Spreading photoparoxysmal EEG response is associated with an abnormal cortical excitability pattern

Michael Siniatchkin, Sergey Groppa, Bettina Jerosch, Hiltrud Muhle, Christoph Kurth, Alex J. Shepherd, Hartwig Siebner and Ulrich Stephani

1Neuropediatric Department, 2Department of Neurology, Christian Albrechts University, Kiel, 3Epilepsy Center, Kehl-Kork, Germany and 4School of Psychology, Birkbeck College, London, UK

Correspondence to: Michael Siniatchkin, MD, Neuropediatric Department, Pediatric Hospital, Christian Albrechts University, Schwanenweg 20, D-24105 Kiel, Germany
E-mail: m.siniatchkin@pedneuro.uni-kiel.de

Photosensitivity or photoparoxysmal response (PPR) is a highly heritable electroencephalographic trait characterized by an abnormal cortical response to intermittent photic stimulation (IPS). In PPR-positive individuals, IPS induces spikes, spike-waves or intermittent slow waves. The PPR may be restricted to posterior visual areas (i.e. local PPR with occipital spikes only) or spread to anterior non-visual cortical regions (i.e. PPR with propagation). The mechanisms underlying the PPR and causing its spread remain to be clarified. In unmedicated PPR-positive individuals and PPR-negative control participants without any history of previous seizures, we used focal transcranial magnetic stimulation (TMS) to investigate the excitability of the visual or primary motor cortex (M1). In the first experiment [18 healthy control subjects (i.e. without PPR in electroencephalography: 6 females, mean age 26.5 ± 7.34 years) and 17 healthy participants with PPR (7 females, mean age 25.18 ± 12.2 years) were studied], occipital TMS was used to elicit phosphenes or to suppress the visual perception of letter trigrams. PPR-positive individuals with propagation had lower phosphen threshold and steeper stimulus–response curves than individuals without PPR or with occipital spikes only. Occipital TMS also induced a stronger suppression of visual perception in PPR-positive subjects with propagation relative to subjects without PPR or with occipital spikes. In the second experiment, we applied TMS over the right M1 without concurrent IPS and measured the motor threshold, the stimulus response curve, and the duration of the cortical silent period (CSP) in PPR positive individuals with propagation and in PPR-negative control participants [15 right-handed healthy subjects without PPR (3 males, mean age 17.7 ± 3.6 years) and 14 right-handed healthy individuals showing a PPR with propagation (3 males, mean age 17.4 ± 3.9 years)]. PPR-positive individuals showed no changes in these excitability measures relative to the PPR-negative control participants. We also measured the modifiability of the CSP by continuous IPS at a frequency of 18 or 50 Hz. While IPS reduced the duration of the CSP in PPR-negative control subjects, IPS had no effect on the duration of the CSP in PPR-positive individuals. Our results provide first time evidence that the propagation of the PPR is associated with increased excitability of the occipital but not the motor cortex. The stronger inhibitory effect of TMS on visual perception and the failure of IPS to shorten the CSP in PPR-positive individuals may possibly reflect adaptive changes that prevent the provocation of seizures during the PPR.

Keywords: cortical excitability; motor cortex; photosensitivity; transcranial magnetic stimulation; visual cortex

Abbreviations: CSP = cortical silent period; EEG = electroencephalography; IPS = intermittent photic stimulation; MEP = motor evoked potential; PPR = photoparoxysmal response; RMT = resting motor threshold; SOA = stimulus onset asynchrony; TMS = transcranial magnetic stimulation

Cortical excitability and photosensitivity

Introduction
Photosensitivity or photoparoxysmal response (PPR) is a highly heritable electroencephalographic (EEG) trait characterized by the occurrence of spikes, spike-waves and intermittent slow waves in response to visual stimulation (Fisher et al., 2005). The prevalence of photosensitivity in subjects without epilepsy ranges from 0.5 to 7.6% of the population (Doose and Gerken, 1973; Trojaborg, 1992; Nagarajan et al., 2003). Patients with epilepsy show a higher prevalence. For example, photosensitivity is a frequent feature of idiopathic generalized epilepsies (IGE). Intermittent photic stimulation (IPS) elicits a PPR in 13–18% of patients with idiopathic absence epilepsy and in 30–35% of patients with juvenile myoclonic epilepsy (Guerrini and Genton, 2004). In some patients, watching TV, playing an electronic screen game, or simply observing stationary or vibrating visual patterns can provoke seizures (Wilkins et al., 1979; Binnie et al., 1985; Ricci et al., 1998). Especially TV screens with a 50 Hz scan frequency seem to be provocative in >30% of photosensitive patients (Jeavons and Harding, 1975; Kasteleijn-Nolst Trenite et al., 2002). Because of the close relation between photosensitivity and epilepsy, studies that explore the mechanisms underlying the PPR are also relevant to the pathophysiology of epilepsy in humans.

The current understanding of the mechanisms underlying photosensitivity is still limited. Psychophysical experiments that varied the patterns and characteristics of visual stimulation suggest that the PPR originates in the cortex and involves the synchronization of large neuronal networks (Wilkins et al., 1979; Binnie et al., 1985; Harding and Fylan, 1999). Electroencephalographic recordings of visual evoked potentials revealed increased cortical reactivity to light flashes and checkerboards in PPR, as well as an abnormal amplitude modulation depending on contrast—a possible indicator of a deficient cortical gain-control mechanism (Guerrini et al., 1998; Porciatti et al., 2000). Magnetoencephalographic recordings have demonstrated an enhancement of phase synchrony in the gamma band in the visual cortex, which is harmonically related to the frequency of photic stimulation and precedes the onset of the PPR (Parra et al., 2003). Moreover, functional magnetic resonance imaging (fMRI) revealed an increased number of voxels in the visual cortex that are activated during IPS in patients with PPR compared with control subjects (Chiappa et al., 1999).

Although most studies point to an increase in excitability in the visual cortex, no study has directly examined cortical excitatory and inhibitory processes in subjects with photosensitivity.

Transcranial magnetic stimulation (TMS) is a well-established non-invasive tool to assess cortical excitability in human motor and visual cortex. Several paradigms have been established to characterize changes in intracortical facilitation and inhibition within the primary motor cortex (M1) (Kobayashi and Pascual-Leone, 2003). For example, a single TMS pulse can elicit excitatory post-synaptic potentials that cause a trans-synaptic excitation of corticospinal output neurons producing a motor evoked potential (MEP) in contralateral limb muscles. At the same time, the TMS pulse can evoke intracortical inhibitory post-synaptic potentials that block the voluntarily generated activation of the corticospinal output neurons. The disruption of the corticospinal output underlies the cortical silent period (CSP) that can be recorded in the pre-innervated muscle (Rothwell, 1997; Di Lazzaro et al., 2004). Excitatory phenomena can also be evoked in the visual system where suprathreshold TMS to the occipital cortex elicits phosphenes (Meyer et al., 1991; Merabet et al., 2003). TMS-induced inhibition within the occipital cortex can be assessed psychophysically by measuring the suppressive effect of occipital TMS on visual perception (Amassian et al., 1989).

Here we used TMS to assess regional excitability of the visual and motor cortex in individuals with and without PPR. Only healthy unmedicated subjects without any history of epilepsy were enrolled in order to achieve sufficient homogeneity of the groups and avoid the influence of anti-epileptic drugs on TMS parameters (Ziemann, 2004). We hypothesized that PPR-positive subjects, especially those with PPR propagation, are characterized by an increase in cortical excitability and deficient inhibition.

Material and methods
Participants
Healthy right-handed volunteers with and without PPR were recruited from the departmental database. None of the participants had a history of epileptic seizures, anti-epileptic medication, migraine with or without aura or other neuropsychiatric disorders. Participants were still included if they reported occasional episodes of tension type headache. Healthy volunteers with PPR have been identified in previous epidemiological studies on PPR and had at least one relative with positive PPR and epilepsy (Tauer et al., 2005). Neurological examination was normal. Visual acuity was normal or corrected to normal as assessed by the Snellen chart. All subjects were blinded to the purpose of the study and gave their written informed consent. Experiments were performed according to the Declaration of Helsinki and approved by the ethics committee of the University of Kiel (No. A 143/04). The excitability of the occipital and motor cortex were investigated in separate experiments on two independent samples.

Electroencephalographic assessment of photosensitivity
In all subjects, the EEG response to IPS was recorded prior to the TMS experiment (Neurofile system, IT-Med Co., France). Twenty-one Ag/AgCl disc electrodes were attached to the scalp in locations according to the International 10/20 system. IPS was performed according to internationally recommended guidelines (Kasteleijn-Nolst Trenite et al., 1999). IPS was performed with the standard xenon-discharge Grass PS22 stimulator (Astro-Med, Inc., USA) with no pattern or grid. The distance between the stimulator and patient’s nasion was ~30 cm (light intensity: 0.5 joule/flash, length of a flash: 10/s, circular field diameter: 13.7 cm). IPS
consisted of 20 s periods of regular frequencies at 5, 10, 12, 15, 18, 20 or 25 Hz followed by a 30 s period of stimulation with irregular frequencies up to 60 Hz. In accordance with internationally recommended guidelines (Kastelein-Nolst Trenite et al., 1999), the IPS was performed in the first 5 s by eyes kept open, after that the participant closed the eyes for 5 s, opened the eyes again (5 s) and finally closed them for the rest of stimulation time during each period of visual stimulation at a particular frequency. Two experienced EEG specialists (M.S. and H.M.) analysed EEGs independently and classified each as PPR with occipital spikes or PPR with propagation according to Harding and Fylan (1999). PPR with occipital spikes was always confined to posterior regions of the scalp and correspond to PPR type I according to the classification proposed by Waltz et al. (1992). The PPR was labelled as PPR with propagation when (i) the appearance of parieto-occipital spikes was followed by biphasic slow waves spreading to frontal cortex or (ii) when the PPR consisted of generalized spike-and-wave discharges (PPR type III and IV according to Waltz et al., 1992).

**Experiment I (excitability of the occipital cortex)**

Eighteen healthy control subjects (i.e. without PPR in EEG: 6 females, mean age 26.5 ± 7.34 years) and seventeen healthy participants with PPR (7 females, mean age 25.18 ± 12.2 years) participated in Experiment 1. In the PPR group, eight subjects had occipital spikes only and nine subjects had PPR with propagation. There were no significant differences in age or gender among groups.

**TMS evoked phosphenes**

Since paired-pulse TMS induces phosphenes more reliably than single-pulses (Fierro et al., 2005; Gerwig et al., 2005; Sparing et al., 2005), pairs of TMS pulses were given through a 90 mm round coil to the occipital cortex at a fixed inter-stimulus interval of 50 ms. Both pulses had the same intensity. The coil was connected with two MagStim 200 stimulators through a Bistim module (Magstim Co., Whitland, Dyfed, UK). Both stimulators were triggered through a CED Micro 1622 A/D converter using Signal 3.0 software (Cambridge Electronic Devices Co., Cambridge, UK). Magnetic stimuli had a nearly monophasic pulse configuration with a rise time of ~100 μs, decaying back to zero over ~0.8 ms. Each TMS pulse produced a counterclockwise current in the coil.

Subjects were seated in a comfortable chair in front of a dark computer screen (luminance 0.03 cd/m²). They wore a tight-fitting cotton swimmer’s cap with a grid of 5 × 5 points (each point 1 cm apart) centred over Oz (International 10/20 system). After 5 min adaptation with closed eyes, paired pulses were applied to the occipital cortex every 8–12 s. The round coil was oriented in parallel to the coronal plane and the handle of the coil pointed downwards. The coil was centred on the mid-sagittal line with its lower rim pressed tangential to the scalp. The lower edge of the lower rim was 1 cm rostral to the upper edge of the inion. Because of the vertical orientation of the coil, the upper rim of the coil was always ≥2 cm away from the head. Subjects were instructed to report any sensations (visual, tactile, auditory) evoked by TMS and describe in detail the shape, colour and location in the visual field of their phosphenes. Stimulus intensity was initially set at 50% of maximum stimulator output. If the subject did not perceive a phosphene, the stimulation intensity was increased in steps of 5% stimulator output until the subject observed a sharply delineated phosphene clearly restricted to the contralateral visual field, maximally up to 80% of stimulator output. If the subject still failed to perceive a phosphene, the coil was moved 1 cm up or 1 cm left or right and the procedure was repeated. Reliable perception of a phosphene was assumed if the phosphenes appeared in the same form and at the same location in three out of five consecutive trials. Stimulus intensity was then reduced in steps of 5% until TMS failed to elicit a phosphene. Stimulus intensity was increased again in steps of 1% stimulator output until the subject reported a phosphene in three out of five consecutive trials. This intensity was defined as phosphene threshold.

In a second step, we gradually increased the intensity of stimulation in 5% steps from 35 to 80% of maximum stimulator output (5 trials for each intensity). At each stimulus intensity, subjects were requested to rate their sensation with respect to the brightness and intensity of perceived phosphenes on an arbitrary scale of 0–5. Mean phosphene intensities were plotted against the intensities of stimulation to generate a stimulus–response curve.

**TMS-induced suppression of visual perception**

Visual stimuli consisted of low contrast letter trigrams presented for 25 ms. The letters were presented foveally in the middle of the screen (100 Hz vertical refresh rate, 17 inch Samsung monitor, Korea, 1025 × 768 pixels resolution) using Arial Black font, size 20 (3 × 4 mm = 8 × 11 pixel). Letters were chosen from a subset of letters of approximately equal legibility (Grimm et al., 1994). The letter trigrams subtended 0.03° × 0.198° of visual angle at a viewing distance of 80 cm. Mean luminance of the stimuli was 1.60 cd/m² whereas the mean luminance of the grey background was 0.03 cd/m². There was no perceptive afterimage at these luminances. Subjects were requested to keep both eyes open and maintain central fixation during the experiment. SuperLab stimulation software (Cedrus Co., Phoenix, USA) and a National Instruments D-1200 A/D converter (National Instruments Co., TX, USA) was used to present the visual stimuli and trigger the Magsttim 200 stimulator.

Participants completed 10 practice trials. Blocks of these trials were repeated until subjects were familiar with the procedure and were able to perceive the stimuli accurately (>90% accuracy level). Before the main experiment, we identified the site over the occipital cortex where TMS evoked maximal visual suppression. The TMS pulse was triggered at a fixed interval of 100 ms after the onset of the target trigram [100 ms stimulus onset asynchrony (SOA)]. Previous studies have demonstrated that TMS at an SOA of 100 ms produces maximal visual suppression (Miller et al., 1996; Amassian et al., 1998; Mulleners et al., 2001; Kammer et al., 2005a). Single TMS pulses were applied at 75% of maximal stimulator output. The circular coil was initially placed as described above for induction of phosphenes. If necessary, the lower edge of the lower rim of the coil was subsequently moved slightly between 1 and 4 cm above the inion to find a position where the stimulus induced maximal suppression of perception. The optimal coil position was marked with a pen on the scalp and kept constant throughout the experiment.

The main experiment consisted of 80 trials in which the SOA between the onset of letter presentation and the magnetic pulse was pseudo-randomly varied. Visual suppression was assessed at eight SOAs, 40, 60, 80, 100, 120, 140, 160 and 180 ms. Ten trials were recorded per SOA. The intensity of TMS was always set at 75% of maximal stimulator output. Participants initiated each
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trial by pressing a computer key. Two seconds after the key press, a letter trigram was presented for 25 ms on the computer screen. In each trial, subjects were asked to write down the correct trigram after TMS and to indicate the position of any letter they were unaware of with a slash ‘/’. The percentage of correct letter identifications was calculated for each SOA and plotted against the delay to assess the magnitude and time course of TMS-induced suppression. The inter-trial interval was jittered between 5 and 12 s.

**Experiment II (excitability of the primary motor cortex)**

Fifteen right-handed healthy subjects without PPR (3 males, mean age 17.7 ± 3.6 years) and fourteen right-handed healthy individuals showing a PPR with propagation (3 males; mean age 17.4 ± 3.9 years) were studied. Groups were matched for age and gender.

Monophasic TMS pulses were delivered to the right primary motor hand area using the 70 mm figure-of-eight coil and a Magstim 200 stimulator. The coil was placed flat on the scalp over the right M1 with the current induced in the centre of the coil from anterior to posterior, approximately perpendicular to the assumed line of the central sulcus. The position of the coil was adjusted in order to evoke a maximal motor response in the contralateral target muscle. The optimal coil position was marked with a pen on the scalp and continuously monitored throughout the experiment.

MEPs were recorded using Ag/AgCl surface EMG electrodes placed over the abductor pollicis brevis (APB) muscle of the non-dominant left hand in a belly-tendon montage. The EMG raw signal was amplified (Neuropack-2, Nikon Kohden EMG device, Tokyo, Japan), bandpass-filtered (50–2000 Hz), digitized at a frequency of 5 kHz (A/D converter CED 16/22 Micro) and recorded on a PC using Signal 3.0 software (CED Co., Cambridge, UK).

We first measured corticomotor excitability in the left APB muscle at rest. First, we determined the resting motor threshold (RMT). The RMT was defined as the minimum TMS intensity necessary to induce an MEP in 5 of 10 consecutive trials. Stimulator output was gradually reduced in 1% steps of maximal stimulator output starting above RMT, until this criterion was met. We applied single-pulse TMS at 110, 130 and 150 of individual RMT to determine stimulus–response curves in the completely relaxed APB muscle. Blocks of 10 consecutive stimuli were delivered at each intensity. The order of stimulus intensity was counterbalanced across participants. The inter-stimulus interval varied between 4 and 6 s.

A second set of measurements were performed in the moderately active APB muscle to assess the duration of the CSP at stimulus intensities of 110, 130 and 150% of RMT. Ten consecutive trials were recorded per stimulus intensity while participants performed a tonic contraction of the target muscle at ~20% of maximal force level. The level of tonic contraction was monitored by audiovisual feedback. The duration of the CSP was measured in individual trials and defined as the period from the first turning point of the MEP to the resumption of any level of tonic EMG activity (Orth et al., 2004). The duration of the CSP was assessed during three experimental conditions: without visual stimulation (baseline), and during continuous IPS at a rate of 18 and 50 Hz. A rate of 18 Hz was chosen for IPS based on previous research (Kasteleijn-Nolst Trenite, 1989; Harding and Harding, 1999; Nagarajan et al., 2003) and our clinical experience that this frequency is the most epileptogenic in patients with photosensitive epilepsy. We also studied the effects of IPS at a higher frequency (50 Hz) because IPS at 50 or 60 Hz caused a shortening of the CSP in a previous TMS study on healthy volunteers (Entezari-Taker and Dean, 2000). Moreover, the 50 Hz of television screens has been implicated in photosensitive seizures (see Introduction). The details of IPS are given above. IPS was started as soon as the subjects closed his/her eyes. The first 5 s period of IPS was without TMS, then the CSP was recorded at stimulus intensities of 110, 130 and 150% of RMT. Blocks of 10 consecutive stimuli were delivered at each intensity using an inter-stimulus interval of 4–6 s. The order of the mode of visual stimulation as well as the TMS intensities during IPS were counterbalanced across participants.

**Statistical analyses**

All data were normally distributed (Kolmogorov–Smirnov-tests) and characterized by homogeneous variances (F-test). For each dependent variable, we conducted separate one-way analyses of variance (ANOVA) to assess overall differences between groups (ANOVA A: PPR versus control; ANOVA B: control versus PPR with occipital spikes only versus PPR with propagation). We also performed mixed ANOVAs with the between-subjects factor Group and the within-subject factors of interest (phosphene threshold: TMS intensity; visual suppression: SOA; MEP stimulus–response curve: TMS intensity; CSP measurements: frequency of IPS and TMS intensity). In order to test for a possible correlation between excitatory and inhibitory TMS phenomena in the occipital cortex, we also calculated a two-tailed Pearson’s correlation coefficient between individual phosphene thresholds and the mean frequency of correct responses across all SOAs for each group. All calculations were performed using SPSS 12 for Windows software package (SPSS, IL, USA).

**Results**

**Experiment I: excitability of the occipital cortex**

**Phosphene thresholds.**

In all participants, double-pulse TMS elicited phosphenes. Phosphenes were perceived as very brief flashes, which were mostly light grey or white although some subjects reported a weak consistent colour impression. Most phosphenes were elicited at a constant location within the visual field, typically in the central part of either lower visual hemifield. The geometric forms were variable: some subjects perceived straight lines only, some described more or less regular patches. Size, form and site of the phosphenes were highly reproducible within a session at a given stimulation site. Phosphenes became stronger and more vivid with increasing stimulus intensity but size, form and size of phosphenes remained constant across the range of stimulus intensities.

Phosphene thresholds for each group are depicted in Fig. 1. When participants with PPR were considered together, there was no significant difference in phosphene thresholds relative to PPR-negative control participants [ANOVA A: F(1,34) = 2.84; P = 0.101]. However, when taking into account the type of PPR, the ANOVA showed a difference among the three groups [ANOVA B: F(2,34) = 3.73; P = 0.035]. Paired comparisons (Scheffe tests) revealed that the photosensitive subjects with propagated discharges
had lower phosphene thresholds than PPR-negative control participants (Scheffé mean diff = −10.06, P = 0.044). They also tended to have lower phosphene thresholds than PPR-positive subjects with occipital spikes only, but this difference was not significant (Scheffé mean diff = −9.47, P = 0.131). PPR-positive individuals with occipital spikes only and PPR-negative control participants had similar phosphene thresholds (Fig. 1).

**Evaluation of phosphene intensity**

Figure 2 shows that the intensity of phosphenes increased with the intensity of TMS. This was confirmed by a main effect of stimulus intensity in the ANOVAs [ANOVA A: F(9,297) = 135.12; P < 0.001; ANOVA B: F(9,288) = 114.35; P < 0.001]. Figure 2A shows that the stimulus–response curves were similar for the subjects with and without PPR. Indeed, there were no significant effects involving group [ANOVA A: main effect of Group: F(1,33) = 1.78; P = 0.162, Intensity × Group: F(9,297) = 2.36; P = 0.08]. As for phosphene threshold, the lack of overall group differences can be explained by the inhomogeneity of the PPR group. The slope of the stimulus–response curve in the PPR-positive group with propagation is much steeper relative to the slopes of the stimulus–response curves obtained in PPR-negative control participants or individuals with local PPR (ANOVA B: Intensity × Group F(18,288) = 3.75; P = 0.002). Figure 2B shows that subjects with PPR propagation experienced phosphenes more intensively at low TMS intensity. Paired comparisons (Scheffe tests) revealed that the PPR group with propagation differed from both the other groups especially for 50% of stimulator output (see Fig. 2B).

**TMS-induced suppression of perception**

The suppressive effects of single-pulse TMS on visual perception are summarized in Fig. 3 which shows the percentage of correct letter identifications for each SOA between the trigram stimulus and the magnetic pulse. In line with results from previous studies (Miller et al., 1996; Amassian et al., 1998; Mulleners et al., 2001; Kammer et al., 2005a), measurements revealed an inverted bell-shaped modulation of the number of correct responses with maximal suppression at SOAs around 80–100 ms. In control participants, the percentage of correct letter identifications at an SOA of 100 ms was similar in magnitude (40–60%) to the letter detection rate reported in previous studies (Miller et al., 1996; Corthout et al., 1999; Mulleners et al., 2001).
ANOVA A revealed two significant main effects: SOA \(F(7,221) = 40.9; P < 0.001\) and Group \(F(1,33) = 13.53; P = 0.001\) and a significant interaction between SOA \(\times\) Group \(F(7,231) = 3.72; P = 0.001\). Paired comparisons (Scheffé tests) revealed that the suppression was more pronounced in the PPR group, particularly at short SOAs (between 40 and 80 ms, see Fig. 3A). ANOVA B revealed two significant main effects: SOA \(F(7,224) = 37.65; P < 0.001\) and Group \(F(2,32) = 9.69; P = 0.001\), and a significant interaction between SOA \(\times\) Group \(F(14,224) = 2.34; P = 0.005\). Post hoc Scheffé tests demonstrated that in the group with propagating PPR, TMS resulted in a stronger suppression than the control group, particularly at short SOAs (40, 60 and 80 ms), whereas the PPR-positive group with occipital spikes lay between PPR-negative control participants and PPR-positive individuals with propagation and did not differ significantly from either group.

Neither PPR-positive nor PPR-negative individuals showed a correlation between individual phosphene thresholds and the amount of TMS-induced suppression as indexed by the rate of correct responses across all SOAs \((r < 0.3; P > 0.05)\).

Experiment 2: excitability of the motor cortex

The results of TMS measurements without IPS are summarized in Figs 4 and 5. ANOVAs failed to show any differences between groups for motor threshold, stimulus–response curves of the MEP amplitude at rest and the duration of the CSP.

None of the subjects developed epileptic seizures or photomyoclonus. IPS was unpleasant in six PPR-positive and five PPR-negative participants. In one PPR-positive subject, we had to stop IPS because of substantial discomfort during IPS at a rate of 50 Hz.

Figure 5 plots the changes in CSP duration during 18 and 50 Hz IPS compared with the baseline condition without IPS. The ANOVA revealed an interaction between the factors Group and IPS \(F(2,46) = 3.408; P = 0.042\). Photic stimulation clearly shortened the duration of the CSP in PPR-negative control participants, but had no consistent effect on the CSP in PPR-positive subjects (Fig. 5). The effects on the control group were sufficient to result also in a main effect of frequency of stimulation \(F(2,46) = 3.296; P = 0.046\) because CSP reduction was more pronounced...
during IPS at 50 Hz compared with IPS at 18 Hz. The main effect of intensity of stimulation was also significant \[ F(2,46) = 231.5; P < 0.001 \] due to a prolongation of the CSP with increasing TMS intensity. There were no other significant effects.

**Discussion**

Compared with PPR-positive subjects with occipital spikes or PPR-negative control participants, individuals with a more generalized PPR exhibited lower phosphene threshold and a stronger suppression of visual perception in response to occipital TMS. PPR-positive individuals with propagation showed a normal motor threshold, stimulus–response curve and duration of the CSP, but lacked a normal modifiability of the CSP during photic stimulation. While IPS reduced the duration of the CSP in PPR-negative control participants, IPS did not modify the duration of the CSP in PPR-positive subjects. Our findings indicate that in healthy individuals without epilepsy, the PPR is only associated with an abnormal pattern of cortical excitability if the PPR spreads to more anterior brain regions.

**Altered excitability of the occipital cortex**

Different studies have demonstrated that the phosphene threshold is inversely related to the overall level of cortical excitability in the visual cortex (Merabet et al., 2003). Several interventions that modulate cortical excitability, such as light deprivation and visual imagery, have produced consistent changes in the phosphene threshold (Boroojerdi et al., 2000a; Sparling et al., 2002; Fierro et al., 2005). Shifts in phosphene threshold have also been observed when the excitability of the occipital cortex was manipulated by transcranial direct current stimulation or repetitive TMS (Boroojerdi et al., 2000b; Antal et al., 2003; Fierro et al., 2005). Finally, diseases that are associated with altered cortical excitability (e.g. migraine) lead to alterations in the phosphene threshold (Aurora et al., 2005; Gerwig et al., 2005).

In our study, subjects with PPR propagation had lower phosphene thresholds than PPR-positive individuals who only showed occipital spikes or PPR-negative control participants. Moreover, in agreement with phosphene thresholds, PPR-positive individuals with propagation had a steeper stimulus–response curve. As demonstrated previously, the slope of the stimulus–response curve is an additional indicator of occipital cortical excitability (Meyer et al., 1991; Boroojerdi et al., 2000a; Boulay and Paus, 2005). We, therefore, infer that photosensitivity with a spread of paroxysmal activity is associated with an enhanced excitability of the occipital cortex. This increase in cortical excitability may explain the abnormal responsiveness of the occipital cortex to visual input, including an overactivation of the occipital cortex during IPS as shown with fMRI (Chiappa et al., 1999), the abnormal contrast gain control for pattern stimuli (Porciatti et al., 2000), the increased amplitudes of visual evoked potentials (Guerrini et al., 1998), as well as the enhanced sensitivity regarding the perception of specific visual patterns (Wilkins et al., 1979; Binnie et al., 1985).

We used a complementary technique to probe occipital excitability by disrupting visual perception with TMS (Amassian et al., 1989). Converging evidence suggests that phosphene induction and disruption of visual perception are caused by stimulation of different neuronal substrates in the visual cortex. First, high stimulus intensities are needed to induce visual suppression while the intensities to elicit phosphenes are consistently lower than the intensity causing visual suppression (Kammer et al., 2005b). Secondly, in patients with migraine, the threshold for phosphene induction is reduced (Gerwig et al., 2005), yet TMS is less efficient at suppressing visual perception relative to control subjects without migraine (Mulleners et al., 2001; Aurora et al., 2005). Thirdly, we found no correlation between individual phosphene threshold and disruption of letter identifications. In the cortex of the cat, strong TMS pulses induce an early suppression of neuronal activity during the first 100–200 ms after the pulse (Moliadze et al., 2003).
This suppression is thought to reflect a direct activation of inhibitory neurons which generate cortical inhibitory postsynaptic potentials (Kamitani and Shimojo, 1999). Therefore, in agreement with Kammer et al. (2005b), we propose that the excitation of intracortical inhibitory circuits contributes to visual suppression after TMS but not to the induction of phosphenes.

Psychophysiological measurements of TMS-induced visual suppression also revealed a difference between PPR-positive individuals with propagation and individuals with occipital spikes only or without PPR. In PPR-positive subjects with PPR propagation, a single TMS pulse induced a stronger suppression of visual perception at short SOAs. This implies that TMS-induced suppression of visual perception in PPR-positive subjects with propagation, is presumably due to a stronger excitation of intracortical inhibitory circuits (Kammer et al., 2005a). Whatever the mechanisms underlying visual suppression, our results demonstrate that subjects with a propagating PPR have an increased sensitivity of (inhibitory and/or excitatory) cortical circuits to transcranial electromagnetic neurostimulation.

The specificity of excitability changes in PPR-positive subjects with propagation underscores the usefulness of distinguishing between PPR with occipital spikes and PPR spreading to other cortical areas (Jeavons and Harding, 1975; Harding and Fylan, 1999). Localized occipital spikes may be seen in conditions other than epilepsy (e.g. migraine). Moreover, a localized PPR is neither predictive of clinical photosensitivity nor associated with an increased risk to develop epilepsy (Maheshwari and Jeavons, 1975). Accordingly, PPR-positive subjects with occipital spikes and PPR-negative control participants displayed an identical excitability pattern. The normal excitability profile supports the view that PPR with occipital spikes represents a variant of the norm (Harding and Fylan, 1999).

In contrast to the PPR with occipital spikes, a propagation of the PPR is often associated with photic-induced or light-independent seizures (Waltz et al., 1992). Furthermore, the anti-epileptic drug, valproic acid, is effective in blocking PPR with propagation but has no effect on occipital spikes (Harding et al., 1978). The clinical relevance of PPR with propagation is corroborated by the clearly abnormal excitability pattern in the occipital cortex as revealed by TMS. We argue that the difference between these two types of photosensitivity needs to be taken into account in genetic and neurophysiological studies of the PPR. Recently, Pinto et al. (2005) demonstrated two susceptibility loci for PPR whereas a locus on 7q32 was characterized by a stronger linkage for the PPR with propagation. This study dovetails with our results as this linkage study provides strong evidence for a genetic heterogeneity of PPR. Clinical, neurophysiological and genetic differences between PPR with propagation and with occipital spikes beg the question whether TMS might be of potential use in individuals with PPR. While TMS-based assessment of cortical excitability changes can provide new insights into the pathophysiology of different PPR types on the basis of group comparisons, it is questionable whether the excitability profiles as indexed by TMS will have a diagnostic value in individuals with PPR. Test–retest reliability, sensitivity and specificity of the described measures are still unknown. In terms of specificity, it is worth to recall that low phosphenе thresholds can also be observed in other pathological conditions such as migraine (Gerwig et al., 2005). We anticipate that the EEG will remain the gold standard to decide whether an individual has a PPR with propagation or with occipital spikes only. However, TMS measurements may turn out to be a useful biomarker in neurogenetic studies on photosensitivity in addition to EEG.

**Involvement of the motor cortex**

Previous studies on photosensitive subjects have disclosed abnormal patterns of neuronal activity outside the occipital cortex, including the motor cortex and frontal areas during photic stimulation. Magnetoencephalography of visually induced spikes has localized additional dipoles in the supplementary motor area, perisylvian region and medial temporal lobe (Inoue et al., 1999). Functional MRI has demonstrated that IPS leads to changes in regional activity not only in the occipital cortex, but also in the perirolandic area (Chiappa et al., 1999). Blood flow measurements have revealed a consistent alteration of frontal regional cerebral blood flow in patients with pure photosensitive epilepsy (Kapucu et al., 1996).

Our results are in line with these observations because photic stimulation was necessary to disclose an abnormal excitability of the M1. Motor cortical excitability was normal when TMS was given without concurrent visual stimulation, but showed an abnormal modulation of corticomotor excitability during IPS. Confirming previous results (Entezari and Dean, 2000), IPS at a rate of 18 or 50 Hz reduced the duration of the CSP in control subjects without PPR. In contrast, IPS had no suppressive effect on the CSP in PPR-positive individuals with propagation. Pharmacological TMS studies suggest that the CSP reflects a TMS-induced activation of intracortical post-synaptic GABAergic inhibitory circuits (Siebner et al., 1999 Werhahn et al., 1999). Therefore, we hypothesize that the shortened CSP in PPR-negative control participants indicates that photic stimulation acutely reduced the excitability of the intracortical GABAergic inhibitory circuits. The failure of IPS to reduce the CSP indicates that the excitability of GABA-ergic inhibitory circuits in the M1 are not efficiently suppressed by photic stimulation in PPR-positive subjects with propagation.

**Physiological significance of the excitability changes**

We can only speculate about the pathophysiological significance of the observed excitability changes. The decrease in...
phosphene threshold indicates a regional hyperexcitability of the occipital cortex. It has been proposed that the generalized spike-wave discharges result from a cortical focus of locally increased excitability (e.g. from the occipital pole in case of the spreading PPR) with a subsequent involvement of cortico-thalamo-cortical pathways (Meeren et al., 2005; Steriade, 2005). Within this model, increased occipital excitability in PPR-positive individuals with propagation may cause a stronger cortico-thalamo-cortical activation, resulting in a spread of the PPR. In PPR-positive subjects with occipital spikes, occipital excitability is normal. Thus, PPR does not sufficiently activate thalamo-cortical pathways to trigger a propagation of the PPR to anterior cortical areas.

Alternatively, a strengthening of inhibitory circuits may protect the brain against the manifestation of epileptic seizures. Two TMS studies have demonstrated a prolongation of the CSP of the M1 in drug-naive patients suffering from generalized epilepsy. The increased excitability of the inhibitory circuits mediating the CSP has also been interpreted as a possible mechanism that protects against the spread or recurrence of seizures (Macdonell et al., 2001; Tataroglu et al., 2004). Therefore, it is possible that the enhanced TMS-induced suppression of visual perception as well as the attenuated suppression of the CSP during IPS, which seem to characterize inhibitory processes in the visual and motor cortex, may represent a compensatory mechanism that prevents the manifestation of seizures in healthy individuals with a generalized PPR pattern. Investigating patients with PPR who are affected by epilepsy should help to clarify the functional significance of the described abnormalities for epileptogenesis.

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References
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