DOI: 10.1093/brain/awg109 *Brain* (2003), **126,** 1164–1172

Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception?

J. Parra,[1] S. N. Kalitzin,[1] J. Iriarte,[2] W. Blanes,[1] D. N. Velis[1] and F. H. Lopes da Silva[1]

[1]*Dutch Epilepsy Clinics Foundation, 'Meer en Bosch', Heemstede, The Netherlands,* [2]*Department of Neurology, Clínica Universitaria de Navarra, Pamplona, Spain*

Correspondence to: Jaime Parra, MD, PhD, Department of Clinical Neurophysiology, Stichting Epilepsie Instellingen Nederland (SEIN), 'Meer en Bosch', Achterweg 5, 2103 SW Heemstede, The Netherlands
E-mail: jparra@sein.nl

Summary

Photosensitive epilepsy (PSE) is the most common form of human reflex epilepsy, appearing in up to 10% of epileptic children. It also offers a highly reproducible model to investigate whether changes in neuronal activity preceding the transition to an epileptic photoparoxysmal response (PPR) may be detected. We studied 10 patients with idiopathic PSE (eight female, mean age 26 years, range 9–51 years) using magnetoencephalography. In addition, we also studied the responses of five normal controls (mean age 24 years, age range 9–35 years) and three non-photosensitive epileptic patients (mean age 10 years, range 8–11 years). Spectral analysis of the MEG signals recorded during intermittent photic stimulation revealed relevant information in the phase spectrum. To quantify this effect, we introduced a second order response feature of the stimulus-triggered visual response preceding the PPR: the phase clustering index, which measures how close the phases of successive periods are grouped for each frequency component for all periods of the stimuli applied. We recorded a total of 86 PPRs, including several absence seizures, in nine of the 10 patients. We found that an enhancement of phase synchrony in the gamma-band (30–120 Hz), harmonically related to the frequency of stimulation, preceded the stimulation trials that evolved into PPRs, and differed significantly from that encountered in trials not followed by PPR or in control subjects. This novel finding leads us to postulate that a pathological deviation of normally occurring synchronization of gamma oscillations, underlying perceptional processes, mediates the epileptic transition in PSE.

Keywords: gamma band oscillations; magnetoencephalography; photosensitive epilepsy

Abbreviations: IPS = intermittent photic stimulation; IPSP = inhibitory post-synaptic potentials; PCI = phase clustering index; PPR = photoparoxysmal response; PSE = photosensitive epilepsy; rPCI = relative phase clustering index

Introduction

Photosensitive epilepsy (PSE), or increased risk of seizures triggered by visual stimuli, appears in ~10% of a paediatric epilepsy population and in 5% of the adult patients (Kasteleijn-Nolst Trenité, 1998), representing the most common form of reflex epilepsy in humans. The photosensitive trait is genetically determined and presents with an age-dependent penetrance (Waltz and Stephani, 2000). Since introduced by Walter *et al*. (1946) the diagnosis of this trait is confirmed by means of intermittent photic stimulation (IPS). The condition is manifest in the EEG in the form of paroxysmal spike/polyspike-and-wave discharges during the IPS procedure, the so-called photoparoxysmal response (PPR), which can be either focal over the posterior head regions or may have a more diffuse or generalized aspect, evolving into a self-sustained discharge, even prolonged beyond the duration of the stimulus (Waltz *et al*., 1992).

Despite the fact that the phenomenon has already been recognized for a long time (Harding and Jeavons, 1994), very little is known about the mechanisms of generation of the PPR, in particular about the relationships between the physiological response during IPS, the steady-state evoked activity or 'photic-following response', and the pathological response, the PPR. Recently, Porciatti *et al*. (2000) demonstrated that cortical mechanisms of contrast gain control for pattern stimuli of relatively low temporal frequency and high

Table 1 *Patient characteristics*

Patient/ gender/ age	Age of onset (years)	Family history	Seizure types	Photosensitive range	Pattern sensitive	AEDs	Stimulations followed by PPR (in Hz)*	Max PPR**
1/F/11	1	+	AS, MS	10–50	+	VPA	10 ,15, 15RB	Type 4
2/F/18	17	+	OS	10–60	–	None	10, 15, 20	Type 3
3/F/51	38	+	EM, GTCS MS	10–60	+	LTG	15RB	Type 1
4/F/51	21	+	AS, EM, GTCS	5–60	–	VPA	–	None
5/F/9	9	+	AS	10–60	+	None	10, 20	Type 4, AS
6/M/17	12	+	GTCS	10–40	–	VPA	15RB	Type 4
7/F/28	5	+	MS, GTCS	10–25	+	VPA	10RB, 15RB	Type 4
8/F/25	23	–	EM, AS	10–60	–	None	10, 15, 15RB	Type 3
9/F/36	13	+	MS, GTCS	15–30	–	VPA	15RB	Type 4, MS
10/M/20	13	–	GTCS	10–40	–	CBZ	15RB	Type 4, EM

AE = absence epilepsy; AEDs = antiepileptic drug treatment at the time of the study; AS = absence seizure; CBZ = carbamazepine; EM = eyelid myoclonias; EMA = eyelid myoclonias with absences; GTCS = generalized tonic-clonic seizure; IGE = idiopathic generalized epilepsy; MS = myoclonic seizures; PPR = photoparoxysmal response; RB = red-and-blue full-field flash stimulation; VPA = valproic acid. *Stimulation with full-field white light flashes unless otherwise specified. **Photoparoxysmal response according to Waltz's classification.

luminance contrast are lacking or severely impaired in patients with idiopathic occipital photosensitive epilepsy, indicating a link between photosensitivity and altered cortical mechanisms of visual perception.

In this study we attempt to clarify whether changes in the dynamics of neuronal activity precede the transition to PPR. If so, the identification of such changes could help to understand how the transition from a normal steady-state evoked activity into PPR takes place. We studied 10 patients with idiopathic PSE, recording their responses to IPS using whole-head MEG, and compared them with control subjects. We used MEG because this technique has several potential advantages over EEG (Hari, 1999). First, whole-head MEG provides a higher spatial density of recording points than are routinely available with scalp EEG recordings. Secondly, MEG offers theoretical advantages in studies of synchronization or coherence because it does not require a reference sensor. Finally, magnetic field fluxes are less distorted than electric potential changes by the smearing effect of the skull.

Methods

Patients

This group consisted of 10 patients with the diagnosis of idiopathic PSE and evidence of a reproducible PPR during IPS in several routine EEGs performed at SEIN (Stichting Epilepsie Instellingen Nederland; Table 1). None of them had any structural lesion on magnetic resonance imaging nor did they have clinical evidence of a progressive neurological condition. Patients with symptomatic generalized epilepsy or localization-related epilepsy (other than occipital photosensitive seizures) were explicitly excluded. The local Institutional Review Board (Commissie Medische Ethiek, Leiden University) approved the study protocol. Informed consent was obtained from all adult patients and the parents/guardians of subjects <18 years of age according to the Declaration of Helsinki.

Control groups

The healthy control group included five healthy subjects (four females, one male) with ages ranging from 9 to 35 years (mean 24 years). Three epileptic patients with no evidence of photosensitivity (one female, two males; age range 8–11 years) formed the epileptic control group. Only one of these non-photosensitive patients received no therapy.

MEG recordings: technical settings

The studies were performed using a 151-channel whole-head MEG system (CTF Systems Inc., Vancouver, BC, Canada) in a magnetically shielded room at the Free University Hospital in Amsterdam. The sensors consisted of first-order axial gradiometers, with a 5-cm baseline, uniformly distributed over the helmet surface. An additional reference array was used for noise cancellation by means of software formation of third-order synthetic gradiometers (Vrba, 1996). Prior to digitization at a sampling rate of 625 Hz, MEG signals were filtered using a digital hardware anti-aliasing low-pass filter at 200 Hz, and the 50 Hz powerline artifact was eliminated using notch filters.

Intermittent photic stimulation

Patients were seated on the MEG recording chair, in dim light (3–4 lux). An intercom system allowed communication

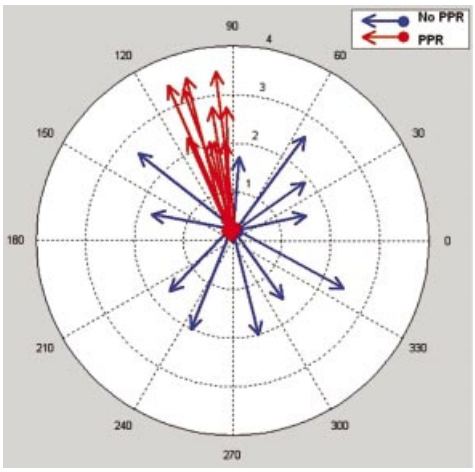

Fig. 1 Illustration of the concept of phase clustering. Each arrow represents a complex number corresponding to a harmonic component of the evoked response with a real part projected on the horizontal axis and an imaginary part projected on the vertical axis. The phase of a complex number is the planar angle of the arrow measured from the horizontal axis. The blue arrows form a sequence of complex harmonics with large phase dispersion (low PCI), pointing in random directions. The red sequence, on the contrary, represents complex harmonics with phases clustered in the vertical direction (+90°) and therefore with high PCI.

between subjects and investigators. A camera system allowed visualization of the patient during the procedure, which was recorded on videotape.

IPS was performed using an ultra-high resolution LCD light-valve projector (Barcographics 8200; Barco Corp., Kortrijk, Belgium), situated outside the magnetic shield of the MEG. The light generated by this projector passed through a small hole cut in the MEG shielded room, and it was redirected by means of mirrors to a 60 × 45 cm vertical screen placed 1 m from the patient's eyes. It conveyed a full-field uniform flash stimulation at a maximal intensity of 200 lux.

The objective of the IPS was to obtain reproducible responses. The investigation was tailored to the characteristics of each patient, starting always with the least provocative stimulation condition and progressively moving to more provocative paradigms until a reproducible PPR was obtained, thereby ensuring patient safety.

All patients had a baseline 2-min sample preceding the IPS. IPS was performed at 10, 15 and 20 Hz, under two different eye conditions ('eyes open' or 'eyes closed'). We only analysed responses obtained under the condition 'eyes-open' as this condition was provocative in all the patients, allowing better comparison of the results. Patient 5 was extremely sensitive and was stimulated with either only one eye open or both eyes open. Coloured stimuli (red and blue flickering) were also used in all cases except in patient 5, due to the reasons mentioned above (Table 1). Red flickering light and red-and-blue flashes are known to be especially provocative, even at a very low luminance intensity, as was the case in our experimental setting (Takahashi and Tsukahara, 1976; Harding, 1998). Investigators had full control over the actual timing of the trials: IPS could be administered or stopped at any time during the course of the recording. On average there were four IPS sessions at the same frequency within a trial. The duration of each session was ~ 5 s. The time interval between sessions was ~ 10 s. Stimuli were withdrawn as soon as a generalized epileptiform discharge was elicited. IPS was resumed at least 20 s after any evoked discharge had ceased.

Data analysis

The raw MEG data were reviewed using a Hewlett-Packard HP-C110/9000 Workstation, using the CTF DataEditor software. A selection was made of the epochs containing the IPS trials free from artifacts. At this point a classification of the PPR was also performed according to Waltz's criteria (Waltz *et al*., 1992). The raw MEG data were converted from CTF files into MATLAB files. All the analyses were made using MATLAB version 5.3 and 6.0 (The Mathworks Inc., MA, USA). Statistical analyses were performed using the statistical software package SPSS 10.0 (SPSS, Inc., Chicago, IL, USA).

Phase clustering analysis

We defined a new term, phase clustering index (PCI), which accounts for a measurement of the phase dispersion of the different frequency components. The methodological details of the phase analysis and its stability have been described elsewhere (Kalitzin *et al*., 2002). Briefly, in order to compute the PCI we determined the phases of the different frequency components of the visual system's response for all periods of the stimuli applied. Dobie and Wilson have used a similar approach when they proposed the magnitude-squared coherence method for the study of steady-state auditory evoked potentials (Dobie and Wilson, 1989, 1994*a*, *b*). For this study we included only those PPRs that occurred after 10 or more stimuli were given, in order to achieve a more stable measurement. Ten stimuli corresponded to the smallest number of measurements necessary to perform proper statistics (Fig. 1). The epoch analysis ended before any paroxysm was detected. The index measures how close the phases of successive periods are grouped, for each frequency component.

Thus, PCI is a measure of the phase consistency, with values ranging from 0 (phases scattered) to 1 (maximal phase grouping) (Fig. 1). PCI was computed per channel and for all MEG channels. To quantify the system's state during any stimulation session, independent of the stimulation frequency, we compared the PCI at all the harmonic frequencies with that at the frequency of stimulation (fundamental frequency) as reference. In this way we obtained a quantity that we termed relative PCI (rPCI), which is comparable

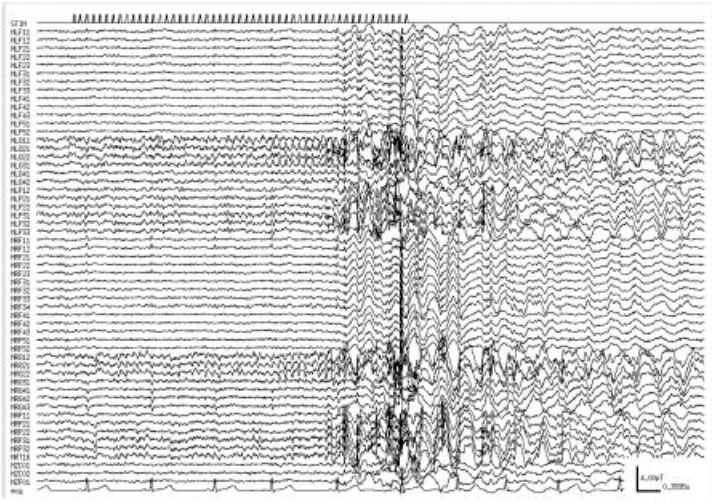

Fig. 2 Photoparoxysmal discharge (type 4) elicited during 10 Hz stimulation with white light and eyes open. Notice the photic following response in the occipital sensors. Legends for the MEG sensors: 1st letter, M = magnetic; 2nd letter, L = left, R = right, Z = zenith (midline); 3rd letter, F = frontal, C = central, P = parietal, O = occipital, T = temporal. Numbering: 1st digit, sensor row, from anterior to posterior; 2nd digit, sensor position; Stim = stimulus.

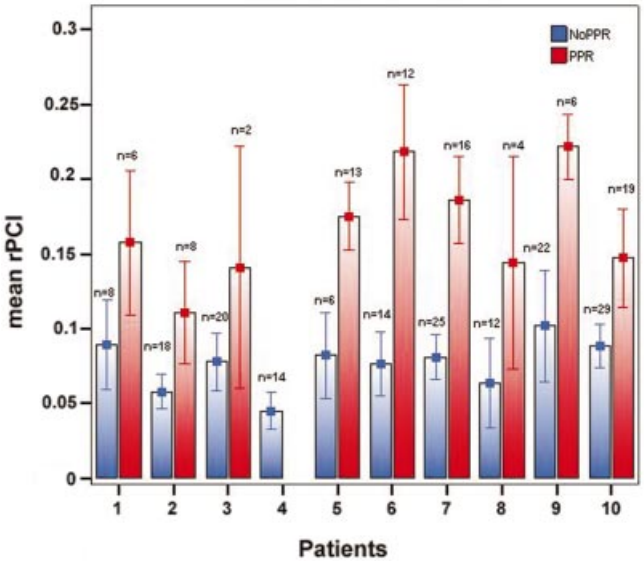

Fig. 3 The relative phase clustering index values averaged over the whole head (mean rPCI) in the trials followed by photoparoxysmal response (PPR) are in red, with those not followed by PPR in blue. Error bars indicate the 95% confidence interval. Note that patient 4 did not have any elicited PPR. The difference between the two groups was statistically significant (Wilcoxon signed ranks test, $P = 0.008$).

across different frequencies of stimulation. Thus, rPCI measures the maximal positive difference between the phase consistency at any of the higher harmonic component of the system's response and the phase consistency at its fundamental frequency.

Results

Population groups

See Table 1.

Photoparoxysmal responses

Nine of the 10 PSE patients studied had PPRs during the investigation, accounting for a total of 86 PPRs elicited (Fig. 2, Table 1). All of them had PPR in the 'eyes open' condition. The 15 Hz red-and-blue flicker stimulus was the most provocative one. Trials where a PPR was not elicited, whether from the same patients or from the one who never displayed a PPR, formed the non-PPR group.

Phase analysis

We found that the PCI in the higher harmonics in the gamma band (30–120 Hz), related to that of the fundamental frequency of stimulation, was larger than the PCI at the fundamental frequency when the stimulation evolved into PPR. Thus, these patients presented larger rPCI values in most of the trials, which elicited a PPR (Fig. 3). This was the case for all the different stimulation paradigms. There was no relationship between the mean rPCI value and the spatial spreading of the discharge as scored according to Waltz's classification (Table 1).

When the stimulation did not provoke a PPR, the PCI in the gamma band harmonics did not exceed the PCI value for the fundamental frequency (Fig. 3), resulting in rPCI values similar to those found in normal controls or non-photosensitive epileptic patients (Fig. 4). Interestingly, at the beginning of a period of IPS that is not followed by PPR, the

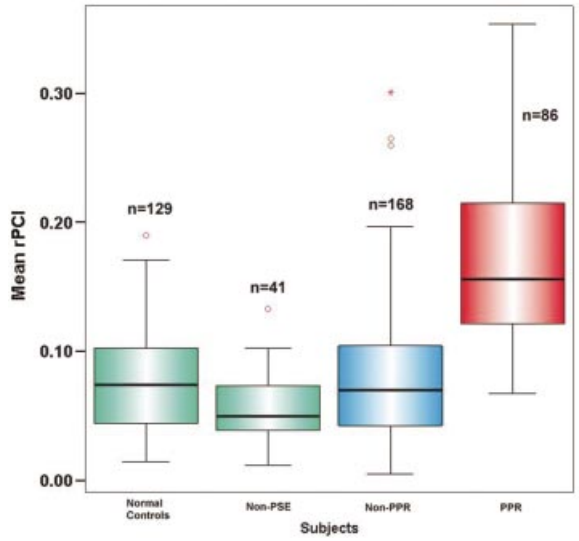

Fig. 4 Boxplots representing the mean values of the whole-head mean rPCI in the different population groups. The box extends from 25th to the 75th percentile. Whiskers extend to the largest and smallest observed values within 1.5 box lengths. The median is represented by a horizontal line. Outliers are represented by stars or circles. n = the number of stimulation trials.

rPCI values may be similar to those of the corresponding period where PPR occurs. However, in the course of the IPS, the rPCI decreases rapidly in the former case, whereas it consistently does not decrease as rapidly or even increases further in the latter (Fig. 5). Receiver operator characteristic (ROC) curves were calculated for the most significant variables. The variable with the larger discriminative power was the whole-head mean of rPCI values across all the sensors (Fig. 6). Mean rPCI values higher than 0.106 were at least 85% sensitive and 80% specific in anticipating the occurrence of a PPR.

Until now, we have considered values of rPCI averaged over all sensors. It is important to examine how the rPCI is distributed over the different sensors according to their locations relative to the subject's head. The spatial distribution of the rPCI differed in trials leading to PPR from those that did not, being greater in the former (Fig. 7). Whereas in trials that did not evolve into PPR the highest values were virtually confined to the sensors above the occipital regions, the trials that were followed by PPR showed greater values beyond the occipital regions, being widely distributed mostly over the sensors located at the parietal, central and temporal regions (Fig. 8). Although the number of subjects with different types of seizures is small, we noted a remarkable difference between one patient with myoclonic seizures (Fig. 8, left) and another with typical absences (Fig. 8, right). In the former case the regional rPCI values were most conspicuous over sensors near the frontal and central regions, while in the latter the rPCI was strongly dominant over the parietal sensor positions.

Discussion

Our data indicate that the phase clustering of higher harmonics in the gamma frequency range (30–120 Hz) is enhanced during IPS, which leads to PPRs or seizure responses, but not in cases where the latter does not occur. This suggests that the value of the rPCI may eventually be used to anticipate the occurrence of the transition between a state characterized by a normal photic driving response to an abnormal one consisting of paroxysmal oscillations.

The fact that PCI appears to be the relevant predictor of the dynamic state transition towards the occurrence of paroxysmal activity indicates that the phase spectrum characterizes important aspects of the dynamics of underlying neuronal networks. The importance of phase in neuronal processes has been emphasized in a number of investigations. In this respect, a seminal observation was that of Sayers *et al.* (1974), who found that electrical cortical responses evoked by auditory stimuli near the hearing threshold could be detected more easily using their averaged phase spectrum than the corresponding amplitude spectrum. This suggests that the modulation of the degree of synchrony, as revealed by the phase spectrum, plays a role in information processing in the brain. This notion has been advanced in a number of other studies (Dobie and Wilson, 1994*a*, *b*; Picton *et al.*, 2001). An important demonstration of the importance of phase synchrony in the cortical processing of information has been provided by Varela *et al.* (2001), who emphasized the necessity of using analytical tools in which the phase component can be obtained separately from the amplitude component.

In agreement with previous observations (Spekreijse and Reits, 1982; Regan, 1989), recent studies have highlighted the existence of non-linear effects in the visual system. López and Sannita (1997) recorded fast-frequency (100–110 Hz) magnetic oscillatory fields in humans from occipital locations in response to monocular transient full-field flash stimulation at frequencies of 0.6 Hz. More recently, Herrmann (2001) showed that the stimulation of human subjects with flickering light at frequencies from 1 to 100 Hz elicited steady-state oscillatory responses that tended to show amplitude enhancement around 10, 20, 40 and 80 Hz. These observations fit well with the findings of Rager and Singer (1998) who recorded local field potentials and multi-unit activity during flicker stimulation from 2 to 50 Hz in the visual cortex of the cat.

These observations suggest that the enhancement of the gamma-band PCI in our experiments is possibly related to natural non-linear resonance properties of the visual system. We hypothesize that the enhancement of synchrony in the gamma band of photosensitive patients may reflect a loss of control of the brain over a high-frequency oscillatory process that normally operates to transiently connect neural assemblies involved in the cerebral cortex (Singer and Gray, 1995; Tallon-Baudry *et al.*, 1997; Singer, 1999; von Stein *et al.*, 1999; Engel *et al.*, 2001; Varela *et al.*, 2001). This would imply that the critical parameters controlling beta/gamma

band oscillations are labile in patients with PSE and may deviate from the normal dynamical range under the influence of IPS. The temporal evolution of the rPCI (Fig. 4) suggests that IPS initially entrains the neuronal populations responsible for these gamma frequencies but that, under normal conditions, control mechanisms exist that counteract this initial increase in synchrony. However, when IPS leads to PPR, this hypothetical control mechanism does not seem to operate normally. This introduces a delay in the 'resetting' of synchronous neuronal assemblies, which allows the emergence of abnormal local resonances and eventually leads to excessive synchrony. The fact that the enhanced rPCI values appear in a number of magnetic sensors widely distributed over the head when IPS leads to PPR suggests that the breakdown of gamma control also governs the spatial spread of synchronization. As a consequence, these oscillations, released from the normal control, can display synchrony over much larger cortical areas. Thus, some sort of recruitment or dynamic capture of neurons into larger assemblies appears to precede the epileptic chain reaction (ictal cascade) that ends in a paroxysmal oscillation, the PPR.

The fact that the most provocative stimuli in our setting were the red-and-blue flashes emphasizes the prominent role of the parvocellullar system in the genesis of the PPR, as has been documented previously by Harding and Fylan (1999). In this regard it is also worth mentioning that internal synchronization mechanisms seem to act differentially on magno and parvocellular pathways, and do not affect the former at those levels of processing where grouping is achieved according to external timing (Singer, 1999). Thus, we can also speculate that the neural activity conveyed by the parvocellullar system may mediate the internal synchronization necessary for the entraining of these neural assemblies. Similar mechanisms have been proposed for the top-down processing mechanisms involved in the construction of visual perceptions (Engel *et al*., 2001).

Intracranial recordings have revealed that gamma band oscillations often appear at the onset of various forms of epileptic seizures (Allen *et al*., 1992; Fisher *et al*., 1992; Alarcón *et al*., 1995; Traub *et al*., 2001). These fast activities appear very close to the site where the seizure starts and are considered to be a reliable indicator of the epileptogenic area. In this regard, our findings suggest that there may be a correlation between the clinical manifestations of the PPR (for instance myoclonic seizures or absences) and the distribution of the rPCI changes over the sensor positions (Fig. 8).

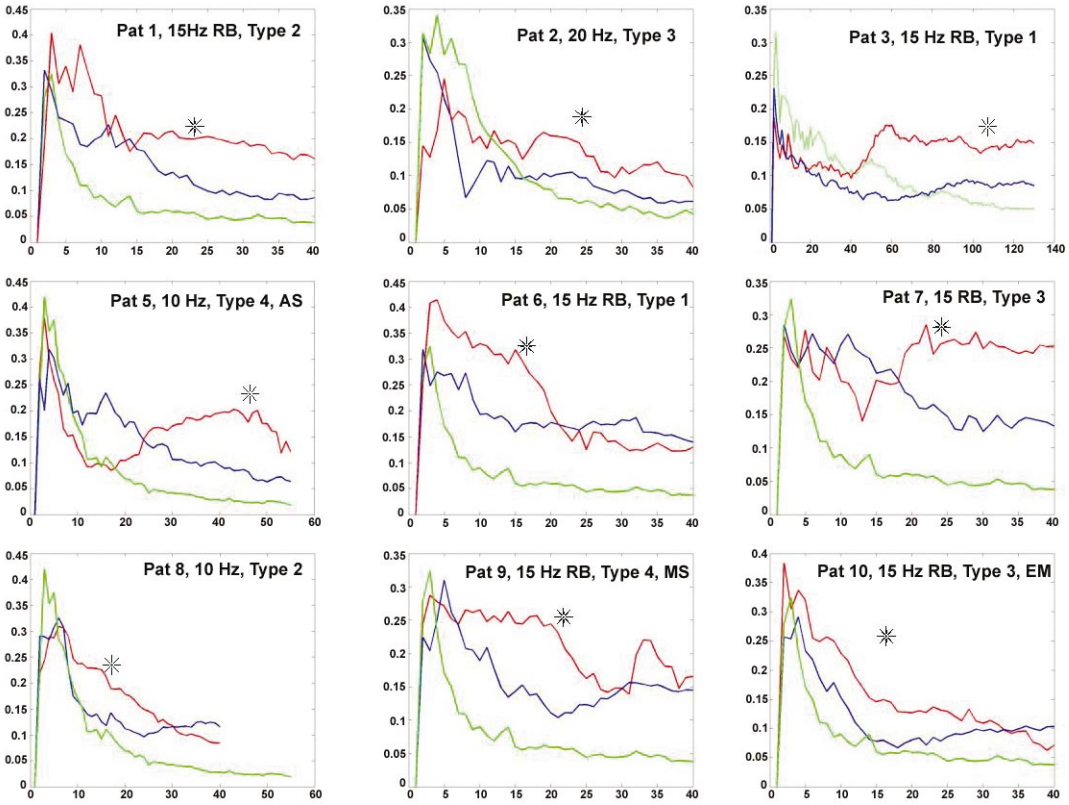

Fig. 5 Temporal properties of rPCI as a function of the number of stimuli. The vertical axis represents the whole-head mean rPCI value. The horizontal axis represents the number of stimuli, starting from the beginning of the session, used to compute the rPCI. The temporal evolution of a representative PPR trial (red line) is shown compared with a trial not followed by PPR (blue line) in the same patient and same parameters of stimulation. The green line represents the temporal evolution in the control subject for the same parameters of stimulation. The star marks the occurrence of the PPR. AS = absence seizure; MS = myoclonic seizure; EM = eyelid myoclonias.

The neurophysiological basis of these gamma-band oscillations has been the object of a number of experimental and modelling studies (Traub *et al*., 1999). Intrinsically oscillating neurons, the 'chattering cells' of Gray and McCormick (1996), may contribute to the generation of such synchronous oscillations. Nevertheless, interactions are required to establish phase synchrony (Kopell *et al*., 2000) in a sufficiently large population to render the oscillations detectable in the EEG/MEG recordings. In the mouse somatosensory cortex *in vitro*, Buhl *et al*. (1998) showed that cholinergic activation of GABAergic interneurons and the resulting inhibitory postsynaptic potentials (IPSPs) play a crucial role in the phasing of gamma oscillations. Thus, the characteristics of the gamma oscillations depend, among other factors, on the time constants of inhibitory interactions. Evidence indicates that subsets of inhibitory interneurons are under the control of other interneuron subsets. In the hippocampus (Banks and Pearce, 2000), one subset is responsible for the generation of GABA(A)ergic IPSPs with fast kinetics on the somata of the

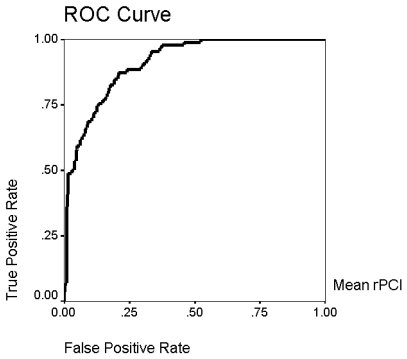

Fig. 6 ROC curve calculated from successive values of the whole-head mean rPCI. Each point of the curve represents the false positive rate (horizontal projection) and the true positive rate (vertical projection) that will be obtained for a given rPCI value used as a threshold criterion for PPR outcome predictions. In the plot, these rPCI values increase from 0 (left, below) to 1 (up, right) along the ROC curve. The true positive scores correspond to those trials that were followed by PPR (n = 86 responses). The false positive scores correspond to cases where PPR did not occur (n = 338 responses, also including normal controls). The value of rPCI that corresponds to a given specificity and sensitivity can be derived from the ROC curve. The former decreases as the false positive rate increases, whereas the latter increases with the true positive rate. A sensitivity of 85% and specificity of 80% correspond to a value of 0.106. Area under the curve: 0.91; standard error under non-parametrical assumption: 0.15; 95% confidence interval: 0.88–0.94.

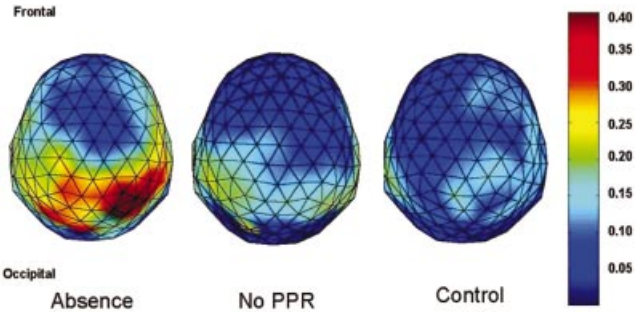

Fig. 7 Spatial distribution of the rPCI changes per magnetic sensor over the helmet. (*Left plot*) average of the mean rPCI from four trials followed by PPR at 20 Hz stimulation, compared with two trials not followed by PPR in the same subject (*middle plot*), and the average of four trials in an age- and sex-matched control (*right plot*).

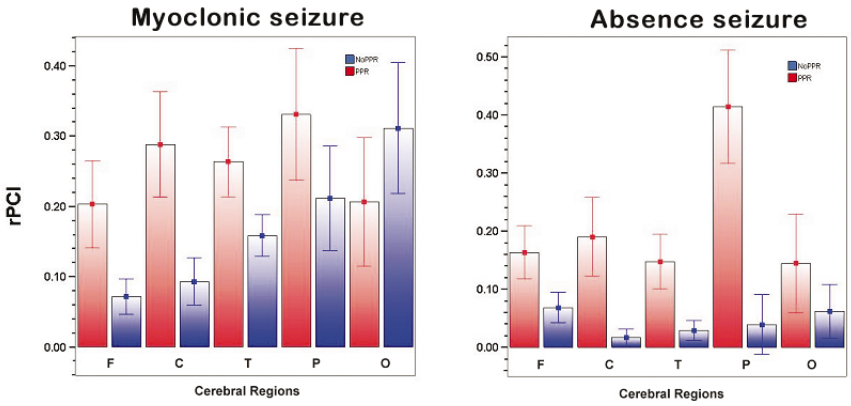

Fig. 8 Distribution of the rPCI changes in different areas of the helmet: photically induced myoclonus (*left plot*) versus photically induced absence seizure (*right plot*). The bars represent the mean rPCI (red for trials evolving into PPR and blue for trials not followed by PPR) with its 95% confidence intervals (error bars) in the different regions of the helmet: F = frontal (35 sensors); C = central (32 sensors); T = temporal (42 sensors); P = parietal (20 sensors); O = occipital (22 sensors). Note the increased relative difference of the frontal, central and parietal regions compared with the occipital region in the patient with myoclonic seizures. In contrast, the patient with absences showed regions of significantly higher values of rPCI over all groups of sensors, especially in the parietal region. Note that the rPCI scale is different for the two outcomes.

pyramidal neurons, while another subset produces GABA(A)ergic IPSPs with slow kinetics on the dendrites of the pyramidal neurons. The latter also makes synapses on the former subset of interneurons. Interestingly, there are indications that the dendritic GABA(A)ergic slow IPSPs would be decreased in some experimental models of epilepsy (Cossart *et al*., 2001). In this way the 'fast' interneurons would be disinhibited, and this could result in an abnormal enhancement of beta/gamma oscillations, since the remaining IPSPs have fast kinetics. It would be interesting to determine whether similar control processes are also operative in the visual cortex and may account for the breakdown of the control of GABAergic processes.

Finally, the computation of rPCI as a measure of phase synchrony between harmonic components of IPS is not only of theoretical interest but it can also be of practical importance in the diagnostic evaluation of patients with visual sensitivity. The finding that a high rPCI value can forecast the appearance of the PPR indicates that the calculation of this parameter could be implemented in the diagnostic evaluation of these patients, eventually allowing us to stop an IPS trial before PPR occurs. This would result in an improvement of the safety of the IPS procedure by decreasing the risk of unnecessarily provoking seizures. Furthermore, such a quantitative measure could be indicative of the degree of photosensitivity of the patient at a particular moment and could be especially helpful in assessing the individual response to antiepileptic drugs. Thus, it could eventually be applied in pharmacological trials where the photosensitive model of epilepsy is used as a measure of drug efficacy (Binnie *et al*., 1986). To achieve these goals, further studies must be performed in order to establish the reliability of the rPCI in the routine IPS procedure in a larger group of patients, with special attention to validating its reliability in subthreshold, non-provocative stimulation paradigms. Preliminary studies suggest that this is feasible. A realistic implementation of the computer algorithm applied to EEG/MEG to compute rPCI in real time is now being tested in practice.

Acknowledgements

We wish to thank the MEG Center staff (Dr B. van Dijk and collaborators) at the Free University in Amsterdam, as well as Dr Kasteleijn Nolst-Trenité, for their assistance in collecting the data, Dr Oosting from the Department of Biostatistics at the Academic Medical Center, University of Amsterdam, for his helpful comments regarding the statistical analysis of the data, and Dr Artieda and Professors R. Hari, J. Jefferys and W. Singer for their critical review of an earlier version of this manuscript. This work was supported by NWO (Netherlands Organization of Scientific Research, The Hague), program grant 903-52-292, and by the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie (Christian Society for the Management of Patients with Epilepsy), Heemstede.

References

Alarcón G, Binnie CD, Elwes RD, Polkey CE. Power spectrum and intracranial EEG patterns at seizure onset in partial epilepsy. Electroencephalogr Clin Neurophysiol 1995; 94: 326–37.

Allen PJ, Fish DR, Smith SJ. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1992; 82: 155–9.

Banks MI, Pearce RA. Kinetic differences between synaptic and extrasynaptic GABA(A) receptors in CA1 pyramidal cells. J Neurosci 2000; 20: 937–48.

Binnie CD, Kasteleijn-Nolst Trenité DGA, De Korte R. Photosensitivity as a model for acute antiepileptic drug studies. Electroencephalogr Clin Neurophysiol 1986; 63: 35–41.

Buhl EH, Tamas G, Fisahn A. Cholinergic activation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. J Physiol 1998; 513: 117–26.

Cossart R, Dinocourt C, Hirsch JC, Merchan-Perez A, De Felipe J, Ben-Ari Y, *et al.* Dendritic but not somatic GABAergic inhibition is decreased in experimental epilepsy. Nat Neurosci 2001; 4: 52–62.

Dobie RA, Wilson MJ. Analysis of auditory evoked potentials by magnitude-squared coherence. Ear Hear 1989; 10: 2–13.

Dobie RA, Wilson MJ. Objective detection of 40 Hz auditory evoked potentials: phase coherence vs. magnitude-squared coherence. Electroencephalogr Clin Neurophysiol 1994a; 92: 405–13.

Dobie RA, Wilson MJ. Phase weighting: a method to improve objective detection of steady-state evoked potentials. Hear Res 1994b; 79: 94–8.

Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2001; 2: 704–16.

Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol 1992; 9: 441–8.

Gray CM, McCormick DA. Chattering cells: superficial pyramidal neurons contributing to the generation of synchronous oscillations in the visual cortex. Science 1996; 274: 109–13.

Harding GFA. TV can be bad for your health. Nat Med 1998; 4: 265–7.

Harding GF, Fylan F. Two visual mechanisms of photosensitivity. Epilepsia 1999; 40: 1446–51.

Harding GFA, Jeavons PM. Photosensitive epilepsy. London: MacKeith Press; 1994.

Hari R. Magnetoencephalography as a tool of clinical neurophysiology. In: Niedermeyer E, Lopes da Silva F, editors. Electroencephalography. Basic principles, clinical applications and related fields. Baltimore: Williams & Wilkins; 1999. p. 1107–34.

Herrmann CS. Human EEG responses to 1–100 Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. Exp Brain Res 2001; 137: 346–53.

Kalitzin S, Parra J, Velis DN, Lopes da Silva FH. Enhancement of phase clustering in the EEG/MEG gamma frequency band anticipates transitions to paroxysmal epileptiform activity in epileptic patients with known visual sensitivity. IEEE Trans Biomed Eng 2002; 49: 1279–86.

Kasteleijn-Nolst Trenité DGA. Reflex seizures induced by intermittent light stimulation. Adv Neurol 1998; 75: 99–121.

Kopell N, Ermentrout GB, Whittington MA, Traub RD. Gamma rhythms and beta rhythms have different synchronization properties. Proc Natl Acad Sci USA 2000; 97: 1867–72.

López L, Sannita WG. Magnetically recorded oscillatory responses to luminance stimulation in man. Electroencephalogr Clin Neurophysiol 1997; 104: 91–5.

Picton TW, Dimitrijevic A, John MS, Van Roon P. The use of phase in the detection of auditory steady-state responses. Clin Neurophysiol 2001; 112: 1698–711.

Porciatti V, Bonanni P, Fiorentini A, Guerrini R. Lack of cortical contrast gain control in human photosensitive epilepsy. Nat Neurosci 2000; 3: 259–63.

Rager G, Singer W. The response of cat visual cortex to flicker stimuli of variable frequency. Eur J Neurosci 1998; 10: 1856–77.

Regan D. Human brain electrophysiology. Evoked potentials and evoked magnetic fields in science and medicine. New York: Elsevier Science; 1989.

Sayers BM, Beagley HA, Henshall WR. The mechanism of auditory evoked EEG responses. Nature 1974; 247: 481–3.

Singer W. Neuronal synchrony: a versatile code for the definition of relations? Neuron 1999; 24: 49–65.

Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 1995; 18: 555–86.

Spekreijse H, Reits D. Sequential analysis of the visual evoked potential system in man: nonlinear analysis of a sandwich system. Ann NY Acad Sci 1982; 388: 72–97.

Takahashi T, Tsukahara Y. Influence of color on the photoconvulsive response. Electroencephalogr Clin Neurophysiol 1976; 41: 124–36.

Tallon-Baudry C, Bertrand O, Delpuech C, Permier J. Oscillatory gamma-band (30–70 Hz) activity induced by a visual search task in humans. J Neurosci 1997; 17: 722–34.

Traub RD, Jefferys JGR, Whittington MA. Fast oscillations in cortical circuits. Cambridge (MA): MIT Press; 1999.

Traub RD, Whittington MA, Buhl EH, LeBeau FE, Bibbig A, Boyd S, et al. A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. Epilepsia 2001; 42: 153–70.

Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001; 2: 229–39.

von Stein A, Rappelsberger P, Sarnthein J, Petsche H. Synchronization between temporal and parietal cortex during multimodal object processing in man. Cereb Cortex 1999; 9: 137–50.

Vrba J. SQUID gradiometers in real environments. In: Weinstock H, editor. SQUID sensors: fundamentals, fabrication and applications. Dordrecht: Kluwer Academic; 1996. p. 117–78.

Walter WG, Dowey VJ, Shipton H. Analysis of the electrical response of the human cortex to photic stimulation. Nature (Lond) 1946; 158: 540–1.

Waltz S, Stephani U. Inheritance of photosensitivity. Neuropediatrics 2000; 31: 82–5.

Waltz S, Christen HJ, Doose H. The different patterns of the photoparoxysmal response—a genetic study. Electroencephalogr Clin Neurophysiol 1992; 83: 138–45.

Received September 30, 2002. Revised December 12, 2002. Accepted December 16, 2002