Modulation of visual evoked potentials by high-frequency repetitive transcranial magnetic stimulation in migraineurs

Petter M. Omland a,⇑, Martin Uglem a, Morten Engstrøm a,b, Mattias Linde a,b, Knut Hagen a,b, Trond Sand a,b

a Norwegian University of Science and Technology, Department of Neuroscience, Trondheim, Norway
b St. Olavs Hospital, Department of Neurology and Clinical Neurophysiology, Trondheim, Norway

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Abstract

Objective: High-frequency repetitive transcranial magnetic stimulation (rTMS) modulates cortical excitability. We investigated its effect on visual evoked potentials (VEPs) in migraine.

Methods: Thirty-two headache-free controls (CO), 25 interictal (MINT) and 7 preictal migraineurs (MPRE) remained after exclusions. VEPs to 80 and 650 checks were averaged in six blocks of 100 single responses. VEPs were recorded before, directly after and 25 min after 10 Hz rTMS. The study was blinded for diagnosis during recording and for diagnosis and block number during analysis. First block amplitudes and habituation (linear amplitude change over blocks) were analysed with repeated measures ANOVA.

Results: With 650 checks, N70-P100 habituation was reduced in MINT compared to CO after rTMS (p = 0.013). With 80 checks, habituation was reduced in MPRE compared to MINT and CO after rTMS (p < 0.016). No effects of rTMS on first block amplitudes were found.

Conclusion: RTMS reduced habituation only in migraineurs, indicating increased responsivity to rTMS. The magnocellular visual subsystem may be affected interictally, while the parvocellular system may only be affected preictally.

Significance: Migraineurs may have increased responsiveness to rTMS because of a cortical dysfunction that changes before a migraine attack.

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1. Introduction

Functional alterations in the migraine cortex may contribute to the development of migraine attacks (Vecchia and Pietrobon, 2012). It has been suggested that the visual cortex in migraineurs is either hyper- or hypoexcitable (Aurora and Wilkinson, 2007; Coppola et al., 2007b), and that the regulation of cortical excitability is altered in migraineurs (Antal et al., 2008).

Visual evoked potential (VEP) amplitude and VEP habituation depend on cortical excitability (Coppola et al., 2007b), but the mechanisms are complex and not fully understood (Coppola et al., 2007b; Rankin et al., 2009). Interictal migraineurs (MINT) may lack habituation. VEP amplitudes decrease during continuous stimulation in CO, but increase or remain stable in MINT (Coppola et al., 2009). However, this finding is controversial because it has not been reproduced in many studies (Afra et al., 2000a; Hansen et al., 2011; Khalil et al., 2000; Oelkers-Ax et al., 2005; Oelkers et al., 1999; Omland et al., 2013; Sand et al., 2008).

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The visual system can roughly be divided into the magnocellular and parvocellular subsystems. The magnocellular system mainly continues in the dorsal pathway of the parietal cortex, which is responsible for the visual guidance of movement (Kandel et al., 2013). The magnocellular subsystem is more sensitive to lower spatial frequency (i.e. VEPs with larger checks) than the parvocellular subsystem (Bassi and Lehmkuhle, 1990; Livingstone and Hubel, 1988). Studies applying both small and large check sizes only found differences in visual responses between migraineurs and CO with the larger check size (Chen et al., 2009; Sand et al., 2009). In addition, deficits of visual motion processing have been reported in migraineurs (McKendrick et al., 2001). The alterations in excitability of the visual cortex may therefore primarily involve the magnocellular subsystem (Chen et al., 2009).

Repetitive transcranial magnetic stimulation (rTMS) can modulate cortical excitability (Pascual-Leone et al., 1994). In one study, high-frequency rTMS restored normal VEP habituation in MINT, but had little effect in CO (Bohotin et al., 2002). However, this result has as far as we know not been reproduced with a blinded study design or a control group matched for age. To our knowledge, the effect of high-frequency rTMS on VEPs in MINT has only been investigated with small 8’ check stimuli (Bohotin et al., 2002) and not with larger (e.g. 65’) checks.

Migraineurs often experience symptoms in the preictal period, including increased sensitivity to light (Giffin et al., 2003). These prodromal symptoms may be related to altered cortical activity (Noseda and Burstein, 2013). Longitudinal studies have reported preictal changes in VEPs (Sand et al., 2008) and in cortical activity measured by quantitative electroencephalography (QEEG) (Bjork et al., 2011). The effect of high-frequency rTMS on VEPs has not been studied previously in preictal migraineurs (MPRE).

The aim of the present study was to compare the effect of high-frequency rTMS on VEPs in MINT, MPRE and CO with a blinded procedure. We hypothesized that the rTMS-induced changes in interictal migraineurs would be more pronounced with large 65’ than small 8’ checks, and that the changes would increase in the preictal period. For small checks, we wanted to confirm that the possibly abnormal VEPs in MINT could be changed and restored to normal by high-frequency rTMS.

2. Methods

2.1. Subjects

Subjects were recruited by intranet advertisement within our university. Subjects were both students and university employees (professors, nurses, technical staff, kindergarten staff, secretaries etc.). Forty-three migraineurs were included by neurologists (professors, nurses, technical staff, kindergarten staff, secretaries etc.). Thirty-four migraineurs were recruited. Migraineurs with 2–6 migraine attacks and at most 10 migraine days per month were included. They kept a headache diary 4 weeks before and after the examination and completed a headache questionnaire. Migraineurs were classified according to migraine subtype and period: Intercital migraineurs without aura (MwoA, n = 14 after exclusions, see below), interictal migraineurs with aura (aura in at least 50% of attacks, MA, n = 11 after exclusions), migraineurs in the interictal period (MINT, n = 25, merging MwoA and MA) and migraineurs in the preictal period (<48 h before attack, MPRE, n = 7 after exclusions). There were too few patients in the headache phase (n = 4) and postictal period (n = 1, <48 h after attack), and these groups were therefore not included in further analysis. RTMS was not performed on the first migraineur (MA) and two first CO because of technical difficulties. Three MwoA were excluded prior to analysis, one because of a temporary pain condition during the examination and two because of drowsiness. Two MPRE were excluded because of drowsiness. Exclusions were made without knowledge of subjects’ diagnosis. Demographical data of the participants are reported in Table 1.

Exclusion criteria were coexisting frequent episodic (≥1–14 days/month for CO and ≥7–14 for migraineurs) or chronic (≥15 days/month) tension-type headache, neurological or psychiatric diseases, first-degree relatives with epilepsy, sleep disorders, active infectious diseases, connective tissue diseases, metabolic, endocrine or neuromuscular diseases, other clinically relevant painful conditions including recent injuries, malignancy, previous craniotomy or cervical spine surgery, heart disease, cardiopulmonary or cerebrovascular diseases, pregnancy, medication for acute or chronic pain, neuroleptic drugs, anti-depressive drugs, anti-epileptic drugs, prophylactic allergy treatment or other drugs which may influence neuronal, vascular or muscular function, alcohol or drug abuse, or ferromagnetic implants. Symptomatic medication during migraine attacks was allowed.

Investigators were blinded to diagnosis and had not met the subjects before the examination. All participants signed an informed consent form. The study was approved by the Regional Committee for Medical Research Ethics.

2.2. Procedure

Examinations were conducted at the same time of day in all subjects.

2.2.1. Visual evoked potentials

Visual acuity was measured on Snellens’ chart. The VEP examination was performed in a quiet room with dimmed light (5 lux). Subjects were sitting in a relaxed position with eyes 100 cm from the screen. All subjects confirmed that they could see both the small and the large VEP checks clearly at this distance. The same instructions were given to all subjects before each VEP recording. They were instructed to relax and to focus on the fixation point in the middle of the checkerboard pattern. Only the right eye was tested. The left eye was covered with an eye-patch. A Viking Select™ system (Nicolet Biomedical Inc., Madison, WI USA) was used for VEP recording. Checkerboard patterns were presented on a NIC-2015® visual stimulator (Nicolet Biomedical Inc., Madison, WI, USA) with 17 × 13° visual field and 93% contrast. Responses were recorded from the mid-occipital (MO, 5 cm above

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical data for healthy controls and migraine patients after exclusions (Mean ± SD or no).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO</td>
</tr>
<tr>
<td>No</td>
<td>32</td>
</tr>
<tr>
<td>Age</td>
<td>30.2 (10.4)</td>
</tr>
<tr>
<td>Women/Men</td>
<td>28/4</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>MwoA/MA</td>
<td>NA</td>
</tr>
<tr>
<td>Headache-history (years)¹</td>
<td>NA</td>
</tr>
<tr>
<td>Headache-frequency (1–4)²</td>
<td>NA</td>
</tr>
<tr>
<td>Headache-intensity (1–4)²</td>
<td>NA</td>
</tr>
<tr>
<td>Headache-days/month last 3 months</td>
<td>NA</td>
</tr>
<tr>
<td>Usual headache-attack duration (hours)</td>
<td>NA</td>
</tr>
</tbody>
</table>

¹ Headache-history: Years since first appearance of headache.
² Headache-frequency: Number of headache days/month, 0: <1; 1: 1–3/month, 2: 4–7/month, 3: 8–14/month, 4: >14/month.
—is: Not applicable. CO: Healthy controls. MINT: Intercital migraine. MPRE: Preictal migraine.

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in the mid frontal (Fz, as defined by the International 10–20 system) deviation with a 2–250 Hz band-pass filter. Rejection level was set to ±90 μV.

The stimulus conditions used were 3 reversals per second (rps) with small (8') checks and 3 rps with large (65') checks. Six hundred pattern-reversals (six blocks × 100 reversals, rejections not included) were delivered continuously for each stimulus condition. The order of check size presentation was randomized for each subject.

2.2.2. Navigated transcranial magnetic stimulation

The participants were scanned with a 3-T Siemens Trio MRI scanner. A T1 weighted 3D sequence was applied. Transcranial magnetic stimulation (TMS) was performed with a MagPro X100 unit with MagOption (Medtronic A/S, Tonsbakken 16–18, 2740 Skovlunde, Denmark) and an MCF-B65 Butterfly Coil (figure-of-eight magnetic coil) cooled with static fluid (MagVenture A/S, Lucernemarken 15, DK-3520 Farum, Denmark). Nextrim eXimia NBS version 2.2 (Nextrim Ltd, Elimäenkatu 9 B, FIN-00510 Helsinki Finland) was used for real-time navigation. Biphasic pulses with 280 μs duration were applied.

Resting motor threshold and phosphene threshold were measured to determine the rTMS output. Resting motor threshold was measured by stimulation of the primary motor cortex. Motor evoked responses were recorded with electromyography (EMG) on a Viking Select system (Nicolet Biomedical Inc., Madison, WI USA). One-channel EMG responses were measured from the abductor pollicis brevis muscle of the right hand. The cathode electrode was placed on the muscle belly while the anode was placed on the first proximal phalanx. The patient-ground electrode was placed at the proximal end of the palmar surface of the hand.

The left gyrus precentralis was identified, and the 3D MRI model was peeled down until the gyrus was clearly visible. A mapping procedure was performed to locate the optimal coil position for stimulation. First, a coarse mapping of the gyrus precentralis was performed at 75% stimulator intensity and with 1 cm between stimulations, while the coil was held perpendicular to the longitudinal axis of the gyrus. This typically identified a 2–3 cm strip-area that included the omega-shaped (Ω) part associated with first order motor neurons controlling the hand muscles. This candidate-area was then mapped more thoroughly with one stimulus for every 1–2 mm. The stimulation point that evoked the highest peak-to-peak motor evoked potential amplitudes was chosen for further stimulation. Optimal coil rotation was determined by rotating the coil 22.5°, 45°, 67.5° and 90° clockwise and counter-clockwise. The stimulator output was thereafter reduced in steps of 5% until less than 5 out of 10 stimulations resulted in motor evoked potentials >50 μV. The output was then increased by 4% and reduced in steps of 1% until the resting motor threshold was found. The resting motor threshold was defined as the lowest output resulting in peak-to-peak motor evoked potentials >50 μV in at least 5 of 10 stimulations.

Phosphene thresholds were determined with a procedure similar to that of Kammer and Baumann (2010), who also used a Medtronic Magpro stimulator X100. Every 5 × 5 mm² of a 5 × 5 cm² grid over the occipital lobe was stimulated. The limits of the grid were 5 cm above the inion and 2.5 cm to each side of the inion. The lower limit was the inion or the border of the cerebellum. The primary visual cortex was always located within the grid. The stimulation took place in a dark room with the subject's eyes closed. Because prolonged light deprivation may increase cortical excitability in the occipital cortex (Borojerdi et al., 2000), a break in the TMS was taken every 10–12 min. During these breaks the subjects’ eyes were open and the lights were turned on. The coil was held with the tail upwards. A stimulator output of 70% was used. The subjects were told to report any visual phenomena observed in relation to the stimulation, and to rate its strength on an arbitrary scale from 1 to 10. Phosphene measurements depend on the subjective perception of phosphenes (Kammer et al., 2005). Therefore, an approved phosphene (to be included in further measurements and analysis) had to occur immediately after the stimulation, on the contralateral side of stimulation and be perceived both when the subject's eyes were closed and open. The stimulation point with the subjective highest rated strength was used to measure a phosphene threshold. If no valid phosphenes were observed, the same procedure was repeated at 100% stimulator output. The phosphene threshold was defined as the lowest stimulator output resulting in visible phosphenes in at least 3 out of 5 stimulations. This was determined by reducing the stimulator output in the same way as for resting motor thresholds.

2.2.3. High-frequency repetitive navigated transcranial magnetic stimulation

Navigated, high-frequency rTMS was performed at the location of phosphene threshold measurement or in the midline near the primary visual cortex (i.e. sulcus calcarinaris) if no phosphenes were observed. Stimulus output during rTMS was equal to the phosphene threshold in subjects with phosphene thresholds below 76% of stimulator output. In accordance with previous studies (Bohotin et al., 2002; Fumal et al., 2006) stimulator output during rTMS was set to 110% of motor threshold in subjects with phosphene threshold above 75% of maximal stimulator output and in subjects not reporting phosphenes.

Each subject received 900 stimulations divided into 18 trains of 50 stimulations. The stimulation frequency was 10 Hz. The duration of each train was 5 s and there was a 10 s break between each train.

VEP examination was performed before rTMS, within 9 min after rTMS and 25 min after rTMS. Because the effects of rTMS on VEPs have been found to last for at least 9 min (Bohotin et al., 2002), the first VEP recordings after the rTMS were started within this time interval.

2.3. Data analysis and statistics

Analysis of VEP recordings was performed with Labchart 7.1.2 software (ADInstrument Pty Ltd, Sydney Australia). VEPs were averaged in 6 blocks of 100 averaged responses. An experienced neurophysiologist (TS) identified N70 (N1), P100 (P1) and N145 (N2) VEP peaks. The neurophysiologist was blinded to block number, subject diagnosis, and relation to rTMS. The neurophysiologist was not blinded to check size because VEP latency is evidently shorter with 65' than 8' checks. To ensure that the same VEP components were selected for all VEP recordings in one subject, the neurophysiologist also knew which blocks of responses belonged to the same subject.

Linear amplitude decrement over the six blocks (habituation slope) was used as primary habituation measure. Ratio between the first and last block (block ratio) was also calculated.

Measurements in CO, MINT and MPRE were compared. In addition, measurements in MwoA and MA were compared.

N70-P100 and P100-N145 VEP peak-to-peak amplitudes were square root transformed prior to analysis. The distributions of VEP amplitudes were skewed, and the transformation improved the distribution. Block ratios were log-transformed. For brainstem auditory evoked potentials it has been shown that square root transformations are best for amplitudes while ratios are best handled by a log-transformation (Sand, 1990). Habitation slopes were calculated with least squares linear regression for each subject. Block ratios, habituation slopes and first block amplitudes were
analysed with repeated measures ANOVA with group as between-subject factor and check size and rTMS (baseline, directly after rTMS and 25 min after rTMS) as within-subject factors. Huynh–Feldt correction was applied. Comparisons of VEP amplitude and habituation at baseline have been published earlier (Omland et al., 2013).

Phosphen prevalence was compared with the chi-square test, and Yates correction was applied. When comparing phosphen thresholds, thresholds were set to 101% in subjects who did not experience phosphenes. Phosphen thresholds and stimulator output applied during rTMS were compared with Mann–Whitney U-test.

A two sample Student’s t-test comparing CO \((n = 32)\) and MINT \((n = 25)\) has 80% power to detect a medium population group difference equal to 0.75 SD. Two sample t-tests comparing MINT \((n = 25)\) and MPRE \((n = 7)\) have 80% power to detect a large difference equal to 1.2 SD. Two-sided p-values <0.05 are reported as significant in the primary two- and three-group comparisons. In post hoc analysis, a Bonferroni-type correction for three-group comparisons was applied and two-sided p-values <0.0167 are reported as significant. No further adjustments for multiple variables were applied because too extensive Bonferroni-type corrections are associated with increased number of type II errors (Perneger, 1998).

3. Results

Grand average VEPs elicited by small 8° checks and large 65° checks are shown in Figs. 1 and 2. For the comparison of CO, MINT and MPRE, significant interactions of group by check size and rTMS were found for the N70-P100 habituation measures (Table 2). Post hoc comparison of N70-P100 habituation slope for CO and MPRE showed an interaction between rTMS and group for large checks (Table 3). With large checks, N70-P100 habituation slope indicated increased habituation in CO and reduced habituation in MPRE both directly after rTMS and 25 min after rTMS (Figs. 3 and 4). With large checks, N70-P100 habituation also tended to be reduced in MPRE after rTMS, but this was not different from the effect in CO (Table 3 and Fig. 3).

Post hoc analysis of N70-P100 habituation measures for the CO and MPRE comparisons and the MINT and MPRE comparisons showed significant group by rTMS interactions for small checks (Table 3). With small checks, N70-P100 habituation measures indicated unchanged habituation in CO, increased habituation in MINT and reduced habituation in MPRE directly after rTMS (Fig. 3). Twenty-five minutes after rTMS the N70-P100 habituation measures approached the values observed before rTMS in all groups (Fig. 3).

Significant interactions between rTMS and group were found for P100-N145 habituation measures (Table 2). Post hoc analysis of P100-N145 habituation slope for the CO and MPRE comparisons and the MINT and MPRE comparisons showed significant interactions between rTMS and group for small checks (Table 3). P100-N145 habituation slopes with small checks indicated unchanged habituation in CO, increased habituation in MINT and reduced habituation in MPRE directly after rTMS (Fig. 3). With large checks, P100-N145 habituation also tended to be reduced in MPRE after rTMS, but this was not different from the effect in CO (Table 3 and Fig. 3).

Significant interactions of group by check size and rTMS were found for N70-P100 and P100-N145 first block amplitudes (Table 4). However, post hoc two-group comparisons for each check size showed no significant rTMS \times\ group or rTMS effects \((p > 0.025)\). The significant three-way interactions were likely related to a complex effect of check size and rTMS, probably reflecting that a general trend for amplitude reduction after 25 min was more pronounced with small checks in CO and with large checks in migraine.

No differences in the effect of rTMS on habituation slope or first block amplitude were found for the comparison of MwoA and MA
As reported previously, VEP amplitude and habituation were not different between CO and MINT before rTMS (Omland et al., 2013). Phosphenes were found in 57.1% of MwoA and 81.8% of MA. Phosphene thresholds (mean ± SD) were 86.7% ± 16.3 in MwoA and 85.3% ± 15.0 in MA. Applied rTMS output was 56.6 ± 10.8% in MwoA and 60.3 ± 9.3% in MA. Phosphene prevalence, phosphene threshold and applied rTMS output were not significantly different in MwoA and MA (p > 0.20).

Phosphenes were found in 78.1% of CO, 68.0% of MINT and 85.7% of MPRE. Phosphenes thresholds (mean ± SD) were 86.7% ± 16.3 in MwoA and 85.3% ± 15.4 in MA. Applied rTMS output was 56.6 ± 10.8% in MwoA and 60.3 ± 9.3% in MA. Phosphene prevalence, phosphene threshold and applied rTMS output were not significantly different in MwoA and MA (p > 0.20).

Phosphenes were found in 78.1% of CO, 68.0% of MINT and 85.7% of MPRE. Phosphenes thresholds (mean ± SD) were 86.7% ± 16.3 in CO, 86.1% ± 15.4 in MINT and 82.1% ± 13.2% in MPRE. Applied rTMS output (mean ± SD) was 57.6% ± 10.5 in CO, 58.2% ± 10.1 in MINT and 58.6% ± 11.0 in the MPRE group. Phosphene prevalence, phosphene threshold or applied rTMS output were not significantly different in CO, MINT and MPRE (p > 0.20).

No serious adverse events (including seizures) occurred in this study.

### 4. Discussion

In this blinded case-control study, our main finding was that MINT, MPRE and CO responded differently to high-frequency rTMS. With large checks, rTMS reduced N70-P100 VEP habituation in MINT compared to CO. With small checks, rTMS reduced habituation in MPRE, while rTMS increased or had little effect on habituation in MINT and CO.

#### 4.1. Comparisons with other studies

We observed increased VEP habituation with small checks in MINT after rTMS. This is similar to findings reported in an earlier study (Bohotin et al., 2002). The same study also reported that rTMS restored first block amplitudes and habituation to normal in MINT. This is in contrast to our findings as we only found differences between groups after rTMS. The authors of the former study concluded that rTMS increased an initially reduced cortical pre-activation level in the migraine group (Bohotin et al., 2002). Unfortunately, the results of earlier VEP studies are conflicting and do not provide a clear answer to how first block amplitude and habituation are altered in MINT. Therefore, these studies cannot prove the proposed and attractive concept of reduced cortical pre-activation in MINT (Omland et al., 2013). There are some differences between the study by Bohotin et al. (2002) and our study. The former study recruited outpatients, while the subjects in the present study were recruited from students and employees at...
Table 3
Post hoc comparison for each check size of VEP habituation measures between CO, MINT and MPRE. Repeated measures ANOVA with habituation slope and block ratio as dependent variables and rTMS (baseline, directly after rTMS and 25 min after rTMS) as within subject factor and group as between subject factor. F-Statistics are tabulated.

<table>
<thead>
<tr>
<th>VEP habituation</th>
<th>CO-MINT (8' checks)</th>
<th>CO-MINT (65' checks)</th>
<th>CO-MPRE (8' checks)</th>
<th>CO-MPRE (65' checks)</th>
<th>MINT-MPRE (8' checks)</th>
<th>MINT-MPRE (65' checks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Habituation slope</td>
<td>Block ratio</td>
<td>Habituation slope</td>
<td>Block ratio</td>
<td>Habituation slope</td>
<td>Block ratio</td>
</tr>
<tr>
<td>N70-P100</td>
<td>2.5</td>
<td>1.1</td>
<td>0.2</td>
<td>1.1</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>P100-N145</td>
<td>5.6</td>
<td>0.9</td>
<td>0.2</td>
<td>1.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>


Fig. 3. VEP habituation slopes (mean ± SD, linear amplitude change over block calculated by the least squares method) before, directly after and 25 min after high-frequency rTMS. CO: Healthy controls; MINT: Migraineurs in the interictal period. MPRE: Migraineurs in the preictal period. *: significantly different effect of rTMS (baseline, directly after rTMS and 25 min after rTMS) on habituation slopes in CO and MINT (significant interaction of group by rTMS in repeated measures ANOVA). **: significantly different effect of rTMS on habituation slope in CO and MPRE (significant interaction of group by rTMS in repeated measures ANOVA).
our university. Still, the reported headache frequency and disease duration in these two studies were similar. Only the present study recruited controls with similar age as the migraineurs.

We found differences between CO and MINT with large checks, but not small checks. This is in agreement with earlier findings indicating that the magnocellular pathway is affected in MINT (Chen et al., 2009). Thus, changes in visual responses may be easier to detect with certain stimulation parameters, and may not be generalized as some authors have suggested (Coppola et al., 2013). RTMS reduced VEP habituation with small checks in MPRE compared to MINT and CO. Therefore the parvocellular pathway may be affected in the preictal period. We found the same tendencies for MPRE with large checks. However, these findings were not significant, possibly because of the rather few MPRE subjects. Increased amplitude in VEPs with large checks has been found in MPRE (Sand et al., 2009), indicating that the magnocellular pathway also is affected.

Phosphene thresholds were not different in MINT and CO before rTMS in the present study. This finding is in accordance with a meta-analysis of phosphene threshold and prevalence in CO, MwoA and MA: No differences in phosphene threshold or prevalence were found in studies using figure-of-eight TMS coils (Brigo et al., 2013).

4.2. Interpretation

We did not find differences in VEPs (Omland et al., 2013) or phosphenes between groups before rTMS. Our results do therefore not support the notion that the migraine cortex is simply characterized by altered cortical excitability. Habituation remained stable or increased in CO after rTMS, while the migraineurs showed an increased responsivity to rTMS. Subtle differences in the visual cortices of migraineurs and CO therefore probably exist, but we were unable to detect these with our baseline measures. Interestingly, MA may have a dysfunction in inhibitory regulative mechanisms of the motor cortex, resulting in a reduced ability to prevent excessive increases in cortical excitability (Antal et al., 2008). We hypothesize that a similar dysfunction in the visual cortex may have caused the relative lack of habituation after rTMS in the migraine groups in the present study.

The underlying mechanisms for the differential involvement of the magnocellular and parvocellular system in migraine are not known. Still, abnormalities of the magnocellular system could explain why we found different effects of rTMS on VEP in MINT and CO. Several studies have indicated that migraineurs have deficits in the processing of visual motion (Antal et al., 2005, 2011; Battista et al., 2010, 2011; McKendrick and Badcock, 2004; Shepherd, 2006; Shepherd et al., 2012). These deficits are likely to represent abnormalities of the magnocellular rather than the parvocellular visual subsystem (McKendrick et al., 2001). In addition, studies have showed increased excitability (Battelli et al., 2002) and thickness abnormalities of the cortical V3A area (Granziera et al., 2006), which is sensitive to motion (Tootell et al., 1997). This area is also close to the possible source of cortical spreading depression, which is believed to cause the migraine aura (Hadjikhani et al., 2001).

Although the effect of rTMS was significantly different in MPRE and CO only when small and not when large checks were applied, the findings in MPRE may indicate that the cortical dysfunction increases close to an attack. An alternative explanation is that only the parvocellular system is affected preictally, but a dysfunction shifting from the magnocellular to the parvocellular subsystem leads to an increased responsivity to rTMS.
in the preictal period does not seem plausible. An increased cortical dysfunction preictally is also in general agreement with longitudinal measurements of QEEG, which found indications of reduced inhibitory mechanisms in the cortex of MPRE (Bjork et al., 2011). On the other hand, pre- and peri-ictal normalisation of visual responses have also been reported (Chen et al., 2009; Judit et al., 2000). The diverging results of the different studies are not easy to interpret. Looking ahead of the divergence, these preictal changes are generally consistent with the concept that a migraine attack starts in the central nervous system. The diversity of the results also suggests that the traits of migraine are multifarious. In addition, results may depend on methodological details.

We could not find support for a reduced cortical pre-activation level in migraine. However, this theory has also been supported by studies that used different methods such as QEEG (Bjork et al., 2011) and somatosensory evoked potentials (Coppola et al., 2005). Hence, first block VEP amplitude may not be a sufficiently sensitive and reliable measure of cortical excitability. For instance it is not known if the “first block” should be defined as the average of 10, 20, 50 or 100 reversals. Differences within the first 10–20 responses are difficult to detect because of the low signal/noise ratio. Such transient changes may not have been detected with the standard VEP protocol applied in the present study. Other study protocols may be better suited to investigate transient effects (i.e. Hoffken et al., 2009).

The effect of rTMS may depend on the underlying cortical excitability (Fierro et al., 2005). High-frequency rTMS over the motor cortex has shown unexpected paradoxical effects in migraineurs in that stimulation with 110% stimulator output resulted in facilitation of motor evoked potentials, while inhibition was seen when 130% stimulator output was applied (Brighina et al., 2011). Thus, the findings by Bohotin et al. (2002) may have an alternative interpretation. The normalisation of VEPs after rTMS may have been caused by high-frequency rTMS reducing the excitability of a primarily hyperexcitable cortex (Brighina et al., 2009). However, the reduction in habituation in our migraine groups after rTMS suggests reduced cortical inhibition as a more likely explanation. In addition, the paradoxical effect of rTMS in migraine was reported with a stimulator output that probably was higher than the output used in the present study (Brighina et al., 2011).

The effect of rTMS on P100-N145 habituation in CO and MINT were similar to the effect on N70-P100 habituation, but it was...
not significant. The effect was also not significant for block ratio. However, many VEP studies have only analysed the N70-P100 component (see Table 5 in Omland et al., 2013) and habituation slope is probably a better measure of habituation than block ratio (Omland et al., 2011). Still, our findings would have been more robust if they were significant for the P100-N145 amplitude and block ratio as well.

4.3. Strengths and limitations

The present study was blinded during recoding and analysis of VEPs, ensuring unbiased evaluation of the effect of rTMS. In addition, the applied stimulator intensities during rTMS were similar in the different groups. It is therefore unlikely that differences related to the procedure could be causing biases. A limitation in the present study is the small MPREG group. Because we did not find any differences in the effect of rTMS on VEPs in MA and MwoA, we chose to merge the MwoA and MA groups. Earlier studies have not found differences in VEP habituation between MwoA and MA (Afra et al., 1998, 2000b; Coppola et al., 2007a; Ozkul and Bozlar, 2002; Schoenen et al., 1995). However, it can be argued that MwoA and MA should be separated both in the interictal and preictal groups if the power of the study is sufficient. For instance, gluta- mamic transmission may differ in patients with and without aura (Conte et al., 2010). Our results should therefore be validated, preferably in a longitudinal study with larger subgroups.

The duration of the effect of high-frequency rTMS is likely short (Bohotin et al., 2002). This limited the number of variables that could be measured after rTMS. We therefore did not measure phosphene thresholds after rTMS.

5. Conclusion

The migraine visual cortex showed an increased responsivity to high-frequency rTMS, causing a relative lack of habituation compared to controls. This dysfunction seems to change in the preictal period, which may be a sign of a developing migraine attack. The magnocellular subsystem may be affected in MINT. In MPREG the magnocellular subsystem may be affected as well. We could not confirm that migraineurs have an altered cortical pre-activation level that can be restored by high-frequency rTMS.

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