (right hand blocks/left hand blocks, 68 ± 3%/69 ± 3%).

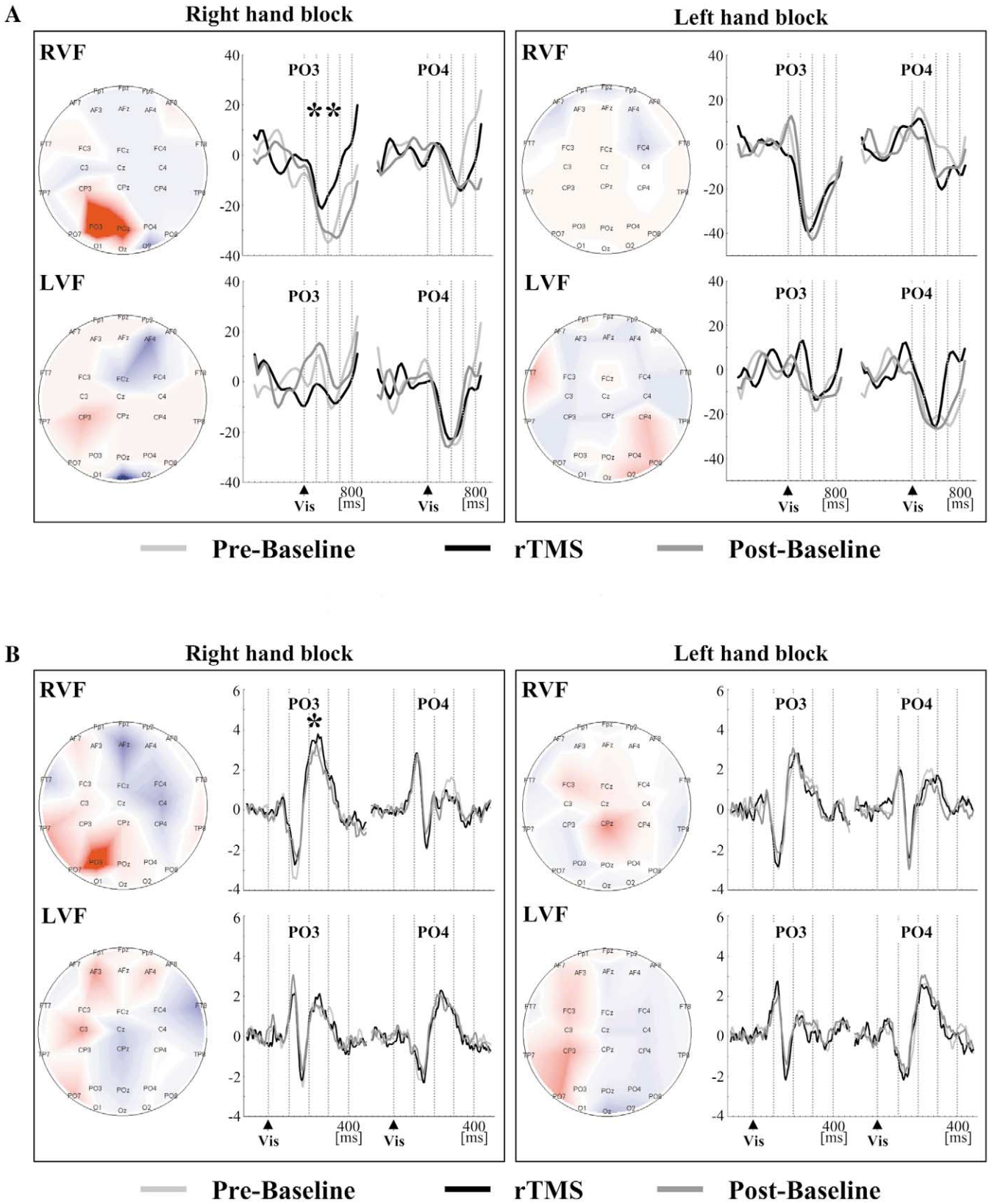

Fig. 3. EEG responses to visual stimulation: Spatial distribution of significant rTMS effects collapsed over time (maps) and temporal evolution over selected occipital electrodes in each of the four conditions (RVF/LVF stimulation × right hand/left hand response) for (A) alpha desynchronization (VID) and (B) visual evoked potentials (VEPs). Statistical maps: significant differences were mapped on the electrode array by calculating *t* tests between the rTMS block and the two baseline blocks (average) for each time frame separately and by averaging significant *t* values over time. Temporal evolution: traces show electrical responses over left (PO3) and right occipital electrodes (PO4) (1) before (prebaseline), (2) immediately following (rTMS), and (3) 20 min after rTMS (postbaseline). The arrows indicate visual stimulus onset. Note that left occipital rTMS significantly changed VID and VEPs over left occipital electrodes in the RVF/R hand conditions.

VID: baseline patterns and influences of rTMS across electrodes and conditions

Baseline pattern

Prominent decreases in alpha power were found over occipital electrodes (Fig. 3A, line drawings illustrating traces over PO3/PO4). Dampening of alpha was observed within 100 ms after the appearance of the visual stimulus and reached its maximum at around 400 ms after stimulus onset. Alpha suppression over these lateral occipital electrodes (amplitude) was stronger in response to contralateral than ipsilateral visual field stimulation (i.e., PO3, $VID_{(RVF)} > VID_{(LVF)}$; PO4, $VID_{(LVF)} > VID_{(RVF)}$) as indicated by a significant two-way interaction Electrode × Visual field ($F(1,5) = 10.1$, $P = 0.025$). No latency differences were found. Simple tests revealed that the difference in VID amplitude with respect to side of visual stimulation was significant for PO3 (main effect Visual field, $F(1,5) = 18.8$, $P = 0.007$) but failed to reach significance for PO4 ($F(1,5) = 3.6$, $P = 0.12$). There was no difference in VID amplitude between pre- and postbaseline blocks (no significant main effect nor significant interactions for factor Baseline, all $F < 1$, NS). Therefore, further comparisons were performed against the two collapsed baseline conditions (pre- and postbaseline).

rTMS effects (rTMS vs. baseline blocks)

Map analyses performed for each of the four conditions separately showed that left occipital rTMS significantly modulated alpha suppression over occipital electrodes PO3 and POz (Fig. 3A, map inset depicting spatial distribution of rTMS effects collapsed over time). The statistical maps suggest that the left occipital effect was present after right visual field stimulation when a right hand response was required (RVF/R hand block) but absent in the other conditions (RVF/L hand, LVF/R hand, LVF/L hand). Overall ANOVAs confirmed that the effect over PO3 and POz was confined to the RVF/R hand condition (significant three-way interactions Visual field × Hand × rTMS, $F(1,5) = 22.0/18.7$, $P = 0.005/0.008$ (PO3/POz)). Alpha suppression was significantly reduced in the RVF/R hand (simple tests, main effect rTMS $F(1,5) = 17.9/169.2$, $P = 0.008/<0.0001$ (PO3/POz)) as opposed to all other conditions (simple tests, main effects rTMS, all $F(1,5) < 2.8/1.55$, NS (PO3/POz)). No effect of rTMS on VID amplitudes was observed over PO4 nor was there any rTMS effect regarding latencies (no significant main effect nor significant interactions).

VEPs: baseline patterns and influences of rTMS across electrodes and conditions

Baseline pattern

VEPs consisted of three components, two early components corresponding to classical visual components P1 (positive peak at around 100 ms) and N1 (negative peak at around 160 ms) as well as a later positive component peaking at 200–250 ms (P200) close to the behavioral response (mean reaction time over all conditions, 251 ms; range, 233–270 ms). Similar to VID, VEP components over lateral occipital electrodes occurred earlier (P1, N1) or were stronger (P200) after contralateral than ipsilateral visual field stimulation (i.e., PO3, $VEP_{(RVF)}$ earlier or stronger than $VEP_{(LVF)}$; PO4, $VEP_{(LVF)}$ earlier or stronger than $VEP_{(RVF)}$) as indicated by significant two-way interactions Electrode × Visual field (P1 latency, $F(1,5) = 22.1$, $P = 0.005$; N1 latency, $F(1,5) = 92.3$, $P = 0.0002$; P200 amplitude, $F(1,5) = 20.4$, $P = 0.006$). Simple tests showed that the differences in VEP timing or amplitude with respect to side of visual stimulation were significant for both PO3 and PO4 (main effects Visual field, all $F(1,5) > 6.7$, $P < 0.049$). In addition, the late positive component (P200) depended in amplitude on the side of the motor response (i.e., PO3, $VEP_{(R\ hand)} > VEP_{(L\ hand)}$; PO4, $VEP_{(L\ hand)} > VEP_{(R\ hand)}$) as shown by a significant Electrode × Hand interaction (P200 amplitude, $F(1,5) = 18.1$, $P = 0.008$).

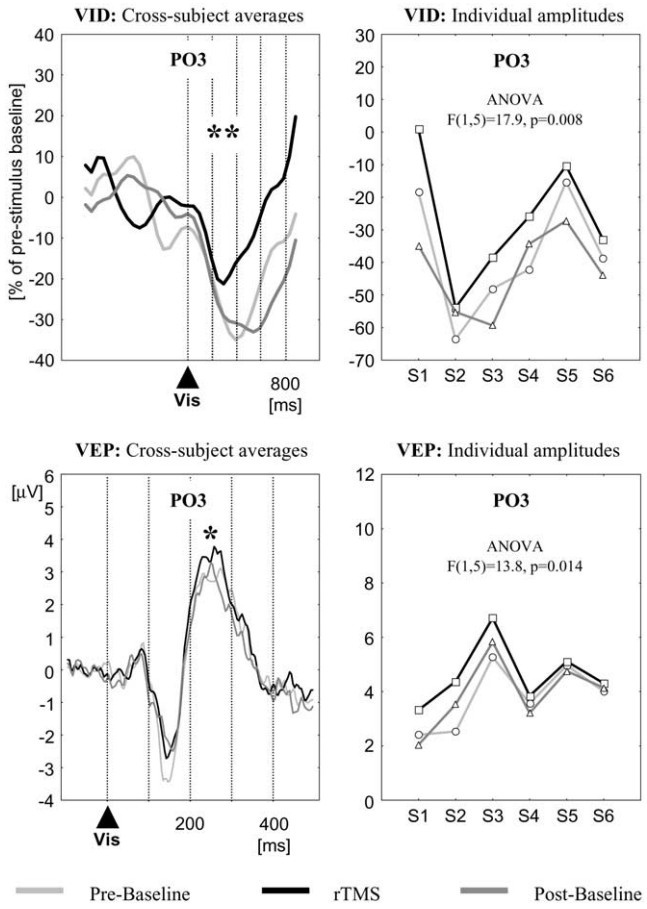

Fig. 4. Cross-subject averages over time (left panels) and individual amplitudes at components of significant effects (right panels) for the RVF/R hand condition. VID (top panels) and VEPs (bottom panels) are shown for electrode PO3 and for the prebaseline, rTMS, and postbaseline blocks. The arrows indicate visual stimulus onset. S1–S6, subjects 1–6. Note the prominent change for VID, the moderate change at the late VEP, and the absence of changes at early VEPs (P1/N1). Note also the opposite direction of the rTMS effects on VID (reduction) and VEP (enhancement), respectively.

This indicates that at these late time points close to movement onset, occipital electrodes capture both visual- and movement-related brain activity (for a detailed description see later, "EEG responses: influences of rTMS on visual stimulus and movement dependency").

In analogy to VID, there was no significant difference between the pre- and postbaseline blocks for P1 and the late positive VEP component (no significant main effect nor interactions for factor Baseline). Over all conditions, N1 showed a significant amplitude reduction over time (main effect of Baseline, $F(1,5) = 10.9$, $P = 0.02$). As for VID, further tests were performed against the data collapsed over the two baseline conditions (pre-/postbaseline) allowing us to extract differences between rTMS and baseline that cannot be explained by linear changes over time.

rTMS effects (rTMS vs. baseline blocks)

Map analysis suggested that left occipital rTMS significantly changed VEPs over PO3 predominantly in the RVF/R hand condition (Fig. 3B, map inset). These changes over PO3 occurred at the late positive component (P200) as shown by an overall ANOVA on P200 amplitudes (significant three-way interaction Visual field × Hand × rTMS, $F(1,5) = 6.6$, $P = 0.049$). The P200 amplitude over PO3 was significantly changed in the RVF/R hand (simple tests, main effect rTMS, $F(1,5) = 13.82$, $P = 0.014$) as opposed to all other conditions (simple tests, main effects rTMS, all $F(1,5) < 1.72$, NS). The early visual components over PO3 (P1, N1) did not show any consistent changes due to rTMS (no significant main effects nor interactions for factor rTMS), nor did any VEP components over PO4. Finally, no effects on latency were observed.

EEG responses: characterization of rTMS effects on the group and the individual level

While rTMS reduced VID by approximately 40% of the prebaseline level (Fig. 4, top left panel, effect illustrated for PO3), the late VEP change at the P200 component was in the order of 10% (Fig. 4, bottom left panel). For both measures, the effect was washed-out 20 min later (postbaseline) speaking in favor of a transient, rTMS-related change (no amplitude differences between pre- and postbaseline blocks for both VID and P200; see previously, "Baseline patterns"). In addition, all subjects showed the rTMS-induced change for both VID (Fig. 4, top right panel) and the late VEP (Fig. 4, bottom right panel). However, in contrast to alpha suppression being reduced due to rTMS, late VEP amplitudes were found to increase following rTMS; that is, they showed changes in the opposite direction.

EEG responses: influences of rTMS on visual stimulus and movement dependency

Stimulus and movement dependency of VID and VEPs are depicted in Fig. 5 as a function of time (subtraction plots). VID over PO3 appeared to be mainly stimulus-dependent (Fig. 5A), as VID displayed a clear, task-related stimulus dependency, but no clear, task-related movement dependency (i.e., no clear differences in movement dependency between pre- and poststimulus intervals). In contrast, VEP responses over PO3 showed initial stimulus dependency, followed by periods in which both stimulus- and movement-dependent activity overlapped (Fig. 5B). The early time periods of stimulus dependency coincided with P1 and N1, while the late period with overlapping stimulus and movement dependency coincided with the P200 component.

Comparison of subtraction data between baseline and rTMS (Fig. 5, left vs. right panels) further confirmed that there was no effect of rTMS on the early VEPs' stimulus dependency (70–170 ms poststimulus, factor rTMS, $F(1,5) < 1$, NS). At late time periods, rTMS led to a significant increase of the VEPs' stimulus as well as movement dependency (170–350 ms after stimulus onset, main effects of rTMS, stimulus dependency, $F(1,5) = 7.6$, $P = 0.04$; movement dependency, $F(1,5) = 122.9$, $P < 0.0001$). In addition, there was less stimulus dependency for VID due to rTMS (0–1024 ms after stimulus, main effect of rTMS, $F(1,5) = 12.9$, $P = 0.02$).

Behavior

Baseline pattern

As for EEG data, overall ANOVAs on baseline performance (reaction times) did not show any main effect of baseline nor any interaction with this factor. The only significant effect was found for the interaction Visual field × Hand ($F(1,5) = 33.2$, $P = 0.002$). Subjects responded faster with the left hand to LVF- as compared to RVF-stimuli (simple test: $F(1,5) = 18.3$, $p = 0.008$) and faster with the right hand to RVF compared to LVF stimuli (simple test, $F(1,5) = 5.6$, $P = 0.06$), which is in accordance with previous behavioral studies (reviewed in, e.g., Marzi et al., 1991).

rTMS effects (rTMS vs. baseline blocks)

Tests for rTMS effects revealed a significant three-way interaction Visual field × Hand × rTMS ($F(1,5) = 8.54$, $P = 0.03$). However, this was not due to differential rTMS effects across visual field–hand pairings (no significant effect of rTMS, all $F > 1.8$, $P < 0.23$). Instead, subjects showed relative changes in behavior within the rTMS block. The two-way interaction Visual field × Hand, present in the baseline blocks (simple test, $F(1,5) = 18.3$, $P = 0.008$), was absent following rTMS ($F(1,5) = 1.4$, $P = 0.3$). In fact, the relative reaction time advantage for right hand responses to RVF compared to LVF stimuli was reversed following rTMS (simple test on rTMS data, main effect of Visual field, $F(1,5) = 7.04$, $P = 0.045$).

Given these relative changes in behavior, rTMS effects were further explored using a relative behavioral measure

expressing performance in the RVF condition relative to the LVF condition (reaction times RVF − reaction times LVF). During baseline, this relative measure was associated with negative values for right hand performance (Fig. 6A, right hand responds faster to RVF than LVF stimuli) and positive values for left hand responses (Fig. 6B, left hand responds faster to LVF than RVF stimuli) independent of blocks (no main effect nor significant interaction for factor Baseline). Comparison between rTMS and baseline revealed a significant two-way interaction Hand × rTMS ($F(1,5) = 8.54$, $P = 0.03$). Following rTMS, the baseline pattern was reversed for right hand (simple test, main effect rTMS, $F(1,5) = 11.05$, $P = 0.02$) but unchanged for left hand responses (main effect rTMS, $F(1,5) = 1.15$, $P = 0.33$). Note in Fig. 6A the positive RT differences after rTMS as opposed to negative values in pre- and postbaseline blocks. That is, left occipital rTMS resulted in a disadvantage for right hand responses to RVF compared to LVF stimuli. The rTMS effect was consistent across subjects (Fig. 6A, right panel) and proved to be statistically significant (one-sample t test against 0, $t = 3.2$, $P = 0.02$).

Relationship between rTMS-induced changes on VID, VEP, and behavior

The rTMS-induced increase in P200 amplitude over PO3 showed a weak tendency for a positive correlation with the rTMS-induced increase in reaction time (RVF/R hand condition, Pearson correlation coefficient $r = 0.73$, $P = 0.09$). Correlations between rTMS-induced changes in VID and reaction time as well as VID and VEP changes were also not significant (RVF/R hand condition, $r = 4.1$, $P = 0.42$; $r = 0.52$, $P = 0.29$).

Discussion

The main finding of the present study is that 1-Hz rTMS over the occipital pole affects VID and VEPs differentially. Alpha desynchronization was affected more prominently and was reduced on average by 40% of basal values. In contrast, there were no TMS-induced changes on early visual evoked potentials (P1/N1 complex). A significant, but small amplitude change was found on a late occipital component of the VEP that appeared close to movement onset (change, <10% of basal values). However, this effect was in the opposite direction to the VID change. That is, while VID was reduced, the VEP amplitude was enhanced. These changes were restricted in space to the targeted left occipital cortex and were present only after right visual field stimulation when a right hand response was required, which rules out nonspecific rTMS effects (i.e., effects unrelated to activation of brain tissue by TMS). Unspecific rTMS effects (e.g., attentional changes due to the loud coil click or the monotonous coil tap on the scalp) would have been expected to be generalized to both hemispheres and all conditions. In addition, all effects were washed out 20 min after delivery of the TMS train, which makes it unlikely that a general change in arousal (e.g., fatigue) can explain our results. Optical tracking of the actual TMS site on each subject's anatomical MRI suggested pericalcarine structures as targeted regions.

Our findings are novel in three regards. First, they show that EEG correlates of occipital activation can be modulated by rTMS on the occipital pole. This agrees with recent rTMS studies demonstrating EEG changes after magnetic stimulation over motor or prefrontal areas (Evers et al., 2001; Jing and Takigawa, 2000; Jing et al., 2001; Okamura et al., 2001; Rossi et al., 2000; Schutter et al., 2001), subsequent to the pioneer TMS-EEG work of Ilmoniemi et al. (1997). In accordance with our findings, rTMS has been reported to modulate the movement-related cortical activity reflected by the Bereitschaftspotential (Rossi et al., 2000), event-related potential components reflecting cognition (Evers et al., 2001; Jing et al., 2001), and oscillatory activity in spontaneous EEG (Jing and Takigawa, 2000; Okamura et al., 2001; Schutter et al., 2001). Second, our findings suggest partial independence of alpha desynchronization and visual-evoked potentials, replicating over visual areas previous electrophysiological findings at motor sites (Babiloni et al., 1999; Feige et al., 1996; Toro et al., 1994). This strongly supports the notion that alpha desynchronization and evoked potentials do not simply reflect one and the same aspect of cortical activation. Of special interest in this respect is the opposite effect of rTMS on VID and the late VEP component. It is unlikely that the late VEP enhancement is due to a rTMS-induced increase in cortex excitability, as a growing number of studies report a reduction in cortex excitability by 1-Hz rTMS (e.g., Boroojerdi et al., 2000a; Chen et al., 1997a; Gerschlager et al., 2001; Maeda et al., 2000; Muellbacher et al., 2000; Münchau et al., 2002; Romero et al., 2002; Touge et al., 2001). We speculate that the late VEPs, whose neuronal bases rather appear to be unaffected by rTMS, represent a possible source of functional reorganization to the inhibitory rTMS effect evidenced by the VID change. If so, the increase in late VEP amplitudes may reflect a mechanism of functional reorganization to rTMS, which however had no compensatory outcome (given the rTMS-induced behavioral effect). Third, our data provide additional information on the possible functional role of visual-induced alpha desynchronization.

Alpha desynchronization signals the transition between a cortical resting (idling) state with low-frequency rhythms and an activated state where higher frequencies occur (e.g., Klimesch, 1996; Pfurtscheller and Lopes da Silva, 1999). What functional role alpha desynchronization serves, however, is still a matter of debate. Lopes da Silva (1991) argued that the blocking of the occipital alpha rhythm is likely to be associated with an increased probability that sensory information is relayed via thalamus to cortex. Accordingly, the blocking of this oscillatory activity would subserve a "thalamocortical gating function." In this case,

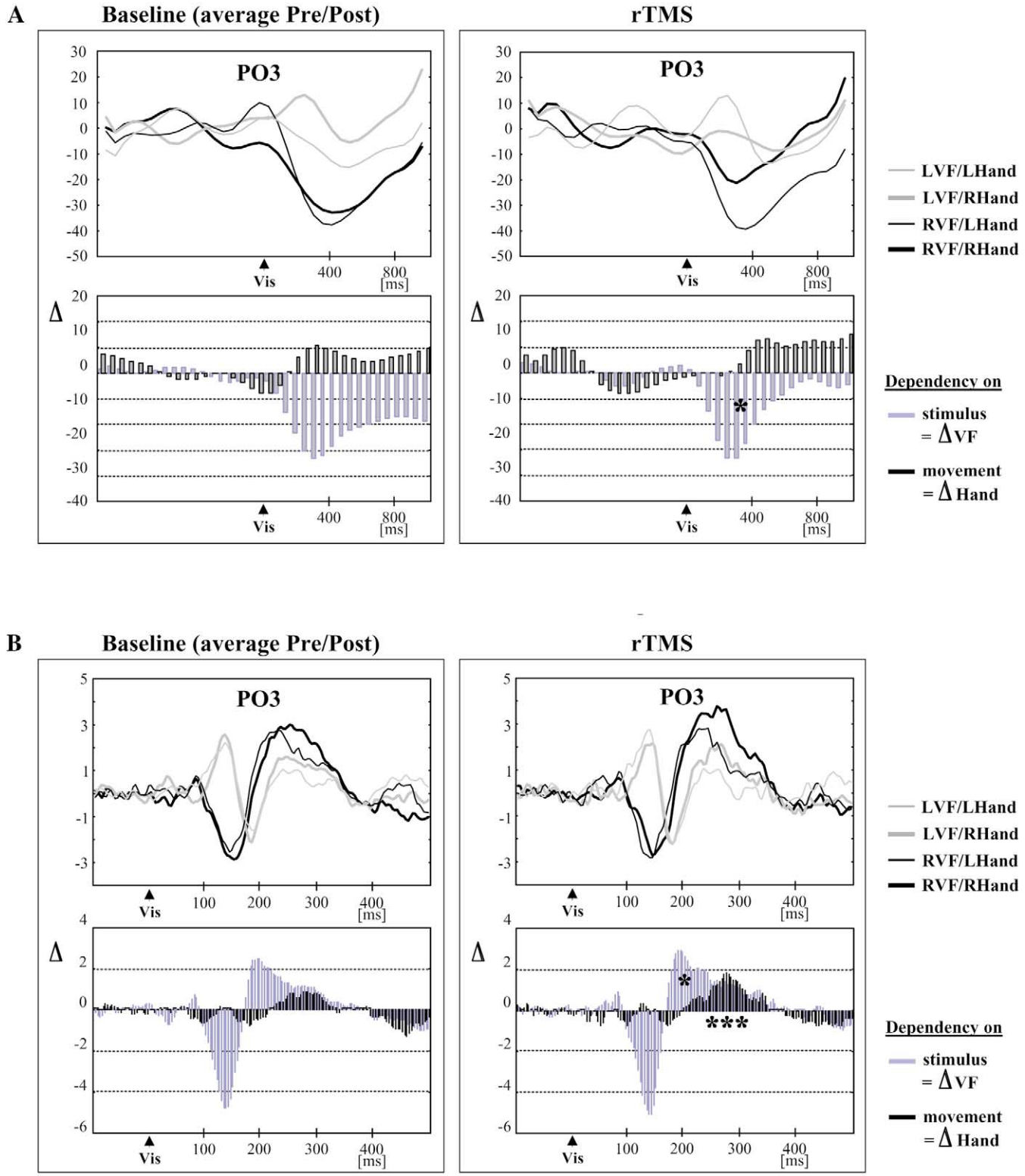

Fig. 5. (A) VID and (B) VEPs (μV) over PO3 in all four conditions (LVF/L hand, LVF/R hand, RVF/L hand, RVF/R hand) for baseline and rTMS blocks (top panels). (Bottom panels) Subtraction plots derived from these VID and VEP traces, respectively. The subtraction plots depict for each time frame the amount of EEG activity that depends on the side of visual stimulation (ΔVF = Mean amplitude$_{(\text{RVF conditions})}$ − Mean amplitude$_{(\text{LVF conditions})}$) or that depends on the side of the motor output (ΔHand = Mean amplitude$_{(\text{R hand conditions})}$ − Mean amplitude$_{(\text{L hand conditions})}$). Note that rTMS led to a reduction of stimulus-dependency for VID (A, rTMS vs. Baseline) and to an increase of both stimulus and movement dependency for VEPs (B, rTMS vs. baseline). Note also that all changes occurred at long latencies, that is, where VEPs are devoid of purely stimulus-dependent activity.

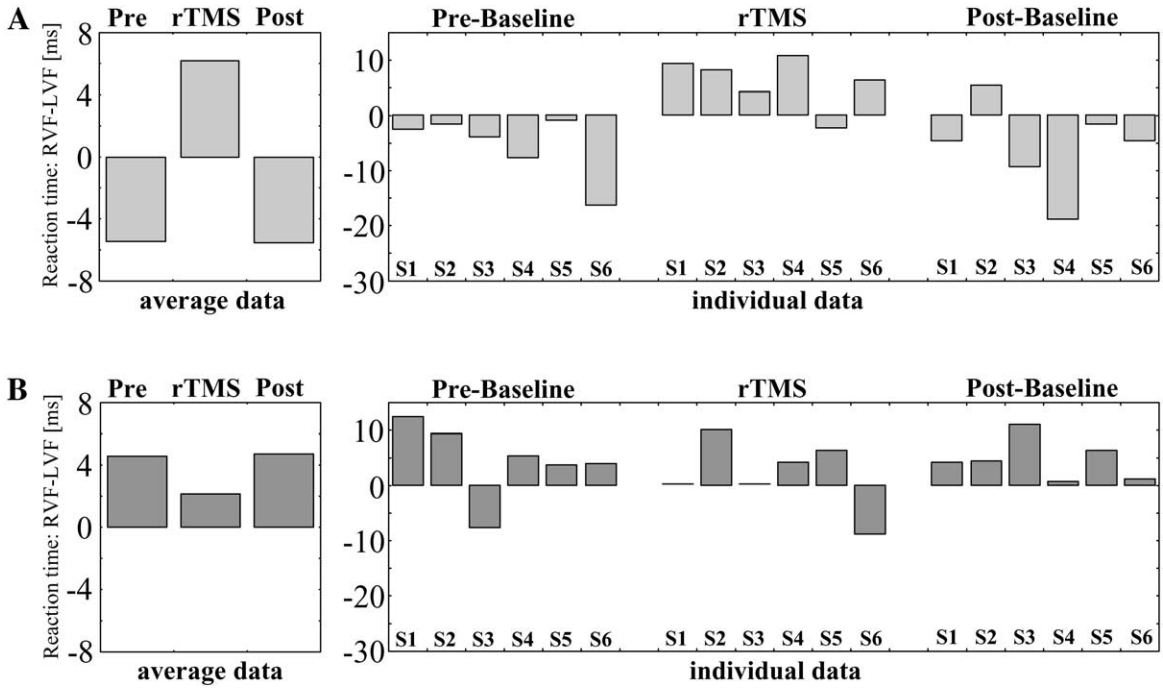

Fig. 6. Performance in the RVF conditions relative to the LVF conditions for the prebaseline, rTMS and postbaseline sessions as well as for (A) right hand and (B) left hand blocks. *y* axis, reaction times in RVF conditions minus reaction times in LVF conditions. Negative values indicate a reaction time (RT) advantage for responses to RVF stimuli (shorter RT to RVF than LVF stimuli), and positive values indicate a RT disadvantage. Right hand blocks (A): note the reversal in this relative performance measure in the rTMS block with respect to pre- and postbaseline. The reversal indicates that rTMS resulted in a RT disadvantage for right hand responses to RVF compared LVF stimuli.

however, one would expect that interference with VID in the alpha band is associated with changes in the thalamocortical input of visual signals, and hence is more likely to affect early than late VEPs. Our results do not support this view, given that rTMS failed to interfere with early VEPs while strongly affecting VID. Toro et al. (1994), on the other hand, speculated that the blocking of lower frequency rhythms serves an integrative role by freeing the way for higher frequency oscillations (beta/gamma) to develop. Higher frequency oscillations are involved in coupling spatially separate neurons or neuronal assemblies through synchronization for visual encoding or visuomotor-integration (Classen et al., 1998; König and Engel, 1995; Singer and Gray, 1995; Von Stein and Sarnthein, 2000). This would correspond to an integrative role of alpha desynchronization through a corticocortical gating function. In this case, one would expect the rTMS effect on VID to be associated with changes on late rather than early VEPs. Our finding that rTMS modulates late VEP components occurring shortly before the behavioral response (i.e., around the time of visuomotor integration) better agrees with the latter view.

Two other aspects of our data argue for rTMS interference beyond visual input, thus speaking against the thalamocortical but in favor of the corticocortical gating model and a potential integrative role for VID. First, if interfering with visual input, the effects of left occipital rTMS should be exclusively dependent on the side of visual stimulus delivery (stronger after RVF than LVF stimulation), apart from occurring on early VEP components. Yet, VID, VEPs, and behavior were modulated only in the condition where the RVF stimulus had to be integrated in a right hand motor command. rTMS thus interfered with higher-order rather than basic visual functions, namely intrahemispheric visuomotor integration, given that the rTMS-induced changes were confined to the condition where the targeted left hemisphere both receives the visual stimulus and controls the motor output (RVF/R hand). Second, our data showed that the late VEP component was characterized by overlapping stimulus and movement dependency, which were both enhanced by rTMS. Such intervals with coinciding stimulus- and movement-dependent activity are likely to be associated with visuomotor integration, thus providing a further argument that rTMS led to changes at this higher-order level of visual function. However, how exactly these VEP changes relate to the VID reduction remains unclear and is left to speculation. It is conceivable that the late VEP increase reflects functional reorganization (see previously), that is, that it signals enhancement of unaffected visual functions to adapt to inhibitory rTMS effects at a functionally similar but physiologically unrelated level.

In our study, rTMS effects were confined to the condition in which visual information had to be transferred intrahemispherically for visuomotor integration. There was no evidence for impaired interhemispheric transfer of visual information, because no changes occurred on early VEP

components (P1, N1) ipsilateral to visual stimulation, that is, over the occipital cortex receiving visual information via the corpus callosum. These components ipsilateral to visual stimulation are delayed with respect to the components at homologous, opposite sites due to callosal relay (Brown et al., 1994; Rugg et al., 1985). In contrast to our findings, Marzi et al. (1998) showed impaired interhemispheric but unaffected intrahemispheric transfer by single-pulse TMS at the left occipital pole using the same visuomotor paradigm that we applied but focusing on behavioral changes. The two studies however differ in several respects, all of which might account for the divergent results. The major difference pertains to TMS type (single vs. repetitive). Single TMS pulses delivered at a specific latency following visual stimulus onset (50 ms in the study by Marzi et al., 1998) are likely to have a different effect than a 10-min train of TMS pulses applied prior to visual stimulation. The two studies also differ slightly in regard to coil position. With respect to Marzi et al. (1998), we stimulated the occipital cortex on average 1.3 cm more caudal and 0.3 cm closer to the midline. Accordingly, we might have stimulated striate rather than extrastriate cortex, while the reverse applies for Marzi and co-workers. Unlike stimulation of extrastriate visual areas, striate cortex stimulation is expected to have minimal effects on interhemispheric transfer. This is because Brodmann area 17 has considerably sparser transcallosal connections than areas 18/19 (Clarke and Miklossy, 1990). Although there are several possible explanations for the dissimilar effects outlined above, there is no argument to favor one particularly.

Finally, our results may help the understanding of the mechanisms of rTMS action. While numerous studies have detailed the suppressive effect of 1-Hz rTMS on motor cortex excitability (Chen et al., 1997a; Gerschlager et al., 2001; Maeda et al., 2000; Muellbacher et al., 2000; Münchau et al., 2002; Romero et al., 2002; Touge et al., 2001), only a few studies have attempted to probe this effect on occipital cortex (Boroojerdi et al., 2000a). In addition, some of these studies have provided evidence that the suppressive effect of 1-Hz stimulation is of cortical origin (e.g., Chen et al., 1997a; Pascual-Leone et al., 1998; Touge et al., 2001). However, the mechanism and site of action are still unclear. One unresolved issue is to what extent rTMS affects corticocortical interneurons or the excitability of neurons responding to afferent or coding for efferent signals. Our data provide indirect evidence that occipital rTMS predominantly affects interneuronal mechanisms. Alpha desynchronization is considered to be subserved by changes in thalamic neurons and cortical interneurons that control the frequency of the ongoing EEG (Lopes da Silva, 1991), whereas visual-evoked potentials reflect the neural response due to changes in afferent activity (Pfurtscheller and Lopes da Silva, 1999). Our findings of prominent changes in alpha desynchronization are thus suggestive of interference at the former level. This complements motor cortex studies which, using different TMS protocols, investigated the effect of 1-Hz rTMS on motor threshold (MT) and intracortical inhibition (ICI) or facilitation (ICF). MT probes membrane-related intrinsic neuronal excitability, given that MT is influenced by drugs that affect voltage-gated sodium and calcium channels (Ziemann et al., 1996a; Chen et al., 1997b). ICI and ICF reflect inhibitory and excitatory interneuronal mechanisms (Ziemann et al., 1996b) correlating with GABA (Ziemann et al., 1996a, 1996c) or glutamatergic function respectively (Liepert et al., 1997). The motor cortex studies have shown that 1-Hz rTMS affects both MT (Muellbacher et al., 2000) and ICI/ICF (Münchau et al., 2002; Romero et al., 2002), providing thus indirect evidence that low-frequency rTMS reduces motor neuron excitability both indirectly via changes in local interneurons and directly via changes of the motor neurons' membrane property.

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