Visual Pattern Adaptation in Subjects with Photoparoxysmal EEG Response: Evidence for Increased Visual Cortical Excitability

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\textbf{PURPOSE.} Photosensitivity, or photoparoxysmal response (PPR), is an abnormal EEG reaction to intermittent photic stimulation (IPS), consisting of spikes, spike-waves, and intermittent slow waves. Depending on the spread of the abnormal activity, PPR subgroups have been defined as having either propagating PPR or localized, occipital spikes (OS) only. Recent research suggests an enhanced excitability in the occipital cortex may underlie this reaction during IPS, but it remains unclear whether changes in excitability affect the function of the occipital cortex to other, less provocative visual stimuli. In this study, cortical function in photosensitivity was assessed using two visual aftereffects that occur after prolonged adaptation.

\textbf{METHODS.} Motion and tilt aftereffects were compared in healthy subjects with ($n=14$, seven with propagating PPR, seven with OS) or without ($n=14$) PPR.

\textbf{RESULTS.} The duration of the motion aftereffect was shorter in the PPR group than in the control group. The size of the tilt aftereffect did not differ between the groups. Thirteen from each group had participated in an earlier study in which occipital transcranial magnetic stimulation (TMS) was used to elicit phosphenes and to suppress the perception of briefly presented letters. The TMS intensity required to elicit phosphenes correlated with the size of the tilt aftereffect (TAE) in the PPR group only.

\textbf{CONCLUSIONS.} This study provides further evidence of enhanced cortical excitability in subjects with photosensitivity, which is likely to reflect changes in excitatory neurotransmission. (\textit{Invest Ophthalmol Vis Sci.} 2009;50:1470–1476) DOI:10.1167/iovs.07-1462

Photosensitivity or photoparoxysmal response (PPR) is a condition evident in EEG recordings as a paroxysmal reaction to intermittent photic stimulation (IPS) or to striped patterns. This visually induced activity varies from localized occipital spikes (OS), or spike and wave discharges, to generalized epileptiform discharges.\textsuperscript{1,2} The PPR is a genetically determined neurophysiologic phenomenon representing an increased risk for mostly generalized epilepsies.\textsuperscript{3} This phenomenon also plays an essential role in the pathogenesis of photosensitive epilepsy, which is the most frequent form of the reflex epilepsies.\textsuperscript{4}

The current understanding of the pathophysiology of human photosensitivity is still rather limited, although studies performed in humans and in experimental animals indicate that the cerebral cortex plays a primary role in its genesis.\textsuperscript{5} There is increasing evidence that subjects with photosensitivity are characterized by an abnormal excitability of the occipital and motor cortex. After several psychophysical experiments, Wilkins et al.\textsuperscript{6} proposed that light- or pattern-induced seizures, as well as the PPR, begin when normal physiologic excitation in the occipital cortex exceeds a critical amount. In such a case, an excessive number of cells become involved in such hypersynchronous activity that inhibitory mechanisms can be insufficient to meet demand, and the synchronized firing spreads (PPR with propagation). Limited regions of synchrony can produce only localized EEG changes (PPR with OS).

The different conditions that elicit a PPR in susceptible individuals have been analyzed in many neurophysiological studies; however, only a few have investigated the neurophysiologic disposition to PPR by comparing persons with and without photosensitivity. In a recent transcranial magnetic stimulation (TMS) study, our group reported significantly increased excitability in the occipital cortex in subjects with propagating PPR, whereas subjects with OS only displayed normal cortical excitability.\textsuperscript{7} These findings are supported by previous scanning and electrophysiological studies in which patients with epilepsy with propagating PPR displayed increased cortical reactivity to light flashes and checkerboard patterns and showed amplitude abnormalities in visual evoked potentials that depended on contrast.\textsuperscript{8,9} It is not clear, however, how these abnormal changes in occipital cortical excitability influence the function of visual neurons to displays that do not induce PPR. The increase in cortical excitability indicated by the TMS, scanning, and electrophysiological studies may not necessarily lead to demonstrable changes in visual perception when other, less provocative stimuli are viewed. Psychophysical studies are needed to determine whether there are changes in the underlying functional abilities of cortical neurons that correlate with the parameters of cortical excitability established electrophysiologically.

Visual adaptation is one technique that can be used to investigate the functioning of the visual cortex. Adaptation can alter the appearance of objects or patterns and affect the ability to detect or discriminate between two objects or patterns. For example, after adapting to a display that moves coherently in one direction, subsequently, a stationary display will appear to move in the opposite direction (the motion aftereffect [MAE]). As a second example, after adaptation to a tilted grating, the subsequent detection of gratings with similar orientations is impaired, and a vertical grating can appear slightly tilted in the opposite direction (the tilt aftereffect [TAE]).

Visual adaptation can result in a variety of aftereffects that can influence the perception of stimulus size, spatial frequency, contrast, depth, as well as orientation and motion. Such selective effects of adaptation have been used conventionally to explore the organization of the visual system and, more recently, to assess cortical function in clinical conditions.

Visual adaptation adjusts the sensitivity of the visual system depending on its recent activity. The responsiveness of neurons in the visual cortex that are tuned to the characteristics of...
the adapting pattern (e.g., motion in a particular direction, lines having a particular orientation) is substantially reduced after continuous exposure to that pattern. When a second test stimulus is subsequently presented, what is perceived is biased away from the adapting pattern, because the neurons tuned to the adapting pattern respond less strongly than they would in normal conditions.9–22 The duration of this neuronal suppression is attributable to two principal mechanisms: a tonic cellular hyperpolarization and a decrease in transsynaptic excitation between cells that respond to the adapting display.23–27

Consistent with this account, both the TAE and MAE have been shown to be abnormal in various disorders that are characterized by abnormal cortical excitability. For example, longer neuronal suppression after adaptation and, correspondingly, longer MAEs, have been reported in schizophrenia28 and migraine.29–31 Larger TAEs have also been reported in migraine,29 schizophrenia, and Parkinson’s disease at short display durations.32 Furthermore, modifying cortical excitability with TMS can shorten the duration of the MAE.32,33 For most of these studies, which component of adaptation is affected in the patient groups, or after TMS, remains to be determined.

A remarkable feature of the MAE, storage, has been used to tease apart the relative contributions of the cellular and synaptic mechanisms of adaptation.30 If the test pattern does not immediately follow the adaptation pattern—for example, if observers close their eyes for the normal duration of the MAE and then reopen them—the illusory motion appears for an additional period only slightly shorter than the original duration. This effect suggests that the decay of the MAE does not necessarily proceed automatically with the passage of time but, instead, can be stored.10,34–36 It has been proposed that when test displays are presented immediately after adaptation, the MAE reflects both cellular and synaptic mechanisms, whereas when test displays are presented after a delay, the MAE reflects principally the synaptic changes that are maintained and decay only when a stimulus is presented that is similar to the adapting display that created it.30–39

In this study, we investigated the MAE, with and without storage, and the TAE in people with and without PPR, to extend our earlier TMS study7 by using perceptual measures and displays that do not elicit PPR. A second purpose was to attempt to confirm, psychophysically, that there is increased cortical excitability in people with PPR as has been suggested by the previous electrophysiological research. As mentioned earlier, one of the consequences of visual adaptation is a withdrawal of mutual excitation between cells that respond to the adapting display.21–27 If people with PPR have increased excitability of the occipital cortex, shorter MAE and smaller TAE could be expected. Finally, most of the participants in this study also completed the earlier TMS experiment.7 It was possible, therefore, to correlate the magnitude of the MAE and TAE with independent measures of cortical excitability, their phosphene threshold, and the amount of perceptual suppression of briefly presented letters after occipital TMS. If adaptation within the occipital cortex contributes to the TAE or MAE, increased excitability should produce a positive correlation between the size of each aftereffect and these TMS measures.

**METHODS**

**Subjects**

Twenty-eight healthy participants were recruited from the database held by the University Hospital of Pediatric Neurology (Kiel, Germany).3 The participants were divided into two groups with 14 in each: participants with photosensitivity, who had a PPR in the EEG response to intermittent photic stimulation (age range, 11–53 years, mean age ± SD: 26.8 ± 12.8 years, seven men) and participants with no PPR in the EEG (age range, 11–47 years, mean age ± SD: 25.9 ± 9.2 years, eight men). Thirteen from each group had participated in the study on TMS.7 None had a history of any neurologic or psychiatric disorder, drug abuse, or alcoholism. None had epilepsy, but they were included in the hospital database because they had family members who had photosensitive epilepsy. In our clinic, if anyone shows PPR in a routine EEG recording, his or her first-degree relatives are also investigated, resulting in a database containing healthy subjects who have never had epilepsy or PPR, healthy subjects who have never had epilepsy but who do have PPR, and patients with epilepsy and PPR. They had been assessed initially between 1 and 5 years earlier (mean, 35.72 ± 12.9 years, minimum 13, and maximum 58 months) and were assessed a second time within 2 weeks before the present experiment to ensure that they had the same classification (Verrotti et al.37). The participants were interviewed about their state of health and were not taking any medication chronically or on the day of the experiments.

The sample size was dictated by the availability of participants with photosensitivity who fulfilled these criteria. None of them was aware of the purpose of the experiment. All had normal or corrected-to-normal visual acuity, as assessed by the Snellen chart, intact confrontation visual fields, normal visual fixation, and normal smooth pursuit and saccadic eye movements. All the participants gave their written, informed consent and were paid for participating. The study was performed according to the Declaration of Helsinki and was approved by the ethics committee of the University of Kiel.

**Electroencephalographic Assessment of Photosensitivity**

In all participants, the EEG response to intermittent photic stimulation was recorded before the experiment according to internationally recommended guidelines as described in Sinitchkin et al.7 Two experienced EEG specialists analyzed EEGs independently and classified each as PPR with OS or PPR with propagation according to Harding and Fylan.38 PPR with OS was always confined to posterior regions of the scalp and corresponded to PPR type I, according to the classification proposed by Waltz et al.41 The PPR was labeled as PPR with propagation when the appearance of parieto-occipital spikes was followed by biphasic slow waves spreading to frontal cortex or when the PPR consisted of generalized spike-and-wave discharges (PPR type III and IV according to Waltz et al.41). There were seven participants in each PPR subgroup: participants with OS only (mean age ± SD: 35.4 ± 12.40 years, two men) and participants with propagating PPR (mean age ± SD: 20.14 ± 9.91 years, five men). All patients produced PPR for a range of stimulation frequencies (10–30 Hz) using white light. Seven subjects had the PPR elicited for a relatively narrow range (15–18 Hz), the rest showed the PPR for frequencies between 10 and 30 Hz.

**Experimental Displays**

The MAE and TAE stimuli were presented on a 16-inch color monitor (Macintosh G4; Apple Computer, Cupertino, CA). The spatial and temporal resolutions were set at 832 × 624 and 80 Hz, respectively. Participants were seated 60 cm from the monitor in an otherwise dark room.

**Motion Aftereffect**

Adapting and Test Displays. A 14° square window displayed random light and medium-gray pixels (average luminance 30 cd·m⁻², Michelson contrast 30%) moving coherently at 3 deg·s⁻¹ in one of four directions (up, down, left, and right) for 45 seconds. After adaptation, the 14° square window displayed stationary light and medium-gray pixels either immediately, or after a 15-second delay, which nonetheless appeared to drift in the opposite direction (the MAE). Participants indicated when the illusory motion stopped by pressing a key.

Storage. Some studies use variable storage periods for each participant matched to their usual immediate MAE duration.30–37 To facilitate group comparisons here a fixed period was chosen (15 seconds) based on previous research.30,36,42,43 Participants closed their eyes at the end of the adapting motion when a tone sounded and

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reopened them after 15 seconds when the tone sounded a second time. They again indicated when the illusory motion stopped with a key press and were asked after each trial whether they had seen illusory motion in the stationary test display.

Procedure. Six practice trials (two with the 15-second storage interval) were followed by 16 experimental trials divided into four blocks, two for each storage condition (none or 15 seconds). The order of the blocks of trials was randomized and, within each block, the particular direction of motion was selected randomly with the constraint that each direction was presented once (up, down, left, and right).

Tilt Aftereffect

Adapting and Test Displays. Low-contrast, 3-cyc/deg Gaussian blurred gratings (Michelson contrast 14.5%) were presented in a circular patch (diameter 15°) on a uniform gray background. The average luminance of the gratings and background was 30 cd · m⁻². The screen was covered with a black-card mask with a central circular aperture (diameter 19°) to prevent participants from being able to use the edges of the monitor as a vertical reference.

Orientation Discrimination. Discrimination was first assessed to ensure that the participants could distinguish gratings tilted ±2°, ±4°, ±6°, ±8°, and ±15° from vertical. After 10 practice trials, each orientation was presented four times, making 40 experimental discrimination trials. Each pattern was displayed for 400 ms and then replaced by a uniform gray screen until a response was made. Participants were instructed to keep their heads upright and to look at the center of the display. They signaled whether the lines appeared tilted to the left or right of vertical by pressing appropriately labeled keys. Auditory feedback was given if a mistake was made.

TAE Procedure. In two blocks of trials, participants were presented with one of two adaptation displays: a grating oriented ±15° from vertical for 60 seconds. To prevent the grating from fading away during adaptation or generating afterimages, participants moved their eyes slowly along a thin gray central horizontal bar (length 2.6°). After 60 seconds, the test phase started, consisting of a uniform gray screen for 200 ms, a test grating for 400 ms, and then the uniform gray screen until a response was made. Participants again had to judge whether the test grating appeared tilted to the left or right of vertical. No feedback was given as, after adaptation, there were no longer correct or incorrect responses. The adaptation pattern was then presented for a top-up period of 15 seconds, followed by a further test phase. This cycle of top-up adaptation and test phase was repeated until 30 test patterns had been presented. Participants then completed the entire sequence again for the second adaptation pattern (±15°).

There were six test gratings for each adaptation pattern: vertical, +2°, +4°, +6°, −2°, and −4°, where + and − indicate gratings oriented in the same or opposite direction from vertical as the adaptation pattern, respectively. The test orientation for each trial was selected randomly with the constraint that each was presented five times. The −2° and −4° patterns were included to balance the response set and as a check on accuracy, as their perceived orientation should not be affected by the adaptation—the degree of perceived tilt may be affected, but the direction of tilt should not be.

In the experiments, we used low-level routines written in C, some of which were based on Denis Pelli’s Video Toolbox collection.⁴⁴

RESULTS

Experiment 1: MAE

The average MAE duration was calculated across the four motion directions (up, down, left, and right) for each group (Fig. 1A). The data from each condition and each group (PPR and control) were normally distributed (Kolmogorov-Smirnov tests, P > 0.63). In Figure 1A it is clear, first, that the MAE lasted a shorter time in the PPR group than in the control group in both conditions (with and without the 15-second delay). Second, although the MAE after the delay was shorter than the immediate MAE, the MAE nonetheless did store in both groups. These effects were confirmed with a mixed one-between (group: PPR or control), one-within (storage condition: none or 15 seconds) analysis of variance (ANOVA). The analysis revealed a significant effect of group (F₁, 260 = 4.4, P < 0.05) and a significant effect of storage condition (F₁, 260 = 33.1, P < 0.001). The group × storage condition interaction was not significant (F₁, 260 = 1.7, P > 0.2).

Siniatchkin et al.⁷ reported changes in occipital cortex excitability that were most pronounced in photosensitive participants with propagating PPR, compared with those with OS only. Here, however, there were no significant differences between the photosensitive subgroups for either MAE (mixed two factor ANOVA, as above, but with group defined as participants with propagating PPR versus OS, both Fs involving group < 1, P > 0.6, Fig. 1B).

Experiment 2: TAE

The number of gratings whose orientation was correctly and incorrectly identified before adaptation was calculated for each grating orientation and each participant. The proportion of incorrect responses is plotted in Figures 2A and 2B (incorrect, rather than correct, responses are depicted to facilitate comparison with Figs. 2C, 2D). It is clear that both groups could discriminate the orientation of the gratings before adaptation, and the discrimination rates were comparable to rates reported previously for similar test gratings.⁹ Most of the data for the different individual orientations were not normally distributed, but the total number correct was (Kolmogorov-Smirnov test, P > 0.39) and was therefore used for analysis. Overall, there were no statistically significant differences between the PPR groups, combined, and the control group; nor between each PPR subgroup (propagating PPR, OS); and the control group (three separate t-tests, P > 0.29).
After adaptation, some of the data for the different individual orientations were not normally distributed, and so nonparametric tests were used. It was expected that vertical gratings and gratings oriented slightly toward the adapting grating would be perceived to be tilted in the direction opposite to that of the adapting grating in both groups (the TAE). In all groups, in more than 90% of the trials the vertical grating was indeed judged to be oriented in the opposite direction, a rate that differed significantly from chance performance (Mann-Whitney U tests, $P < 0.001$; Figs. 2C, 2D). Similarly, the gratings oriented 2° and 4° in the same direction as the adapting grating were judged to be oriented in the opposite (non-visual) direction at rates that differed significantly from the judged orientation of the same gratings before adaptation (Wilcoxon matched-pairs signed-ranks tests, control: $P < 0.05$; PPR: $P < 0.005$). Thus, participants did experience the TAE.

Figures 2C and 2D show that the large effects of adaptation were orientation specific, biasing the perception of those gratings that were vertical and those that had the same orientation as the adapting grating. Adaptation did, however, also improve performance for those gratings that were oriented in the direction opposite to that of the adapting pattern (−2° and −4°). For example, the control group correctly judged 89% of the 2° gratings before adaptation, but judged 98% correctly after adaptation. These improvements were significant for the 2° gratings for both the control and the combined PPR groups (Wilcoxon matched-pairs signed-ranks tests, control: $P < 0.05$, PPR: $P < 0.01$).

To compare the groups’ performance, an overall index of the TAE was calculated from the proportion of times the vertical grating and the gratings oriented 2°, 4°, and 6° in the same direction as the adapting grating were judged to be oriented in the opposite direction. These data were normally distributed (Kolmogorov-Smirnov tests, $P > 0.85$). The overall size of the TAE did not differ significantly between the PPR groups, combined, and the control group; nor between each PPR subgroup (propagating PPR, OS) and the control group (three separate t-tests, $P > 0.50$).

**TMS Parameters**

Siniatchkin et al. used two TMS measures to explore changes in occipital cortex excitability: phosphene thresholds and the suppression of the perception of briefly presented letters. Thirteen photosensitive participants (7 with OS, 6 with propagating PPR) and 13 control participants completed both the present and the earlier TMS studies. In the combined photosensitive group, phosphene thresholds correlated significantly only with the overall TAE (Spearman’s $r_s = 0.61$, $P < 0.05$; Fig. 3A, Spearman’s selected due to small sample size). There were similar correlations for each photosensitive subgroup separately, but they did not both reach statistical significance (OS: $r_s = 0.82$, $P < 0.05$; propagating PPR: $r_s = 0.70$, $P = 0.12$). There were also positive correlations between the number of letters correctly identified during occipital TMS and the overall TAE in the photosensitive group ($r_s = 0.40$) and subgroups (OS: $r_s = 0.48$; propagating PPR: $r_s = 0.44$, Fig. 3C), but they were not statistically significant ($P > 0.18$). Conversely, in the control group there was no significant correlation between the overall TAE and phosphene thresholds ($r_s = -0.32$, $P > 0.28$, Fig. 3B); nor between the overall TAE and the number of letters correctly identified during occipital TMS ($r_s = -0.25$, $P > 0.4$, Fig. 3D). There were no significant correlations between either TMS measure and (1) the discrimination of gratings before adaptation or (2) the MAE in either group.

**DISCUSSION**

Participants with photosensitivity saw the MAE for a shorter time than those without, both when tested immediately after adaptation and after a delay. This result was equally apparent in the data from each of the PPR subgroups (Fig. 1). As will be
discussed, shorter MAEs are consistent with increased excitability in several cortical areas, likely to include at least V1, V3/V3a, and V5/MT.43,45,46 This study is the first to demonstrate functional changes within the visual system in participants with photosensitivity using visual stimuli that do not elicit the PPR. Shorter MAEs were not mirrored in smaller TAEs (Fig. 2); however, this is not necessarily an inconsistency. Although the mechanisms underlying adaptation to different stimulus attributes, such as motion or orientation, are presumed to be the same, albeit involving different neuronal populations, various factors may affect one type of aftereffect and not another. For example, the low-contrast adaptation gratings (necessary to avoid eliciting a PPR) may have been less salient than the moving adaptation displays. If the neurons that respond during the adaptation are not driven vigorously, the neuronal suppression after adaptation will be weak, which would make group differences unlikely. One feature of the TAE data is nevertheless consistent with increased cortical excitability in the photosensitive groups: the positive correlations between the TAE and TMS induced phosphene thresholds.

Enhanced Cortical Excitability in PPR

**Models.** Shepherd29,30 discussed various models of cortical hyperexcitability and concluded each predicts shorter MAEs. For example, increased excitability could result in increased general noise in the visual system against which the MAE signal (a suppression in the response of adapted cells) must be detected. This model would produce weaker MAEs, as the MAE signal would be more readily masked by the elevated background noise. Alternatively, increased excitability may result in a broader range of cells responding to the adapting displays. Since the perception of a MAE depends on the relative suppression of cells tuned to the adapting display, adapting a broader range of cells should result in smaller aftereffects. A third alternative is that increased excitability raises the activity of direction-selective cells to a uniformly higher rate without increasing variability, similar to the increase in firing rate that can occur with increasing contrast.43,47 Since the strength of both the MAE and TAE are reported to be at their maximum with low-contrast test patterns,48–53 this account again predicts smaller aftereffects in any condition characterized by increased excitability. Thus, shorter MAEs are consistent with enhanced cortical excitability in the photosensitive group.

**Transcranial Magnetic Stimulation.** As mentioned, one component of the TAE experiment is also consistent with increased cortical excitability producing smaller aftereffects: the correlation between the TAE and the lowest TMS intensity needed to elicit phosphene in the photosensitive group. The correlation was positive, indicating that those participants with the lowest phosphene thresholds and, by implication, enhanced occipital excitability also had the smallest TAE.

There were, however, no significant correlations between the TMS-induced phosphene thresholds and either MAE. This difference is likely to reflect the different cortical areas involved in the MAE and TAE and the fact that the TMS was applied over the occipital cortex. Both aftereffects involve adaptation across multiple cortical areas, however, several recent studies indicate that adaptation within V1 contributes more to the TAE than to the MAE.54–56 TMS can affect the MAE if it is applied more laterally so as to stimulate MT/V5 rather than V1.
than V1.\textsuperscript{32-35} Further studies are needed to determine whether phosphene thresholds elicited by TMS over MT/V5 correlate with the MAE duration, as would be predicted.

**Mechanisms of Adaptation.** As described in the introduction, adaptation is followed by a suppression of the activity of those neurons that responded to the adapting display, which is attributed to two principal mechanisms. One involves a tonic cellular hyperpolarization,\textsuperscript{24,25} which is intrinsic to the cell rather than of synaptic origin and makes activated cells less likely to fire again, whatever the visual input.\textsuperscript{25,28-27} That the response suppression is greatest for test displays that are the same as the adapting display has been attributed to a second component: a decrease in mutual excitation between cells that respond to the adapting display.\textsuperscript{25} For example, in vivo studies in cat and monkey during normal adaptation\textsuperscript{24,26,27,59-57} and after iontrophoretically blocking or activating GABA\textsubscript{A}, GABA\textsubscript{B}, or glutamate receptors in cat striate cortex\textsuperscript{38,59} have shown that either blocking or activating inhibition does not affect the strength of adaptation, whereas manipulating excitation can.

Shorter aftereffects in the PPR group could result from less hyperpolarization and, consequently, a more rapid recovery of the membrane potential to an active state. Alternatively, shorter aftereffects could result from a smaller withdrawal of mutual excitation between cells that respond to the adapting display. Both of these explanations imply increased cortical excitability in the photosensitive group.

The 15-second delay between the end of the real motion and the test displays was included to try to assess the relative strengths of the cellular and synaptic components of adaptation. The MAE that is seen when the test displays are presented immediately after the adapting motion reflects the operation of both mechanisms. The residual aftereffect after the delay is more likely to reflect principally the synaptic changes that have built up during the adaptation.\textsuperscript{24,30,32-34} In both groups, the MAE did store during the 15-second delay. Its duration was approximately halved in both groups compared with the immediate MAE duration suggesting the proportional contribution of each mechanism is broadly similar in each group. Interpreting this result is complicated, however, in the context of shorter MAEs overall. The 15-second delay was more than twice the average immediate MAE duration seen by the PPR group but was only 1.4 times the average immediate MAE duration seen by the control group. Therefore, the MAE needed to be stored a comparatively longer time in the PPR group. To evaluate the resilience of the network changes that build up during adaptation, a range of storage times could be used to determine, for each group, whether the MAE duration plateaus or continues to decline with storage times that extend beyond their immediate MAE duration (after van de Grind et al.\textsuperscript{56}).

**Converging Evidence.** Other lines of research are consistent with increased cortical excitability in patients with PPR. As described earlier, our recent TMS study revealed lower phosphene thresholds in individuals with propagating PPR compared with control groups\textsuperscript{7}. One functional magnetic resonance imaging (fMRI) study has reported an increased number of voxels in the visual cortex that are activated during photic stimulation in patients with PPR compared with control participants.\textsuperscript{8} Electroencephalographic recordings of visual evoked potentials have revealed increased cortical reactivity to light flashes and checkerboards in PPR, as well as stronger VEP habituation and an abnormal amplitude modulation depending on contrast—a possible indicator of a deficient cortical gain-control mechanism.\textsuperscript{9,0,06,61}

Increased excitability may be attributed to deficient GABA-ergic inhibition, or to increased glutamate-mediated excitation. In an animal model of PPR, the photosensitive baboon Papio papio, it has been shown that the pharmacologic manipulation of not only GABA-ergic neurotransmission,\textsuperscript{62,65} but also injection of glutamate antagonists, can alter the threshold of PPR.\textsuperscript{64,65} Moreover, the degree of photosensitivity in the baboon correlated strongly and positively with the level of asparagine (metabolite of the excitatory amino acid aspartate) and negatively with GABA and taurine in the cerebrospinal fluid.\textsuperscript{66} Meldrum et al.\textsuperscript{64,65} concluded that both decreased inhibition and increased excitation could increase photosensitivity. However, these studies were performed in the baboon. The present study provides evidence that changes in excitatory neurotransmission may contribute to the mechanisms underlying PPR in humans.

**Propagating PPR versus OSs**

The sample recruited by Sniatchkin et al.\textsuperscript{7} in their recent TMS study included most of the participants involved in this study. They reported increased occipital cortex excitability in the photosensitive participants that was most pronounced in those with propagating PPR. Significantly lower TMS stimulation was required to elicit phosphens and to suppress the perception of letters in the propagating PPR group compared with the control group, whereas the stimulation required for each measure in the OS group lay in between. In the present study, however, there were no significant differences between the photosensitive groups with propagating PPR or OS for any of the visual tests. This may simply reflect the smaller sample size, however, where there were differences between the photosensitive and control groups (each MAE), the performance of the two photosensitive subgroups was similar. This suggests that cortical excitability may be enhanced in both photosensitive subgroups, although it may be more easily revealed in those with propagating PPR.

**References**

38. Verstraten FA, van der Smagt MJ, van de Grind WA. Aftereffect of
37. Verstraten FA, Fredericksen RE, Van Wezel RJ, Lankheet MJ, Van
36. Shepherd AJ. Local and global motion aftereffects are both en-
35. Thompson P, Wright J. The role of intervening patterns in the
34. Spigel IM. The effects of differential post-exposure illumination on
31. Smith S, Wenderoth P. Large repulsion, but not attraction, tilt
29. Sanchez-Vives MV, Nowak LG, McCormick DA. Cellular mecha-
28. Carandini M, Ferster D. A tonic hyperpolarization underlying con-
27. Sanchez-Vives MV, Nowak LG, McCormick DA. Membrane mech-
24. Carandini M, Movshon JA, Ferster D. Pattern adaptation and cross-
23. Carandini M, Ferster D. A tonic hyperpolarization underlying con-
22. Barlow HB, Hill RM. Evidence for a physiological explanation of the
21. Maffei L, Fiorentini A, Bisti S. Neural correlate of perceptual adap-
20. Barlow HB, Hill RM. Evidence for a physiological explanation of the
19. Tolhurst DJ, Thompson PG. Orientation illusions and aftereffects:
18. Blakemore C, Julesz B. Stereoscopic depth aftereffect produced
17. Blakemore C, Muncey JP, Ridley RM. Stimulus specificity in the
16. Blakemore C, Gruenwald G, Murray A. Motion aftereffect as a function of
14. Hallonsten AJ, de Weerd P. Motion aftereffect as a function of
13. Hallonsten AJ, de Weerd P. Motion aftereffect as a function of
4. Shepherd AJ. Local and global motion aftereffects are both enhanced in migraine, and the underlying mechanisms differ across cortical areas. Brain. 2006;129:1833–1843.
-9. Huk AC, Rees D, Heger DJ. Neuronal basis of the motion afteref-
12. Van Wezel RJ, Britten KH. Motion adaptation in area MT. J Neu-
24. Vidyasagar TR. Pattern adaptation in cat visual cortex is a co-
32. Lloyd KG, Scatton B, Voltz C, Bryere P, Valin A, Naquet R. Cere-