Mechanisms of altered cortical excitability in photosensitive epilepsy

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Despite the multiplicity of approaches and techniques so far applied for identifying the pathophysiological mechanisms of photosensitive epilepsy, a generally agreed explanation of the phenomenon is still lacking. The present thesis reports on three interlinked original experimental studies conducted to explore the neurophysiological correlates and the phatophysiological mechanism of photosensitive epilepsy. In the first study I assessed the role of the habituation of the Visual Evoked Response test as a possible biomarker of epileptic visual sensitivity. The two subsequent studies were designed to address specific research questions emerging from the results of the first study. The findings of the three intertwined studies performed provide experimental evidence that photosensitivity is associated with changes in a number of electrophysiological measures suggestive of altered balance between excitatory and inhibitory cortical processes. Although a strong clinical association does exist between specific epileptic syndromes and visual sensitivity, results from this research indicate that photosensitivity trait seems to be the expression of specific pathophysiological mechanisms quite distinct from the "epileptic" phenotype. The habituation of Pattern Reversal Visual Evoked Potential (PR-VEP) appears as a reliable candidate endo-phenotype of visual sensitivity. Interpreting the findings of this study in the context of the broader literature on visual habituation we can hypothesise the existence of a shared neurophysiological background between photosensitive epilepsy and migraine. Future studies to elucidate the relationship between the proposed indices of cortical excitability and specific polymorphisms of excitatroy and inhibitory neurotransmission will need to be conducted to assess their potential role as biomarkers of photosensitivity.

Key words: photosensitivity, cortical excitability, evoked potentials, thalamocortical dysrhythmia, gamma oscillations.

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Chapter 1

Introduction

1.1 Overview and terminology

Photosensitive epilepsy is the most common type of reflex epilepsy. In recent times it has attracted considerable attention because of numerous reports of seizure occurrence precipitated by the growing widespread use of television and video games. Photosensitivity is clinically defined as an abnormal sensitivity of the brain in response to intermittent photic stimulation (IPS); photosensitivity manifests itself with poly-spikes or spike-and-wave EEG discharges, also known as photoparoxysmal response (PPR). The term “photosensitive” is often used broadly and is applied to patients with a history of visually induced seizures - with or without PPR - and to those with PPR only (Kasteleijn-Nolst Trenité, 2006).

The IPS-evoked epileptiform EEG abnormalities range from localised occipital spikes to generalised spike-and-wave discharges; a morphologically based classification of PPR has been proposed (Waltz et al., 1992). This defines the following four types of PPR:

- Type 1 = spike within the occipital background activity;
- Type 2 = parieto-occipital spikes with biphasic slow wave;
- Type 3= parieto-occipital spikes with biphasic slow wave and spread to the frontal regions;
- Type 4= generalised spike and waves or poly-spike and waves. This corresponds to the previously used term photoconvulsive reaction (Bickford et al., 1952).

The photoparoxysmal response is to be differentiated from the photomyoclonic response which is anteriorly located and is always associated with myoclonus of the peri-ocular and facial muscles, vertical eyeball oscillations and is timed-locked with the frequency of the IPS. This response is rarely observed in children and it is considered in the spectrum of photic cortical reflex myoclonus (Artieda and Obeso, 1993). Table 1.1 summarises extant definitions of photic-induced responses.

Photosensitive epilepsies can be divided into two broad categories. The first includes patients with epileptic seizures only in response to flickering light, in laboratory or in their normal environment (pure photosensitive epilepsy); the second is characterised by the coexistence of unprovoked seizures and seizures provoked by flickering light. Epileptic sensitivity to visual stimuli is also seen in "pattern sensitivity epilepsies", in which seizures are triggered by exposure to spatially structured isoluminant stimuli. A relatively small percentage of individuals present a PPR without clinical seizures. The relationship between this electrophysiological finding and risk of seizure occurrence has been investigated in 33 adults who showed a photoparoxysmal response on intermittent photic stimulation and no history of overt seizures (So et al., 1993). Over the 6 to 12 year follow-up, none of the 33 individuals had developed overt seizures, and the authors concluded that the mere presence of a photoparoxysmal response does not influence the probability of developing seizures. A further study on 14 children who showed a PPR without history of seizures demonstrated that this EEG

trait was not related to the presence of seizures and should therefore not be considered predictive of the development of epilepsy (Verrotti et al., 2002). The prevalence of a PPR in the healthy population has been estimated at 0.35% based on data from 13,658 male applicants to Royal Air Force training (Trojaborg, 1992), and 2.4% based on data from 5,893 applicants to the Danish Air Force training (Gregory et al., 1993).

Table 1.1. Definitions of photic-induced responses and epilepsy types

Definition	Description
Photosensitivity	Abnormal sensitivity of the brain in response to intermittent photic stimulation
Photoparoxysmal Response (PPR)	Focal or most often generalised paroxysmal of epileptic abnormalities elicited by IPS
Photomyoclonic Response	EEG response anteriorly located and always associated with myoclonic jerks of the peri-ocular and face muscles
Photoconvulsive reaction	PPR type 4 characterised by EEG generalised spikes and waves or polyspikes and waves and convulsions
Pure photosensitive epilepsy	Epilepsy in which seizures are only triggered by flickering lights, in laboratory or in normal environment
Epilepsy with photosensitivity	Epilepsy in which subjects have spontaneous seizures and in addition seizures provoked by flickering lights
Idiopathic occipital lobe epilepsy (IPOE)	Idiopathic localisation-related epilepsy with age-related onset and specific mode of precipitation

Source: Author

1.1.1 History

The first description of photosensitive epilepsy dates back to the 19th century (Gowers et al, 1885). Gowers reported the case of a girl whose seizures were induced by walking through bright sunshine and of a man whose aura and following attack could be provoked by looking at the sunshine. Subsequently a description that sunlight coming through a wire window screen was able to induce fits in a patient was published (Goodkind, 1936) as well as the first report of the effect of intermittent photic stimulation during EEG recording (Adrian and Matthew, 1934). However, the application of IPS as an activating technique in EEG recordings became part to the routine protocol thanks to Grey Walter (Walter et al., 1946), who introduced the electronic stroboscope. With the invention and availability of television during the 1950s, the first case of seizures induced by television was reported (Livingston, 1952). Since then, many cases have been documented in the literature (Jeavons and Harding, 1975; Binnie and Wilkins, 1998; Zifkin and Kasteleijn-Nolst Trenité, 2000). In late 1990, two major TV incidents occurred in Japan and the United Kingdom. The first, the so called “Pokemon” incident, involved 685 Japanese children and adolescents experiencing epileptic seizures watching a sequence of the cartoon Pokemon. The second was related to an advertisement shown on commercial TV in the United Kingdom (Harding and Harding, 1999). This led to an official guideline solicited by the *Independent Television Commission (ITC)* for advertisements and TV programs in the UK. Besides television, video

games and flashing computer screens were also considered capable of inducing epileptic seizures. The widespread availability of these technologies led to the definition of another nosographic entity called “video game epilepsy”. The first case of epileptic seizures induced by the flickering light of video games’ screens was reported by Rushton (1981); since then several cases were documented subsequently in the literature (Graf et al., 1994; Kasteleijn-Nolst Trenité, 1994; Quirk et al., 1995).

1.2 Epidemiology

The incidence of photosensitivity reported in the literature varies considerably, depending on the definition of photoparoxysmal response, the stimulation technique and the age of the studied population. The peak age for photosensitivity is puberty (Kasteleijn-Nolst Trenité, 2006) and there is no general agreement as to whether it declines during adulthood. To fully understand the epidemiological implications, a distinction needs to be made between epileptic syndromes with photosensitivity and pure photosensitive epilepsy.

1.2.1 Photosensitivity in other epilepsy syndromes

The prevalence of photosensitivity in generalised epilepsies has been estimated at approximately 15% (Wolf and Goosses, 1986), five fold higher than for focal epilepsies. The highest prevalence of PPR is found in Dravet Syndrome (40%) especially in the early stages of the disease, followed by juvenile myoclonic epilepsy (JME) (30%), childhood absence epilepsy (CAE) (18%), West and Lennox syndromes (17%); only 8% of the patients with juvenile absence epilepsy (JAE) present a

PPR. Light-induced seizures may also be associated with neuro-degenerative disorders, such as progressive myoclonic epilepsy in adolescents (Lafora body disease, Unverricht Lundborg Disease, type III Gaucher Disease) and neuronal ceroid lipofuscinosis in younger children. The latter condition is mainly associated to single posterior spikes evoked by each flash during low frequency (1-3 Hz) photic stimulation .

1.2.2 Pure photosensitive epilepsy

Pure photosensitive epilepsy has been found in 40% of photosensitive patients (Binnie and Jeavons, 1992) including patients whose seizures are provoked only by environmental flickering stimulation. Frequency of seizures is variable and depends on the range and modality of exposure to triggers. The age of onset is between 8 and 19 years and female/male ratio is 1.5:1. The most common seizure types in pure photosensitive epilepsy are generalised tonic-clonic seizures; myoclonic, absence and focal seizures have been described in sporadic cases. Since patients with pure photosensitive epilepsy present normal neurological and cognitive development and their seizures are mostly generalised, they have been traditionally classified as a subtype of generalised epilepsy in the ILAE classification and terminology (Engel, 2006 and 2010 revision). However about 25% of patients with pure photosensitive epilepsy present only focal seizures; clinical and EEG features of these patients appear sufficiently homogeneous to be defined under a separate syndromic subgroup; this has been recently proposed as pure photosensitive idiopathic occipital lobe epilepsy (IPOE). (Guerrini et al., 1995). In the

ILAE classification IPOE is defined as “idiopathic localization-related epilepsy with age-related onset and specific mode of precipitation”. The definition includes patients with visual symptoms, blurring of vision, blindness, hallucinations, white or coloured lights, followed by epigastric discomfort, vomiting and ictal headache. IPOE shares several clinical features with migraine (Panayiotopoulus, 1999). The seizure duration can be extremely variable and secondary generalisation can occur within a few minutes form seizure onset.

1.2.3 Pattern-sensitive epilepsy

Commonly associated with photosensitivity in the same patient is pattern-sensitivity. Linear patterns can evoke epileptiform discharges in 30% of photosensitive patients if the pattern is static and in 70% if the pattern oscillates (Wilkins et al., 1979a). The occurrence of PPR in pattern sensitive patients depends on the spatial frequency, orientation, contrast, and size of the pattern (Wilkins et al., 1975, 1979b; Porciatti et al., 2000). Oscillating and phase-reversing pattern are more epileptogenic than drifting or static pattern (Binnie et al., 1985). The induced seizures are usually tonic-clonic, but absences, myoclonic and partial seizures can also occur (Binnie and Jeavons, 1992; Guerrini et al., 1995). Pattern-induced seizures are associated with sensitivity to flickering light in 70% to 100% of patients. Sometimes the condition is unrecognised; a report of Jeavons and Harding (1975) suggested that only 2% of their patients studied for photosensitivity reported symptoms suggestive of pattern

sensitivity, but when carefully questioned this percentage increased to 20% (Binnie and Jeavons, 1992).

1.2.4 Video games epilepsy

Since the first case of video-game (VG) epilepsy was reported in 1981, many more cases of seizures triggered by VGs have been identified, not only in photosensitive, but also in non-photosensitive children and adolescents with epilepsy. The term "video game seizures" encompasses a diverse group of reflex epilepsies, which may occur in the context of idiopathic generalised epilepsy syndromes. Video game induced seizures are not synonymous of television induced seizures. Although 50% of the photosensitive patients are also sensitive to material presented on 50-Hz television, non-photosensitive patients with a history of VG seizures have also been described. Like pattern-sensitive epilepsy, video-game induced seizures are usually tonic-clonic, but absences, myoclonic and focal seizures have also been reported. Factors conducive to seizure include fatigue and stress, the reaction to the television screen itself, or the movement and colours of video games' animations (Kasteleijn-Nolst Trenité et al., 1999a).

1.3 Triggering factors

The range of stimuli able to induce a PPR and/or clinical signs includes flickering sunlight through tree-lined road, screens, oscilloscopes, reflection of sunshine on snow, from ripples on water as well as intermittent photic stimulation performed in laboratory. The most common precipitant factor is television (Kasteleijn-Nolst Trenité et al.,

2002; Jeavons and Harding, 1975). The role of television in inducing attacks was related to its widespread availability and to the screen refresh rate; this is 50 Hz in Europe and 60 Hz in USA and Japan. These frequencies have been recognised to be strong triggers in inducing seizures. Screen refresh rate is responsible for the stability with which the images appear on the screen. It is measured in frames per second. Phase alternate line (PAL) and National Television System Committee (NTSC) TVs use interlace technique to display images. This technique utilised two fields to create a frame. One field contains all the odd lines in the image, the other contains all the even lines of the image. A PAL based television display, for example, scans 50 fields every second (25 odd and 25 even). The two sets of 25 fields work together to create a full frame every 1/25th of a second, resulting in a display of 25 frames per second. Thus the perceived frequencies frames are 25 Hz and 30 Hz per second (in 50 Hz and 60 Hz television respectively), which fall in the peak of photosensitive triggering frequencies. For the above mentioned reason the 100 Hz TV screen are much safer in term of seizure induction (Fylan and Harding, 1997; Ricci et al., 1998). Nowadays the most recent plasma and Liquid Crystal Display (LCD) screens are less conducive to seizures than the traditional 50Hz and 60Hz ones.

The physical properties of the images are important as well. Geometric patterns with particular characteristics in terms of frequency, luminance and contrast can be effective in triggering photoparoxysmal EEG responses or epileptic seizures. A well-known example is the

“Pokemon” accident in 1997, in Japan, in which 685 children and adolescents experienced epileptic seizures watching a sequence of the cartoon including bright red/blues frames, alternated at 12.5 Hz. Computer screens may also cause photic-induced seizures. Fatigue and stress have also been shown to contribute to seizures during video game playing (Ferrie et al., 1994). Despite the attention raised in the media, discotheque lighting and flickering sunlight are less common precipitant factors of photosensitivity.

1.4 Pathophysiology

A range of approaches and techniques have been applied to identify the possible pathophysiological mechanisms of photosensitivity.

1.4.1 Animal models: the *Papio papio* baboon

From the incidental discovery in a Parisian laboratory of excessive sensitivity to luminance changes in a large proportion of Papio papio Baboon from the southern Senegal region of Casamance (Killam et al., 1966), several studies have been conducted to confirm the analogy between human photosensitive epilepsy and the one observed in the baboon. These experiments allowed researchers to consider the Papio papio as a valid experimental model of the human condition and of epilepsy in general, although some characteristics of the baboon's photosensitive epilepsy differ from those observed in humans. In 60-80% of the Casamance Papio papio, intermittent photic stimulation (IPS) to 25 Hz is able to induce bilateral and synchronous myoclonus associated with PPR predominating in the frontal cortex, and can be followed by

generalised tonic-clonic seizures. Numerous electrophysiological and neuropharmacological studies have been performed on the Papio papio in order to explain its photosensitivity.

1.4.1.1 Electrophysiological studies

The manifestations of photosensitivity in Papio papio have been attributed to paroxysmal activity in the fronto-rolandic cortex (Broadmann Area 6), activated by visual afferents from the occipital lobe. During IPS, neurons in this region behave as the hyperexcitable neurons seen in human and animal focal epileptogenic lesions (Naquet et al., 1975; Menini, 1976; Menini et al., 1977). The only modification observed in the occipital cortex during photic stimulation is a change in the resting membrane potentials, in the direction of reduced inhibition. The corpus callosum determines the interhemispheric synchronisation of response. An unbalance between GABA-ergic neurotransmitter systems and excitatory amino acids was considered to be responsible for the hereditary predisposition of baboons to photosensitive epilepsy (Menini and Silva-Barrat, 1990). In the light of neurophysiological findings suggesting the disappearance of light sensitivity after ablation of the occipital cortex, the role of frontal cortex in light-sensitive epilepsy of the baboon Papio papio was challenged (Naquet et al., 1975; Menini and Silva-Barrat, 1990). Nevertheless the large numbers of direct occipito-frontal connections - as suggested by a subsequent multi-unit activity analysis (MUA) (Silva-Barrat et al., 1986) - was used to reconcile the two opposing arguments. The study by Silva-Barrat et al. (1986) offered

an intriguing description of cortical and subcortical structures involved in genesis of paroxysmal discharges and generalised seizures in baboons photosensitive induced by a subconvulsant dose of DL-allylglycine. During the induction of fronto-rolandic paroxysmal discharges by IPS trains, the visual structures (occipital cortex, colliculi superioris, and pulvinar) show a significant increase in MUA, which is unrelated to the photoparoxysmal spike-wave but time-locked to the flash. The fronto-rolandic cortex is the first structure showing bursts of MUA preceding the photoparoxysmal discharge. The pontine and mesencephalic reticular formations and the facial nuclei are activated in bursts after the fronto-rolandic photoparoxysmal discharges reached a precise threshold. The thalamic nuclei ventralis lateralis, centrum medianum and lateralis posterior are activated only later, requiring even greater amplitude of the fronto-rolandic photoparoxysmal discharges. In essence, the activation of visual structures is necessary for fronto-rolandic photoparoxysmal discharges to appear; the secondary pontine and mesencephalic activation reinforces that of the fronto-rolandic cortex and thalamus, thus determinining the myoclonus observed in non-paralysed animals.

1.4.1.2 Biochemical and pharmacological studies

The effect of different pharmacological compounds on the photoparoxysmal response in the animal model of Papio papio has been tested systematically. Eserine, Atropine and Reserpine have shown to be ineffective (Meldrum et al., 1970). Drugs which were able to modify gamma-aminobutyric acid (GABA) metabolism (Thiosemicarbazide and

Isoniazid) facilitate the appearance of electrophysiological paroxysms (Meldrum et al., 1970). Lysergic acid Diethylamide (LSD) tends to block photosensitivity but this effect is not specifically related with the hallucinogenic mechanisms (Meldrum and Naquet, 1971). The participation of serotoninergic systems involved in light sensitivity of Papio papio has been suggested studying the acute pharmacological effects of melatonin (Brailowsky, 1976; Trimble et al., 1977). A further study demonstrated the correlation between the level of photosensitivity and cerebrospinal fluid neurotransmitters (Lloyd et al., 1986). At maximum photosensitivity the inhibitory amino acids gamma-aminobutyric acid and taurine were lower, and those of asparagine were higher than when the animals were not photosensitive, suggesting a relation between decreased inhibition, increased excitation and level of photosensitivity.

1.4.1.3 Neuroimaging studies

From the end of the ’80s, following the European Union Directive 86/609/EEC on the protection of animals and thanks to the increasing availability of novel techniques, a decline in the use of Papio papio as an experimental model of epilepsy occurred. Only a few EEG studies have been conducted since 2000 to define clinical and EEG phenotypes of epilepsy in the baboon (Szabó et al, 2004; 2005). Furthermore, the same group carried out a case-control Positron Emission Tomography (PET) study in which they compared changes in cerebral blood flow (CBF) during IPS between photosensitive and asymptomatic baboons (Szabó et

al., 2007). The non-photosensitive baboon presented a widespread IPS-induced activation, greatest in the left middle frontal and inferior temporal gyrus, left brainstem structures, right post-central gyrus, bilateral occipital lobes, the posterior cingulate gyrus and the cerebellum. On the contrary, the photosensitive animals showed strongest IPS activation in the right anterior cingulate and medial orbital gyri, amygdala, globus pallidum, and left inferior and superior temporal gyri. The right orbito-frontal and anterior cingulate cortices of the non-photosensitive baboon and the posterior cingulate gyrus, brainstem and cerebellum of the photosensitive animals present significant de-activation. The most interesting finding in this study is the absent occipital and variable motor cortex activation in the photosensitive animals. A further neuroimaging study compared "resting" cerebral blood flow between photosensitive and non-photosensitive animals, and correlated cerebral blood flow with ketamine dose and interictal epileptic discharges (Szabó et al., 2008). Photosensitive baboons demonstrate relative CBF increases in the occipital lobes and decrease in the frontal lobes. While frontal lobe CBF was negatively correlated with interictal discharge rate, positive correlations were found in the parietal lobe. See Table 1.2 for a summary of the principal studies on animal models based on Papio papio baboon.

Table 1.2. Summary of principal studies on Papio papio.

Authors	Methods	Findings
Naquet et al. (1975); Menini (1976); Menini et al. (1977)	Electrophysiological studies	Role of Fronto-rolandic cortex (area 6) as a neuronal generator of paroxysmal discharges Role of occipital cortex: its ablation induced disappearance of light sensitivity
Menini and Silva-Barrat (1972)	Biochemical study	Unbalance GABA or excitatory amino acids responsible for the hereditary predisposition to photosensitive epilepsy
Silva-Barrat et al. (1986)	Multiunit activity analysis (MUA)	First structure to show MUA was fronto-rolandic cortex, followed by pontine and mesencephalic reticular formations, facial nuclei, thalamus Activation of visual structures was necessary for PPR appearance
Brailowsky (1976); Trimble et al. (1977)	Acute pharmacological effects of melatonin	Participation of serotoninergic mechanisms in PPR generation
Lloyd et al. (1986)	Measure of the cerebrospinal fluid amino acid and monoamine metabolite	Low dosage of the inhibitory amino acids gamma-aminobutyric acid and taurine at maximum of photosensitivity
Szabó et al. (2004, 2005)	Neurophysiological-EEG studies	Definition of clinical and EEG phenotypes of epilepsy
Szabó et al. (2007)	PET study	Specific cortical-subcortical networks in photosensitive baboon Activation in the right anterior cingulate and medial orbital gyri, amygdala, globus pallidum, and left inferior and superior temporal gyri Absence of occipital and motor cortex activation
Szabó et al. (2008)	H(2)(15)O-PET study	Increase cerebral blood flow in the occipital lobes and decreases in the frontal lobes

Source: Author

1.4.2 Human data

1.4.2.1 Neurophysiological studies

Different approaches have been applied to understand the pathophysiology of human photosensitivity. The discovery that the majority of the patients sensitive to intermittent photic stimulation is sensitive to patterns of various kinds has allowed several inferences concerning the features of the triggering factors. In this respect it is possible to recognise three main research strands:

1) Definition of the physical characteristics of visual stimuli involved in precipitating seizures

Specific characteristic of luminance, size, orientation, brightness, colour, contrast can determine the photoparoxysmal response or epileptic seizures. A previous investigation on the physical proprieties of square-wave gratings (Wilkins et al., 1975) suggested that the likelihood of provoking a PPR depends on pattern's spatial frequency (optimum spatial frequency between 1 and 4 cycles/degree), orientation, contrast (the probability of paroxysmal EEG activity increased dramatically as contrast was increased from 0.2 to 0.4), and size. A further finding of this study, in line with previous investigations (Bickford and Klass, 1962; Chatrian et al., 1970), was the reduced effectiveness of monocular vision in triggering seizures compared to binocular vision. This finding was explained invoking a seizure generator in the striate cortex, dismissing the possibility of a generator in the lateral geniculate nucleus of the thalamus. The geniculate nucleus is, in fact, divided into layers of cells

which respond to stimulation of one eye and not the other, in marked contrast to striate cortex in which the majority of cells are binocular and respond to stimulation in corresponding retinal fields of both eyes. Subsequently the existence of two distinct pathophysiological mechanisms was proposed: a "wavelength–dependent" and a "quantity-of-light-dependent" mechanism (Takahashi et al., 1995; 1998; 2001; Harding, 1998).

The first mechanism suggests that photoparoxysmal responses are elicited only if they contain specific wavelength in the 600-800nm spectrum range (Carterette and Symmes, 1952). This was confirmed by more recent studies, which showed greater incidence of PPR to red flicker compared to other colours or to white flicker (Takahashi et al., 1995). There are however reports of red flicker being less effective (Rao and Prichard, 1955; Leijten et al., 1998) or equivalent (Harding et al., 1999) in provoking PPR. A systematic trial demonstrated that the specific wavelength between 680 nm and 770 nm was essential for eliciting a PPR in photosensitive patients. In addition it was suggested that wavelength-dependent pathophysiological mechanisms usually play a role in persons with "predisposition photosensitivity", and that quantity of light-dependent pathophysiological mechanisms play a role in persons with "non-predisposition" photosensitivity. More recently Parra and coworkers (Parra et al., 2007) investigated the potential for different colours, colour combinations and white light to trigger photoparoxysmal responses under stringent controlled conditions. Their study identified

two separate mechanisms of colour sensitivity: one, dependent on colour modulation, playing a role at lower frequencies (<30 Hz), the other dependent on single-colour light intensity modulation correlated to white light sensitivity and activated at higher stimulus frequency. A causal relation between photosensitivity and wavelength was thought to be supported by studies showing a pathophysiological mechanism of photosensitivity depending on wavelength, but not by studies finding a pathophysiological mechanism depending only on the quantity of light.

The quantity-of-light dependent mechanism suggests that PPR is elicited only if stimulus contains a minimum quantity of light, independent of the wavelength composition of the flashing light (Takahashi et al., 1999). The idea that both visual pathways, magnocellular and parvocellular system, might be involved in photosensitivity generation with respect to the stimuli characteristics was proposed (Harding and Fylan, 1999). This study suggested a subcortical primary generalised mechanism, in which a visual stimulus produces generalised discharges (PPR) and a secondary generalised mechanism, in which a visual stimulus produces occipital spikes (OS) in the hyperexcitable visual cortex, which then spread to produce secondary generalised discharges. These two visual pathways have response characteristics that vary in contrast sensitivity, spatial and temporal frequency sensitivity, and in chromatic selectivity. In brief, magnocellular cells have high contrast gain and respond preferentially to low-spatial-frequency and high-temporal-frequency stimuli, and are not

chromatically selective. Parvocellular cells respond preferentially to stimuli of higher contrast, higher spatial frequency, and lower temporal frequency than those preferred by magnocellular cells. Because PPR and OS are elicited most readily by brief light flashes presented at high flash rates, it has been suggested that the abnormal responses are probably mediated along the magnocellular pathway. This would, however, be inconsistent with the results of experiments designed to elucidate the role of stimulus contrast: increasing the contrast of simple black-and-white patterns produces an approximately linear increase in the probability of abnormal responses. Furthermore, these abnormal responses show dependence on the spatial frequency of the patterned stimulus, occurring most frequently at 4 cycle-degree. See Table 1.3 for a summary of the principal neurophysiological studies.

Table 1.3. Principal neurophysiological studies on physical characteristics of visual stimuli

Authors	Findings
Carterette and Symmes (1952)	Red flicker more effective in provoking PPR than other colours
Rao and Prichard (1955)	Red flicker less effective than other wavelengths in provoking PPR
Wilkins et al. (1979)	PPR depend on: spatial frequency, orientation, brightness, size
Binnie et al. (1984)	Only one class of retinal cones if stimulated (red cones) could elicit PPR
Takahashi et al. (1995)	Only specific wavelength, the spectrum around 700 nm (680-770 nm) is essential for PPR
Fylan and Harding (1997)	High contrast pattern and screen flickering may elicit PPR
Harding and Fylan (1999)	PPR elicited by parvocellular and OS by magnocellular visual pathways
Takahashi et al. (1999)	PPR are elicited by IPS containing more than a certain quantity of light
Takahashi et al. (2000)	Peripheral stimulation is more effective than central stimulation in PPR generation
Parra et al. (2007)	Two different mechanisms of colour sensitivity: 1- dependent on colour modulation, role at lower frequencies (<30 Hz) 2- dependent on single-colour light intensity, role at higher frequencies

Source: Author

2) *Definition of excitability properties of occipital cortex*

The pathophysiology of visual sensitivity has also been investigated using specific parameters of the visual evoked potentials (VEP) to detect the cortical mechanisms underneath the abnormal response to light and indirectly infer the excitability of the occipital cortex. Idiopathic photosensitive occipital lobe epilepsy (IPOE), characterised exclusively by reflex seizures originated by the occipital lobe, represents an ideal model to apply this technique. Based on the increased VEP amplitude in transient flash and pattern reversal VEP (PR-VEP), hyperexcitability of the occipital cortex as the pathophysiological background for abnormal visual sensitivity in idiopathic occipital lobe epilepsy was recently suggested (Guerrini et al., 1998). A further study showed the reduced or absent amplitude saturation at high contrast and phase advance with increasing contrast in patients compared with healthy controls (Porciatti et al., 2000). These two studies led to hypothesise altered cortical excitability as the basis of photosensitivity in idiopathic photosensitive occipital lobe epilepsy.

In the same direction a subsequent study (Wilkins et al., 2004) proposed that light or pattern-induced seizures, as well as photoparoxysmal response, begin when normal physiologic excitation in the occipital cortex exceeds a critical threshold. An excessive number of cells become involved in such hypersynchronous activity thus inhibitory mechanisms can be insufficient to meet demand, and the synchronised firing spreads (propagating PPR). Limited regions of synchrony can

produce only localised EEG changes (PPR with only OS). Visual habituation- the amplitude reduction of the visual evoked response to sequential presentation of spatially structured visual stimuli – has recently been investigated as an indirect measure of visual cortex excitability (Siniatchkin et al., 2007). PPR-positive individuals with propagating PPR and no history of epileptic seizures showed increased amplitude of the N75-P100 and P100-N135 components of the PR-VEP for low and high spatial frequencies, whereas PR-VEP amplitude in individuals with a local PPR were within normal limits. Independent of the spatial frequency, increased VEP amplitudes (stronger habituation), are related to increased neuronal excitability in the parvocellular and magnocellular pathway and are interpreted as a compensatory mechanism to stabilise excitability in the visual system. The same findings were confirmed by the same group of researchers using transcranial magnetic stimulation (TMS) (Siniatchkin et al., 2007; Groppa et al., 2008). See Table 1.4 for a summary of the principal occipital cortex excitability studies.

Table 1.4. Summary of principal studies on excitability of occipital cortex

Authors	Type of study	Population studied	Findings
Lucking et al. (1970); Martinovic et al. (1990); Verrotti et al. (2000)	Pattern Reversal VEP amplitude	IGE Controls Photosensitive epilepsy	No differences in PR-VEP amplitude
Faught and Lee, 1984; Genç et al. (2005)	Pattern Reversal VEP amplitude	IGE Controls	Increased amplitude in IGE
Guerrini et al. (1998)	Definition of occipital cortex properties Pattern Reversal VEP	IPOE	- Increase VEP amplitude - Hyperexcitability of the occipital cortex
Porciatti et al. (2000)	Definition of occipital cortex properties Steady-state VEP	IPOE	- Increased VEP amplitude for stimuli at low frequency (4-10 Hz) and high contrast (90%) - Lack of contrast gain control
Wilkins et al. (2004)	Definition of occipital cortex properties	Photosensitive and pattern sensitive epilepsy	Light- or pattern-induced seizures and PPR begin when normal physiologic excitation in the occipital cortex exceeds a critical amount
Siniatchkin et al. (2007)	Definition of occipital cortex properties Pattern Reversal VEP	PPR-positive individuals with propagating or local PPR	- Stronger habituation - Increase in the N75-P100 and P100-N135 pattern reversal VEP for low and high spatial frequencies in PPR-positive individuals with propagating PPR - Normal VEP amplitudes and habituation in PPR-positive individuals with local PPR
Groppa et al. (2008)	Definition of occipital cortex properties Transcranial Magnetic stimulation	IGE subjects PPR-positive and PPR-negative, PPR-negative healthy subjects	Failure of ILS at 50Hz to reduce cortical silent period in IGE subjects PPR-positive and PPR-negative

Source: Author

3) *Spectral analysis*

Spectral properties of EEG and MEG signals have been applied to understand cortical excitability and neuronal synchrony in patients with photosensitivity. The hypothesis that changes in the dynamics of brain systems during intermittent photic stimulation (IPS) may precede the transition to seizure activity in photosensitive patients was tested by estimating the phase clustering of harmonically related MEG/EEG frequency components evoked by light stimulation (Kalitzin et al., 2002). Patients who developed epileptiform discharges during IPS showed an enhancement of the phase clustering index at the gamma frequency band, compared with that at the driving frequency. A further study suggested that synchronisation of specific neuronal populations in response to visual stimuli might be the bases for PPR generation (Parra et al., 2003). Abnormal phase clustering in the gamma band was detected: the phase synchrony in the gamma-band (30±120 Hz) was enhanced and harmonically related to the frequency of stimulation, preceded the stimulation trials that evolved into PPR and differed significantly from that seen in trials not followed by PPR or in control subjects. More recently, both gamma and alpha EEG generators were thought to be involved in PPR generation and in the widespread synchronisation characterising photosensitivity (Visani et al., 2010). Two spectral measures, power spectrum density and coherence profiles, were investigated at rest and during 14 Hz IPS in photosensitive idiopathic generalised epilepsy (IGE). At rest, the intra- and inter-hemispheric

coherence spectra showed a significantly larger number of coherence peaks in the gamma band for patients than for controls. During intermittent photic stimulation (IPS), coherent gamma activity was mainly presented as IPS frequency harmonics. See Table 1.5 for a summary of the principal spectral analysis studies.

Table 1.5. Principal spectral analysis studies

Author	Method	Findings
Kalitzin et al. (2002)	Phase clustering of harmonically related frequency components evoked by the light stimulation EEG/MEG	PPR associated with enhancement of phase clustering index at the gamma frequency band compared with that at the driving frequency
Parra et al. (2003)	Phase clustering of the gamma band in the occipital cortex MEG	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 PPR
Visani et al. (2010)	Power spectrum density and coherence profiles	Both gamma and alpha EEG generators were involved in the PPR generation and in the widespread synchronisation characterising the IGE-associated photosensitivity

Source: Author

1.4.2.2 Neuroimaging studies

The development of novel neuroimaging techniques has allowed investigations on haemodynamic correlates of PPR. Simultaneous EEG-fMRI and magnetic resonance spectroscopy (MRS) studies have revealed prominent visual cortex activation in healthy controls and patients, but failed to detect any specific PPR-related blood oxygen dependent level (BOLD) signal changes in the photosensitive patients (Chiappa et al., 1999; Hill et al., 1999). Four characteristic findings in photosensitive patients emerged from the above studies:

(a) Slightly elevated lactate levels in the occipital cortex in the resting state;

(b) Increased area of visual cortical activation associated with photic stimulation;

(c) Signal attenuation in the peri-rolandic regions alongside the occipital cortex activation;

(d) Decrement in BOLD signal intensity in the occipital cortex and in the region of the posterior cingulate gyrus after the photic stimulation.

Neuroimaging studies, although performed using a range of different techniques, demonstrate an activation of visual occipital regions plus the involvement of subcortical structures such as the thalamus and hypothalamus in PPR generations and seem to suggest a disruption of thalamocortical connections. The involvement of a complex brain network can be interpreted considering that short photoparoxysmal responses without clinical concomitants seem to be initially a cortical

phenomenon and are followed by subcortical involvement is only seen in some patients. Repeated intermittent photic stimulation can lead to increased neuronal activity in the visual cortex and photoparoxysmal response with the associated motor manifestations manifest themselves when a critical threshold is reached. A [^{15}O]-water positron emission tomography (PET) study performed during IPS (da Silva et al., 1999) demonstrated varying degrees of visual cortex involvement (Brodmann's areas 17 and 18) when high and low IPS frequencies were compared. The occipital changes were associated with significant cerebral blood flow (rCBF) increase in the hypothalamic region, suggesting that this structure is involved in the pathophysiology of PPR. Furthermore, rCBF changes were seen in the left caudate nucleus, hippocampus, and insula when IPS was not associated with a photoparoxysmal response; no activation of the frontal cortex or peri-rolandic regions was suggested. In the same direction, a recent case report demonstrated increased BOLD signal in the visual cortex, the thalamus, and both superior colliculi, and decreased BOLD signal in the fronto-parietal areas when the photoparoxysmal response precedes a generalised tonic-clonic seizure (Moeller et al., 2009a).

The possible role of altered thalamocortical mechanisms in photosensitivity is also indirectly supported by evidence of bilateral grey matter volume reduction in the thalamus and occipital cortex in photosensitive patients with juvenile myoclonic epilepsy (JME) not seen in juvenile myoclonic epilepsy without photosensitivity (Lin et al., 2009).

More in detail, the study by Lin et al. (2009) revealed significantly reduced bilateral grey matter volume (GMV) in thalami, insula cortices and cerebellar hemispheres; while significantly increased GMV was observed in the right superior frontal, orbitofrontal and medial frontal gyri of JME patients compared to controls. Recently, an attempt to define BOLD signal changes, before and during a PPR (Moeller at al., 2009b), suggested an early involvement (3 sec prior the actual photoparoxysmal response) of the parietal cortex in the vicinity of the intraparietal sulcus and the premotor cortex. These findings were associated to a deactivation of the same cortical areas at the onset of the photoparoxysmal response. The specific role of the intraparietal sulcus in PPR generation was interpreted taking into account the role of this region in saccades and visual attention as demonstrated by previous researches (Sereno et al., 2001; Schluppeck et al., 2005).

Studies on brain neurotransmitter metabolites (N-acetylaspartate, N-acetylaspartate/creatinine ratio) have suggested an asymmetrical neuronal dysfunction with higher levels in the occipital cortex and thalamus of the dominant hemisphere in photosensitive patients compared to idiopathic generalised patients without photosensitivity (Aydin-Ozemir et al., 2010).

Finally, differences in brain activations have also been found among the different epileptic syndromes associated with photosensitivity. A functional MRI study on occipital lobe epilepsy (Leal et al., 2006) suggested a consistent difference in the BOLD signal between two

patients with late onset occipital lobe epilepsy and one with idiopathic photosensitive occipital lobe epilepsy (IPOE). The BOLD changes were more constant and restricted to the medial parietal-occipital cortex in the first two cases whereas the patient with IPOE presented the same medial parietal cortex with a consistent widespread over the inferior and bilateral occipital areas and also posterior temporal ones. See Table 1.6 for a summary of the principal neuroimaging studies on human data.

Table 1.6. Summary of principal neuroimaging studies

Authors	Type of study	Population studied	Findings
Hill et al. (1999)	EEG-fMRI and MRS	IGE with PS	Visual cortex activation in all normal CTR and PZ; No PPR-related BOLD signal changes in IGE with PS
Chiappa et al. (1999)	EEG-fMRI and MRS	IGE with PS	↑ lactate levels in the occipital cortex in resting state; ↑area of visual cortical activation with IPS; signal attenuation in peri-rolandic regions; ↓of fMRI signal intensity after ILS in occipital cortex and posterior cingulate gyrus
da Silva et al. (1999)	[15O]-water PET	IGE with PS	Occipital cortex rCBF with additional activations in visual cortex (Brodmann's areas 17 and 18) when higher IPS
Leal et al. (2006)	EEG-fMRI study	IPOE	BOLD activation in medial parietal cortex widespread over the inferior and bilateral occipital and posterior temporal areas
Moeller et al. (2009a)	EEG-fMRI study	IGE with PS	↑BOLD signal changes in visual cortex, thalamus, both superior colliculi in PPR; ↓BOLD signal changes in fronto-parietal areas; contribution of the thalamus in PPR preceding a GTCS
Moeller et al. (2009b)	EEG-fMRI study	Subjects with generalised PPR	Early involvement of parietal cortex close to intraparietal sulcus and the premotor cortex; deactivation same cortical areas at PPR onset
Lin et al. (2009)	VBM	JME with and without PS	Bilateral grey matter volume reduction in the thalamus and occipital cortex in JME with PS
Aydin-Ozemir et al. (2010)	MRS	IGE with PS and IGE without PS	Asymmetrical neuronal dysfunction in favour of the dominant occipital cortex and thalamus

Source: Author

1.5 Genetics

Since the late 1940s (Walter et al., 1946) family and twin studies have suggested a genetic aetiology for PPR. Family studies have indicated a sibling recurrence risk of 20-30% that increases to 40% if one parent is also affected, and to 50% when restricted to the 5-15 years age group examined (Doose and Waltz, 1993; Kasteleijn-Nolst Trenité et al., 2005). Most authors have suggested an autosomal-dominant mode of inheritance with reduced penetrance (Watson and Marcus, 1962; Jeavons and Harding, 1975; Waltz and Stephani, 2000). Until recently, despite the increasing interest in the genetics of photosensitivity and efforts to understand its syndromic associations, no single gene responsible for the phenomenon has been identified. A case report (Van Esch et al., 2002) suggested the association between susceptibility to PPR and rearrangement in chromosome 2. A genome-wide screening using a single-locus MOD-score analysis on families with IGE and PPR found evidence supporting linkage at 6p21.2 in 19 out of 60 families with PPR and at 13q31.3 in 25 PPR-IGE families (Tauer et al., 2005). Subsequently, a genome-wide linkage analysis on 16 multiplex families identified susceptibility loci for photosensitivity in chromosomal regions 7q32 and 16p13 (Pinto et al., 2005). These loci are homologous of genes known to play a fundamental role in cortical synchronization and control of sensory input in rats. The 7q32 region contains genes encoding the metabotropic glutamate receptor 8 (human: GRM8), the cholinergic-muscarinic type 2 acetylcholine receptor M2 (human: CHRM2) and a

locus (7q31-34) for spike-and-wave discharges in the Genetic Absence Epilepsy in Rats from Strasbourg (GAERS) model of IGE (locus SWD/GAERS1). The region 16p13 contains at least two genes potentially involved in epileptogenesis, the synaptogirin III (SYNGR3) and a sodium/hydrogen-exchanger (SLC9A3R2). The latter belongs to the same Naþ/Hþ Exchanger (NHE) gene family, as the NHE1 gene known to be mutated in slow-wave epilepsy mutant mice.

A linkage mega-analysis for photoparoxysmal response in a cohort of European and Australian families showed suggestive linkage peak 5q35.3, 8q21.13 and 16q13 (de Kovel at al., 2010). The locus 5q35.3 has been reported for the first time in this study. The locus at 8q21 is overlapped by very broad locus previously reported for non-JME type IGE (Durner et al., 1999). The locus at 16p13 has been found linked to PPR in precedent studies (Pinto et al, 2005, 2007) and interacts with a locus on 7q32. The findings discussed above seem to suggest that multiple loci are probably related to the photosensitivity trait, with subtle differences in phenotypic expression or with genetic differences between geographically detached populations.

It is also interesting to note that in the animal model Papio papio no genetic mutation has been detected so far. Nevertheless, differences in genetic background between humans and animals must be considered; as an example the mouse model of Unverricht-Lundborg disease, a condition strongly associated with marked photosensitivity in humans,

does not exhibit photosensitivity. See Table 1.7 for a summary of the principal genetic studies.

Table 1.7. Principal genetic studies

Authors	Findings
Walter et al. (1946)	Support for a genetic aetiology for PPR
Watson and Marcus (1962); Jeavons and Harding (1975); Waltz and Stephani (2000)	Autosomal-dominant mode of inheritance with reduced penetrance
Doose and Waltz (1993); Kasteleijn-Nolst Trenité et al. (2005)	Sibling recurrence risk of 20-30% that increased to 40% if one parents is also affected and to 50% when restricted to the 5-15 years age group
Van Esch et al. (2002)	Case report- Association between susceptibility to PPR and rearrangement in chromosome 2
Tauer et al. (2005)	Linkage at 6p21.2 in 19 PPR families and suggestive evidence for linkage at 13q31.3 in 25 PPR-EGE families
Pinto et al. (2005)	PPR susceptibility related to 7q32 and 16p13 loci
Pinto et al. (2007)	7q32 and 16p13 susceptibility loci may have similar functions or act in the same biochemical pathway
de Kovel at al. (2010)	PPR susceptibility related also to 5q35.3 and 8q21.13 loci

Source: Author

1.6 Conclusions

To date a clear definition of the pathophysiological basis of photosensitive epilepsy and PPR is still lacking. Several studies have been conducted on the animal model Papio papio baboon although detailed analysis of the electroclinical manifestations observed in photosensitive humans and baboons have shown differences concerning the localization of photically induced EEG changes. Electrophysiological studies suggested that the manifestations of photosensitivity in Papio papio can be attributed to the activity of fronto-rolandic cortex (Broadmann Area 6), triggered by visual afferents from the occipital lobe. The occipital cortex in the photosensitive baboon is not, however, the site of hyperexcitability as it is in humans. Neuroimaging studies on human patients have indicated variable involvement of specific brain regions such as the visual cortex and the thalamus; the latter probably involved in seizure generation rather that in PPR genesis. Neurophysiological studies on human photosensitivity have also addressed the question of how the physical characteristics of the visual stimuli could interfere with the PPR, finding a relationship between PPR genesis and size, brightness, colour, contrast and spatial frequency of the visual stimulation. Studies in pattern-sensitive subjects have suggested that generalised seizures can occur if normal physiologic excitation in the occipital cortex exceeds a critical amount with synchronisation and subsequent spreading of excitation from the occipital lobe trigger. Furthermore, some researchers have suggested that the electro-clinical

manifestations are due to an increased excitability of the visual cortex and to an increased neuronal synchrony in relation with the frequency of the visual stimulation. The hypothesis that changes in the dynamics of brain systems in the course of intermittent photic stimulation (IPS) may precede the transition to seizure activity has also been proposed. Finally, from a genetic point of view, a strong genetic background for PPR has been postulated since the earliest studies and recently some susceptibility loci for PPR, such as 6p21.2, 13q31.3, 7q32, 16p13, 5q35.3, 8q21.13 have been detected. Therefore, shelved the idea of an autosomal dominant monogenic mode of inheritance a multigenic way of transmission has appeared to be more plausible to explain the variety of endo-phenotypes which characterise the wide spectrum of what we define as photosensitive epilepsy and photoparoxysmal response.

Chapter 2

Abnormal Visual Habituation in Paediatric Photosensitive Epilepsy

2.1 Abstract

Purpose: a previous study (Porciatti et al., 2000) had suggested altered cortical excitability and visual sensory gating as the basis of photosensitivity in idiopathic photosensitive occipital lobe epilepsy (IPOE). To further elucidate whether visual sensory gating mechanisms are impaired in paediatric patients with photosensitivity associated with IGE we investigated visual habituation - a direct measure of excitability of the visual cortex - in 57 children: 19 with Photosensitive Epilepsy (PS), 21 normally developing children (ND) and 17 with IGE without photosensitivity. The choice of this paradigm was motivated by its relative ease of administration in paediatric age, whilst retaining physiological specificity.

Methods: Stimuli consisted of a full-field black-and-white checkerboard pattern, reversing at 3/second with a 100% contrast presented binocularly for 600 consecutive trials. Trials were averaged off-line in six sequential blocks of 100 responses and analysed separately. Peak latencies of the N75, P100 and N145 components of the visual Evoked Potential (VEP) and N75-P100, P100-N145 inter-peak amplitudes were measured. Habituation was expressed as the percentage change of amplitudes between the first and the subsequent blocks.

Results: Statistical analysis revealed differences between the three groups in the slope index of N75-P100 amplitude, with increased or constant amplitude of this component in the PS group across the 6 blocks with respect to the IGE and ND.

Conclusions: Our findings support the view that photosensitivity is associated with altered control of excitatory and inhibitory cortical processes and a compensatory mechanism of visual gating control.

2.2 Objectives

Considering the epileptic brain "experimentum naturae" of altered balance between excitatory and inhibitory mechanisms and linking with previous findings on the lack of sensory gating as a peculiar trait of focal epilepsy of the occipital lobe with photosensitivity (Porciatti et al., 2000), we set out to investigate the role of cortical excitability in generalised epilepsy syndromes with photosensitivity. We chose visual habituation as a probe due to its ability to demonstrate alteration in the excitability of occipital cortex requiring a relatively simple experimental setting, which makes it appropriate for routine clinical testing. We investigated whether paediatric patients with photosensitive epilepsy presented a derangement of visual sensory gating with respect to normally developing children and patients with idiopathic generalised epilepsies.

2.3 Background

2.3.1 Habituation

2.3.1.1 Definition

" A fox who had never yet seen a lion, when he fell in with him for the first time in the forest was so frightened the he was near dying with fear. On his meeting with him for the second time, he was still much alarmed, but not the same extent as at first. On seeing him the third time, he so

increased in boldness the he went up to him and commenced a familiar conversation with him"

(From "The fox and the lion", Esopo's Fables, cited in Thompson, 2009)

Habituation (etymologically "to become used to") is defined as a behavioural response decrement resulting from exposure to repeated stimulation, which does not involve sensory adaptation/sensory fatigue or motor fatigue (Rankin et al, 2009). Behavioural responses that undergo habituation may include any final output of the nervous system (simple reflexes, motor neuron activity, and hormone release). It is difficult to determine who first used the term habituation in a scientific context; experimental observations of the phenomenon of habituation to a variety of stimuli in a wide range of organisms - from amoebas to humans - had an exponential growth in the late 19th and early 20th centuries. It became generally agreed that habituation was a central phenomenon and an instance of elementary learning (Humprey, 1933; Harris, 1943). Modern interest in habituation commenced with an influential paper of Sharpless and Jasper (1956) on habituation of EEG arousal. Using repeated presentations of brief acoustic tones, they found that cortical EEG arousal of the normally sleeping cat became progressively shorter and finally disappeared. After cessation of stimulation the arousal response exhibited spontaneous recovery over a period of minutes or hours. A further study on the human alpha blocking response, which mimics EEG arousal in the cat, shown it habituated to tactile, auditory, and visual stimulation (Sokolov at al., 1960). In 1966 Thompson and Spencer

(1966) overviewed the already very extensive behavioural literature on habituation and identified nine basic properties or characteristics exhibited by behavioural habituation. In a recent revision of habituation characteristics an additional one was added (Rankin et al., 2009).

2.3.1.2 Characteristics of habituation

Characteristic 1. Repeated application of a stimulus results in a progressive decrease in some parameter of the response to an asymptotic level. This change may include decreases in frequency and/or magnitude of the response. In many cases, the decrement is exponential, but it may also be linear; in addition, a response may show facilitation prior to decrementing because of (or presumably derived from) a simultaneous process of sensitisation.

Characteristic 2. If the stimulus is withheld after response decrement, the response recovers at least partially over the observation time (‘‘spontaneous recovery”).

Characteristic 3. After multiple series of stimulus repetitions and spontaneous recoveries, the response decrement becomes successively more rapid and/or more pronounced (this phenomenon can be called potentiation of habituation).

Characteristic 4. Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery (if the decrement has reached asymptotic levels).

Characteristic 5. Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioural response decrement. Very intense stimuli may yield no significant observable response decrement.

Characteristic 6. The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level (which may or may not be zero, or no response). This effect of stimulation beyond asymptotic levels can alter subsequent behaviour, for example, by delaying the onset of spontaneous recovery.

Characteristic 7. Within the same stimulus modality, the response decrement shows some stimulus specificity. To test for stimulus specificity/stimulus generalisation a second, novel, stimulus is presented and a comparison is made between changes in the responses to the habituated stimulus and changes in response to the novel one.

Characteristic 8. Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed ‘‘dishabituation.” It is important to note that the proper test for dishabituation demonstrates an increase in response to the original and not to the dishabituating stimulus. Indeed, the dishabituating stimulus by itself need not even trigger the response on its own.

Characteristic 9. Upon repeated application of the dishabituating stimulus, we observe a decrease in the amount of dishabituation (this phenomenon can be called habituation of dishabituation).

Characteristic 10. Some stimulus repetition protocols may result in properties of the response decrement (e.g. more rapid re-habituation than baseline, smaller initial responses than baseline, smaller mean responses than baseline, less frequent responses than baseline) that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.

2.3.1.3 Theories of habituation

A number of theories concerning the process of habituation have been proposed over the years to explain the phenomenon as a form of non-associative learning. The three most popular theories have been:

1) *Stimulus-Model Comparator Theory*

2) *Wagner-Konorski Gnosic Unit Theory*

3) *Groves and Thompson Dual Process Theory*

1) Stimulus-Model Comparator Theory (Sokolov, 1960): the basic notion is that as a result of repeated stimulation, a stimulus model is formed in the brain at the cortical level. An amplifying system is responsible of modifying behavioural output. A novel stimulus will result in a large orienting response, mediated by the amplifying system, identified with the ascending reticular activity system in lower brain regions. With stimulus repetition and model development increasing inhibition of the amplifying system takes place via descending corticofugal connections, resulting in habituation. If a new or altered stimulus which does not match the

model occurs, then the inhibition is removed and response strength recovers accordingly.

2) *Wagner-Konorski Gnosic Unit Theory* (Konorski, 1967): the basic of this model is that a stimulus is processed through afferent connections and projects to a memory system, the Gnosic assembly, and to the arousal system. Since the stimulus is repeated, a gnosic unit is formed, an accurate neuronal model or memory of the stimulus. This model activates an inhibitory system with inhibits the arousal system, resulting in habituation. Subsequently Wagner (1979) added the concepts of the reverberating circuit of transient memory and the influence of the pre-existing associative network .

3) *Groves and Thompson Dual Process Theory* (Groves and Thompson, 1970; 1973): the basic assumption is that any effective stimulus will result in two independent processes in the central nervous system, one decremental (habituation) and one incremental (sensitisation) that interact. Strong supporting evidence for this theory came from studies of the activity of interneurons in the spinal cord .

These first theories and descriptions of habituation focussed primarily on reflex-type responses; more recent definitions, however, expanded the notion of habituation to a wider set of response types, including responses to conditioning paradigms in behavioural psychology, response to stress of the hypothalamic-pituitary-adrenal axis response

to stress and the notion of habituation as decrement of event related potentials in neurophysiology. The latter definition of habituation as decrement of event related potentials will be adopted as the reference definition in the remainder of this thesis work.

2.3.1.4 Visual habituation

In the visual domain habituation can be quantified using the amplitude reduction of the visual evoked response to sequential presentation of spatially structured visual stimuli. Neural mechanisms of visual habituation are normally present during the first month of life, and its emergence can be delayed in neurological conditions such as periventricular leukomalacia (González-Frankenberger et al., 2008). At cortical level habituation has been interpreted as a protective mechanism against over-stimulation, a direct measure of visual cortex excitability (Schoenen, 1996) and of sensory gating. Researchers have investigated habituation as an indirect neurophysiological method to detect the complexity of the so-called cortical excitability in different brain areas. Lack of habituation has been demonstrated in conditions characterised by alterations in cortical excitability such as migraine (Afra et al., 1998; Sandor et al., 1999; Oelkers-Ax et al., 2005; Coppola et al., 2007). In particular, some authors have noticed a lack of habituation during sustained stimulation in visual and auditory evoked potentials and auditory evoked potentials of patients affected by migraine with or without aura between attacks (Schoenen, 1996). More recent studies have shown that amplitudes of the N1-P1 and P1-N2 components decreased

(i.e. habituated) during repetitive stimulation in healthy volunteers while they remained unchanged or increased (i.e. potentiated) in migraineurs between attacks (Afra et al., 1998; Schoenen, 2003). The degree of the visual evoked potential habituation deficit was very similar in related parent-child pairs of migraineurs, which favours its familial, probably genetic, character and raised expectations of its role as an endo-phenotype (Sandor et al., 1999). These studies have been conducted mainly adults with migraine (Afra et al., 1998); in paediatric age findings have so far been contradictory (Sandor et al., 1999; Oelkers-Ax et al., 2005). Its application in epilepsy is still limited and no studies in paediatric photosensitivity are available. In a recent paper Siniatchkin et al. (2007) studied habituation in adults with PPR without motor manifestations, using visual evoked responses performed at low and high spatial frequency in subjects with different phenotypic expression of photoparoxysmal response. They reported an increase in VEP amplitudes independent of the spatial frequency of visual stimulation and a stronger habituation in subjects with propagating PPR compared with healthy controls and subjects without a propagating PPR. The authors interpreted these findings as a compensatory mechanism to stabilise excitability in the visual system.

2.4 Materials and methods

2.4.1 Subjects

Fifty-seven participants (33 males, mean age=12.8 years, SD=2.44, range 7-18) entered the study. The participants were recruited between

October 2008 and January 2009 at the Birmingham Children Hospital, and at the Neurophysiology Department of Aston University in Birmingham, UK and the Department of Child and Adolescent Neuropsychiatry “Istituto Casimiro Mondino”of Pavia, Italy. Nineteen (10 males, mean age=13, SD=1.97) had clinical photosensitivity and PPR on EEG, 17 (11 males, mean age=13.1, SD= 2.28) had an idiopathic generalised epilepsy without photosensitivity. Twenty-one normally developing (ND) children (12 males, mean age= 12.4, SD= 2.98) matched for age and gender, with no personal or family history of epileptic seizures, migraine (with or without aura) or other neurological disorder were recruited as controls. Participants in the IGE group received a syndromic diagnosis according to the International Classification and Terminology of Epileptic Syndromes (Engel, 2006). Nine of them presented idiopathic generalised epilepsy with absences, 8 were diagnosed with other idiopathic generalised epilepsy syndromes. Four were taking Valproate, 1 Lamotrigine, and 1 Ethosuximide.

Participants in the PS group presented a history of photoparoxysmal response and clinical photosensitivity but no clinical manifestations at the time of recording. Photoparoxysmal response was classified according to Waltz criteria (Waltz et al., 1992). In 9 subjects the PPR was of type II, 10 presented a propagating PPR type III-IV; 12 were taking Valproate at the time of recording. See Table 2.1 for details on sample characteristics and Figures 2.1-2.7 for details on EEG characteristics.

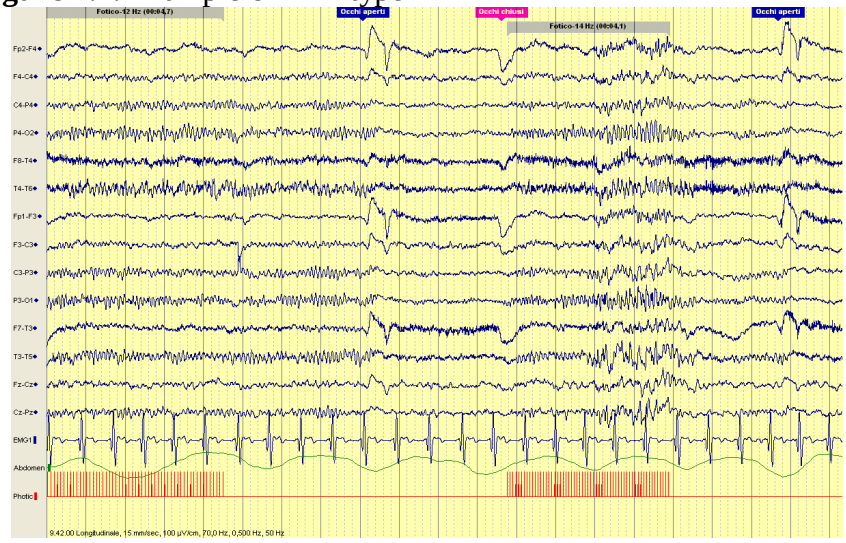
Informed consent was obtained from both the patients and their parents. The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the respective Institutions.

Table 2.1. Clinical data of PS and IGE patients

Variable	PS (n=19)	IGE (n=17)
Gender (F/M)	9/10	6/11
Mean age (SD) in years	13 (1.97)	13.1 (2.28)
Photosensitivity	100%	0%
Antiepileptic drugs		
None	37%	65%
One	63%	35%
Two or more	0%	0%
PPR		
I-II Type	47%	0%
III-IV Type	53%	0%

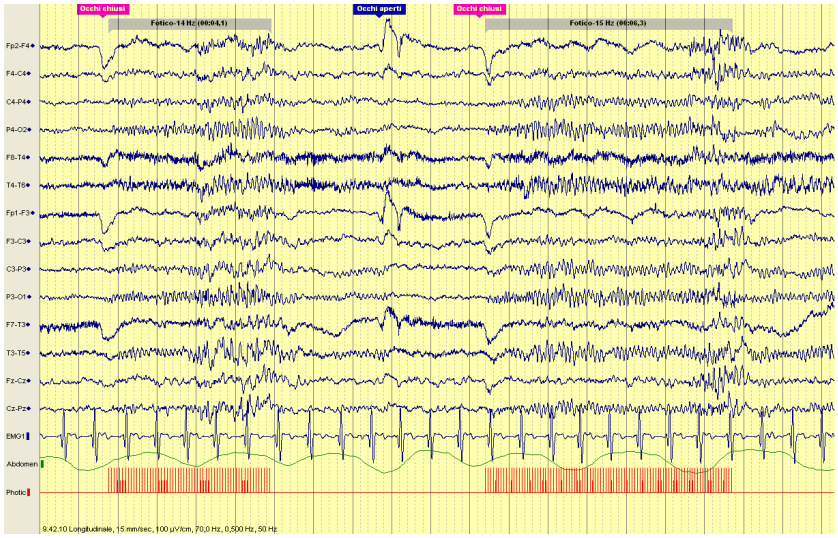
Source: Author

Figure 2.1. Example of PPR type 1-2



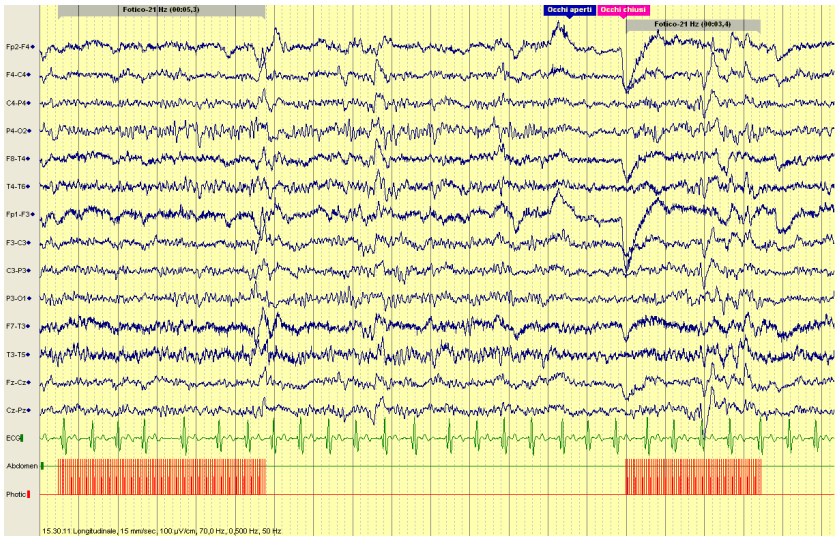
Source: Author

Figure 2.2. Example of PPR type 1-2



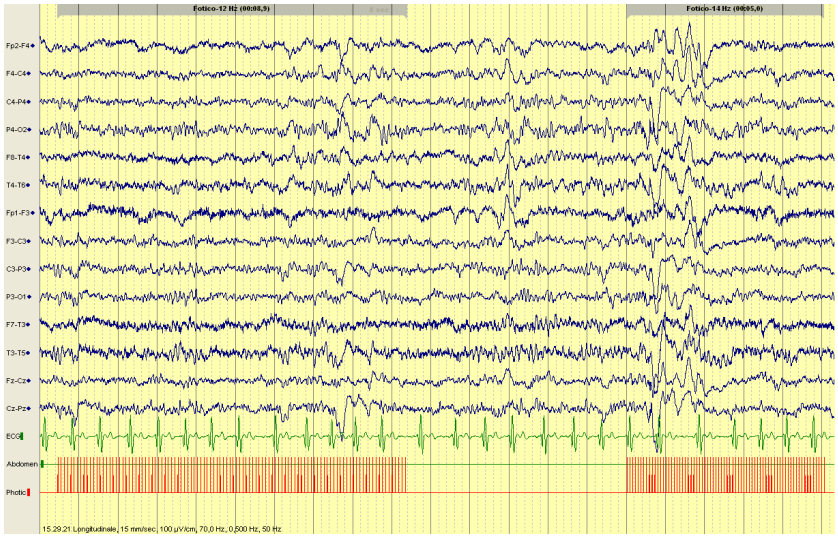
Source: Author

Figure 2.3. Example of PPR type 2



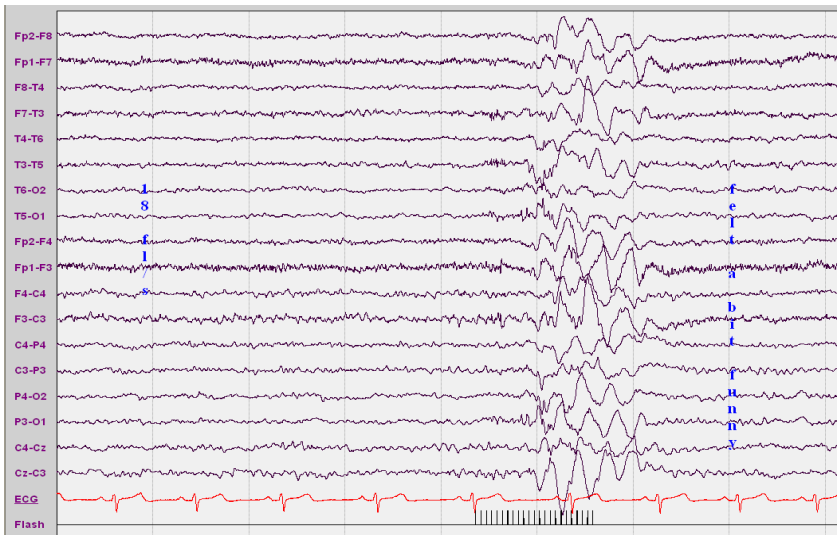
Source: Author

Figure 2.4. Example of PPR type 3



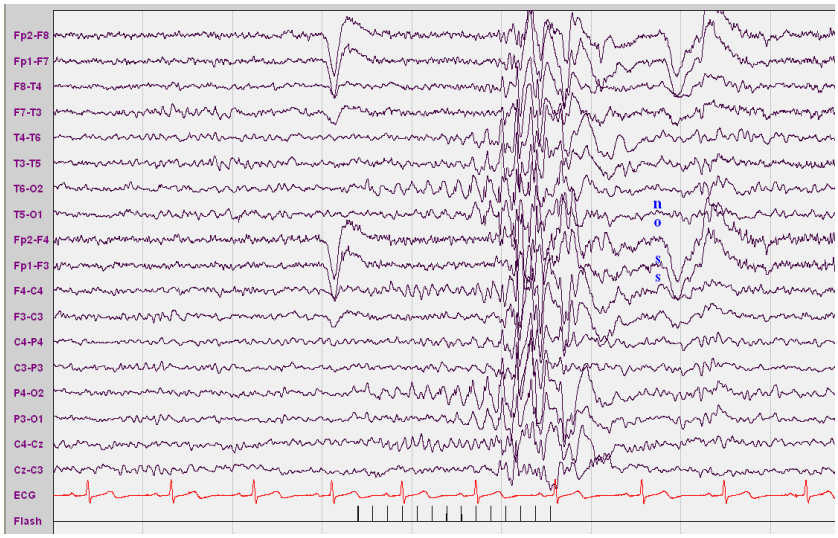
Source: Author

Figure 2.5. Example of PPR type 3-4



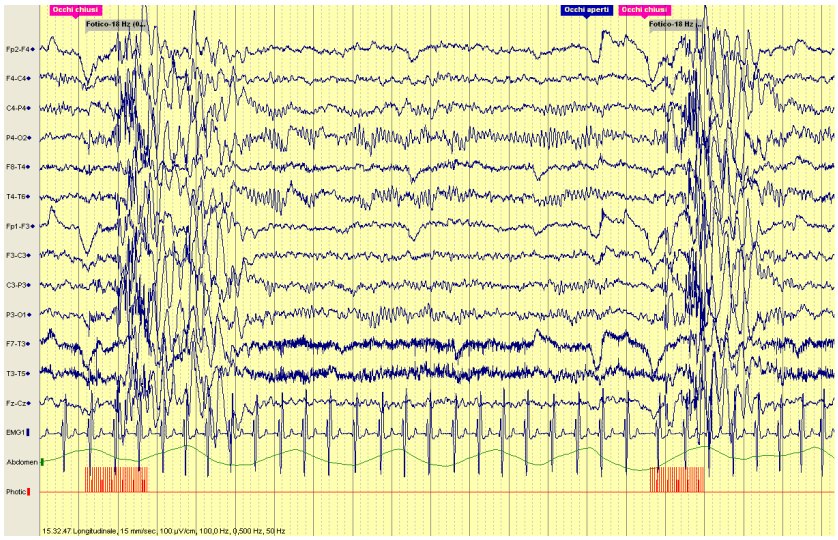
Source: Author

Figure 2.6. Example of PPR type 4



Source: Author

Figure 2.7. Example of PPR type 4



Source: Author

2.4.2 Data acquisition

The EEG recordings were performed using 21 Ag/AgCl disk electrodes attached to the scalp in the standard locations according to the international 10-20 system, including Oz and Fpz; a cephalic ground electrode was placed on Cz. Impedances were kept below 5KΩ for the duration of the recording. Two electro-oculographic channels were used to monitor eye movement. Photic stimulation was performed at least 15' prior to VEP recordings using a Grass PS 22 stimulator and consisted of ten-second periods of regular frequencies at 5, 10, 12, 15, 18, 20, 25, 50, 60 Hz. In accordance with recommended guidelines, subjects had their eyes opened during the first 5 seconds of each period of visual stimulation at a particular frequency and were then asked to close their eyes for remaining 5 seconds (Kasteleijn-Nolst Trenité et al., 1999b).

2.4.3 Visual habituation paradigm

Stimuli consisting of a full-field black-and-white checkerboard pattern subtending 15' of arc, reversing at 3/second with a 100% contrast were generated using a VSG 2-5 graphic stimulator (Cambridge Research Systems) and presented binocularly on a high-resolution CRT screen with a 120Hz refresh rate. Participants were seated at a distance of 1 m and instructed to fixate a 1 cm^2 dot placed in the centre of the screen. Eye movements were monitored by technical staff through a video camera positioned behind the video screen. The test consisted of 600 consecutive trials. Digital data was exported to European Digital Format (EDF) and analysed in the EEGLAB environment (Delorme and Makeig,

2004) under Matlab 7.5.0 R2007b (Mathworks Inc.), filtered using a high-pass filter of 1 Hz and low-pass filter of 100 Hz and segmented into epochs of 300 ms duration (from 50 ms pre- to 250 ms post-stimulus). The 50 ms pre-stimulus was used as baseline. Artefactual sources (eyes blinks, movements and 50 Hz) were rejected using Independent Component Analysis (Barbati et al, 2004; Porcaro et al, 2009). Trials were averaged off-line in six sequential blocks of 100 responses and analysed separately. Peak latencies of the N75, P100 and N145 components of the visual Evoked Potential (VEP) and N75-P100, P100-N145 inter-peak amplitudes were measured at Oz position of the international 10-20 system. See Tables 2.2 and 2.3 for raw latencies and amplitudes. Peaks were defined as the maximum negative or positive deflection in the following time ranges: 60–110 ms for N75, 90– 160 ms for P100, 130–210 ms for N145. Peaks were detected manually by a qualified neurophysiologist. Habituation was expressed as the percentage change of amplitudes between the first block and the subsequent ones.

Table 2.2. Raw latencies in ms for the three groups

LD.	Group	Lat 1° Block			Lat 2° Block			Lat 3° Block			Lat 4° Block			Lat 5° Block			Lat 6° Block		
		N75	P100	N145	N75	P100	N145	N75	P100	N145	N75	P100	N145	N75	P100	N145	N75	P100	N145
1	ND	73	109	185	79	107	153	67	109	148	71	110	147	64	112	151	75	106	155
2	ND	72	106	163	78	117	164	78	113	160	78	106	164	78	133	172	73	108	187
3	ND	68	106	129	70	113	125	70	113	156	68	110	131	68	107	131	70	109	133
4	ND	76	102	139	76	11	135	76	107	143	74	104	131	74	109	143	74	109	154
5	ND	73	107	123	70	104	137	76	104	141	76	106	129	76	102	145	74	107	139
6	ND	68	102	170	74	106	170	76	113	174	66	106	172	74	107	178	74	109	168
7	ND	72	129	164	72	104	152	74	104	164	72	100	164	74	102	162	68	98	158
8	ND	66	108	154	66	107	137	70	106	141	72	107	148	72	107	139	66	107	176
9	ND	72	129	172	68	109	176	72	133	174	68	129	172	68	133	176	66	135	174
10	ND	47	72	113	49	72	115	51	70	113	49	72	113	47	72	113	49	72	109
11	ND	74	102	117	72	100	117	74	102	117	74	102	117	74	102	119	74	100	117
12	ND	84	107	170	78	104	135	84	106	133	82	106	131	84	106	133	86	106	139
13	ND	66	109	133	64	111	152	63	107	170	64	107	172	68	107	154	66	110	155
14	ND	65	99	148	72	100	148	76	113	152	68	106	150	74	96	147	70	106	156
15	ND	78	112	186	75	115	134	82	113	158	79	116	133	80	112	167	80	105	197
16	ND	90	159	218	90	131	193	86	143	178	90	135	193	88	125	190	86	146	197
17	ND	70	98	156	61	106	163	68	105	165	74	117	164	66	101	165	66	101	165
18	ND	61	109	168	88	107	153	92	111	162	88	104	160	94	113	162	80	106	145
19	ND	59	102	186	61	100	131	61	102	111	61	100	119	68	102	117	68	102	117
20	ND	78	102	135	76	106	139	78	104	135	78	102	141	76	106	141	80	104	135
21	ND	65	102	169	68	104	135	64	102	131	66	104	133	64	104	129	65	100	159
22	IGE	65	88	106	65	87	105	68	88	106	70	86	129	72	101	160	53	126	159
23	IGE	78	113	148	75	112	140	199	116	188	78	114	155	78	116	150	78	115	151
24	IGE	62	98	174	63	102	171	66	100	168	71	99	174	68	107	169	64	93	167
25	IGE	82	147	194	78	137	184	82	152	184	86	152	180	82	141	188	49	98	100
26	IGE	59	106	152	76	104	143	70	104	143	74	104	154	76	104	145	68	106	154
27	IGE	73	94	123	64	107	170	67	107	166	63	90	143	66	104	154	74	97	126
28	IGE	72	113	160	63	115	158	68	115	158	74	117	164	66	117	164	80	123	160
29	IGE	70	102	117	70	104	137	66	102	127	70	104	137	68	104	123	66	106	135
30	IGE	51	82	158	72	96	133	64	107	133	64	108	133	68	107	170	63	100	169
31	IGE	74	106	143	70	104	145	72	106	150	76	104	141	74	106	137	74	107	141
32	IGE	78	107	166	74	109	164	78	107	164	74	106	170	81	104	166	74	107	160
33	IGE	61	86	148	66	86	149	66	86	137	63	84	154	64	88	166	59	82	164
34	IGE	53	78	100	53	80	100	55	76	100	53	76	98	55	78	98	59	78	98
35	IGE	72	98	121	74	100	125	78	98	123	76	98	121	74	98	121	78	100	121
36	IGE	72	98	121	74	100	125	78	98	123	76	98	121	74	98	121	78	100	121
37	IGE	47	97	127	66	98	127	63	96	127	70	96	131	68	96	129	66	98	117
38	IGE	51	74	110	55	72	111	55	74	107	51	74	113	55	72	109	55	72	109
39	PS	100	121	145	90	121	154	92	123	147	84	119	154	84	121	154	90	121	145
40	PS	80	106	133	78	109	129	78	107	127	78	107	133	78	104	127	78	106	129
41	PS	85	107	141	86	113	133	88	107	135	76	109	133	86	109	133	84	113	133
42	PS	68	106	156	74	107	150	68	115	166	74	113	139	70	107	147	74	115	145
43	PS	76	110	143	74	111	143	72	111	147	74	107	145	74	109	150	74	104	139
44	PS	80	111	131	72	111	127	80	111	131	68	115	133	78	115	133	80	115	135
45	PS	70	104	166	61	100	143	70	102	139	74	107	166	76	104	168	57	107	164
46	PS	76	109	170	51	100	137	51	100	137	82	106	135	82	106	135	86	106	121
47	PS	78	106	156	82	111	156	84	104	156	80	107	160	78	107	156	78	106	156
48	PS	76	100	129	78	102	135	78	104	127	76	102	141	78	104	131	78	106	133
49	PS	76	104	145	74	104	141	76	104	156	74	107	141	74	104	127	76	107	125
50	PS	71	101	171	68	96	174	65	92	178	65	96	171	66	98	171	63	95	174
51	PS	67	96	130	74	96	126	72	96	125	66	92	127	51	96	127	67	100	130
52	PS	75	113	141	75	114	147	43	110	162	47	109	142	47	109	142	47	109	142
53	PS	68	100	131	64	100	129	68	98	127	64	98	129	68	102	127	61	104	127
54	PS	64	98	131	59	102	145	88	100	148	84	100	133	88	100	135	61	104	127
55	PS	98	74	122	70	98	137	70	98	137	74	94	144	74	144	144	75	98	144
56	PS	76	98	170	74	109	174	72	109	174	70	106	178	72	107	176	66	107	174
57	PS	73	97	158	59	109	141	61	111	156	90	106	131	64	111	133	66	101	178

Source: Author

Table 2.3. Raw amplitudes in μV for the three groups

I.D.	Group	Amp 1° Block		Amp 2° Block		Amp 3° Block		Amp 4° Block		Amp 5° Block		Amp 6° Block	
		N75-P100	P100-N145	N75-P100	P100-N145	N75-P100	P100-N145	N75-P100	P100-N145	N75-P100	P100-N145	N75-P100	P100-N145
1	ND	12	16	16	18	19	14	16	17	13	13	16	13
2	ND	8	8	9	6	7	9	5	4	5	4	5	6
3	ND	11	10	7	8	9	11	2	2	2	2	3	3
4	ND	8	8	11	10	8	8	6	4	6	4	5	7
5	ND	8	13	7	7	7	8	3	8	6	3	5	6
6	ND	21	16	18	33	21	22	28	26	26	24	16	14
7	ND	10	11	8	9	10	8	5	5	6	7	7	6
8	ND	12	10	8	13	11	15	11	6	3	11	7	13
9	ND	27	23	28	24	27	27	26	23	31	25	26	26
10	ND	33	36	30	24	26	19	61	56	50	35	52	25
11	ND	14	13	15	15	13	12	4	5	4	4	4	3
12	ND	10	10	9	5	8	9	22	14	12	6	8	14
13	ND	20	14	16	15	17	17	14	27	32	29	21	26
14	ND	17	16	14	21	12	20	13	7	5	6	6	11
15	ND	8	11	6	7	8	8	6	2	4	1	5	5
16	ND	22	23	18	18	15	13	14	10	7	8	6	7
17	ND	16	10	12	12	11	11	8	10	10	10	8	8
18	ND	5	3	2	2	3	3	6	6	7	9	8	6
19	ND	5	5	5	4	4	3	1	1	1	1	1	1
20	ND	12	11	11	12	10	10	16	13	14	15	19	17
21	ND	9	13	9	11	11	9	14	7	6	5	7	11
22	IGE	9	7	8	8	0	1	9	6	8	6	0	0
23	IGE	31	35	27	27	35	33	16	9	23	14	16	15
24	IGE	8	17	13	7	16	10	12	22	17	15	17	16
25	IGE	13	11	12	9	7	2	15	12	12	12	11	1
26	IGE	13	9	11	14	9	2	10	10	10	11	11	15
27	IGE	11	9	5	6	6	6	10	10	9	8	7	12
28	IGE	6	11	9	10	11	5	6	12	8	9	8	2
29	IGE	11	13	11	10	12	12	4	8	6	6	4	4
30	IGE	5	5	8	2	7	5	8	6	7	8	12	8
31	IGE	29	29	31	27	30	36	20	23	22	20	17	19
32	IGE	17	20	19	17	18	18	16	19	17	15	14	14
33	IGE	8	6	7	6	5	6	16	15	16	18	18	18
34	IGE	11	7	6	8	5	5	9	7	8	9	8	9
35	IGE	18	17	15	16	13	15	25	21	18	22	20	19
36	IGE	18	17	15	16	13	15	25	21	18	22	20	19
37	IGE	13	14	10	9	10	7	12	19	18	23	19	8
38	IGE	13	15	16	14	10	10	17	25	22	18	20	20
39	PS	5	7	7	9	8	6	6	8	6	10	9	4
40	PS	11	11	4	14	14	15	7	3	4	5	6	5
41	PS	9	23	13	24	20	20	15	13	16	15	14	9
42	PS	7	5	8	5	4	5	6	5	8	3	5	4
43	PS	18	14	17	20	20	14	16	10	16	31	31	14
44	PS	5	5	4	8	7	7	6	4	4	3	5	5
45	PS	11	13	12	7	13	12	12	7	8	13	16	12
46	PS	8	15	15	7	7	9	5	15	12	11	11	4
47	PS	6	6	6	5	6	6	5	6	4	4	5	3
48	PS	7	8	9	9	9	9	3	4	4	4	5	5
49	PS	9	10	9	8	8	7	7	8	7	6	5	4
50	PS	6	11	8	9	11	8	8	12	8	10	10	9
51	PS	8	7	7	7	12	11	8	8	9	11	11	12
52	PS	10	10	6	23	17	17	12	10	9	19	8	8
53	PS	13	12	13	12	12	14	13	10	12	11	8	11
54	PS	7	12	6	4	3	10	13	14	11	10	10	10
55	PS	8	8	10	6	6	10	3	3	2	0	0	1
56	PS	7	11	15	11	12	12	6	15	13	10	10	11
57	PS	10	5	3	1	6	14	8	4	7	4	3	11

Source: Author

The choice of a temporal frequency of 3 reversals per second mainly reflects a careful review of the literature. Suggestions have been provided by a review of the paradigms used to study visual habituation and cortical excitability in migraineurs (Schoenen et al., 2003). Furthermore, previous investigations have shown that spatial frequencies between 0.5 and 6 cycles per degree are considered to be the most provocative triggers and

vertical and horizontal stripe patterns were found to be more likely to provoke PPR than grid patterns (Wilkins et al., 1975; 1979a). In addition, it has also been demonstrated that pattern reversal frequency does not constitute an important element in PPR induction (Funatsuka et al., 2001). Thus, the purpose of the study was to study the involvement of the occipital cortex and the neurophysiological basis of photosensitivity whilst minimising the risk of seizures precipitation in our subjects.

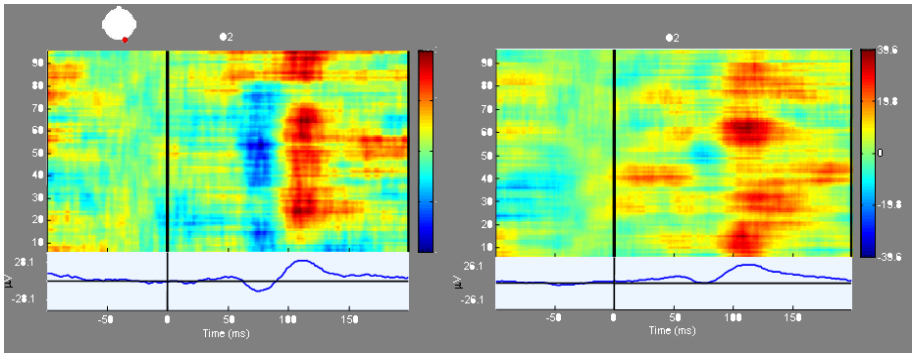
The duration of the paradigm (3 minutes and 20 seconds) was a compromise, in both practical and neurophysiological terms. From a review of the literature 600 stimuli seemed enough to activate visual habituation and at the same time this duration was acceptable for the sustained attention of a 7-years-old child. In so doing, a reasonable compliance was obtained. In terms of EEG analysis, the decision to select 50 ms prestimulus and 250 post stimulus was made to avoid an overlapping of the epochs.

2.4.4 Power calculation and statistical analysis

Study design was based upon data collected from an independent pilot group (10 ND, 10 IGE, and 10 PS), which was used to perform sample size calculation. Desired power was set at 0.80 and an α error of 0.05. Since our primary endpoint was to detect differences between ND, IGE, and PS, we used the slope index (see below for details) of N75-P100 peak amplitude of six blocks in the three groups (ND, mean (SD) = - 0.32 (0.72) ; IGE = - 0.58 (0.64); PS= 0.5 (0.6)) to calculate the sample size. Required sample size resulted to be 51 subjects, 17 for each group.

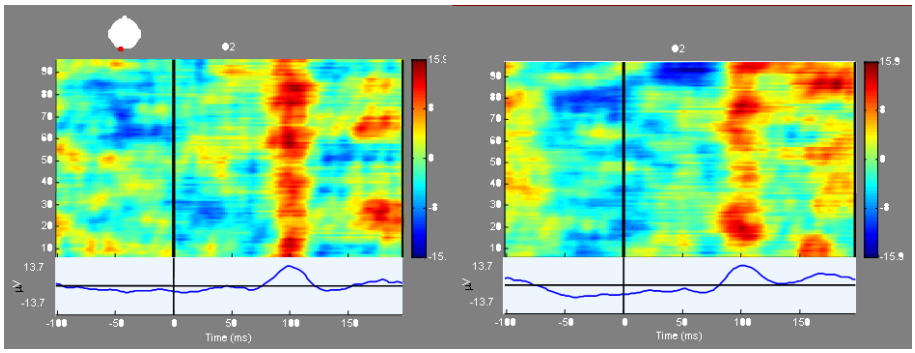
Descriptive analysis revealed that evaluated indices showed a non-normal distribution. All the variables were logarithmically transformed prior to statistical analysis, to achieve an appropriate equivalence to a normal distribution (Kolmogorov-Smirnov test, $p > 0.2$). Models of repeated measures analysis of variance (rm-ANOVA), followed by univariate ANOVAs, were employed to investigate the group effect (between-subject factor: ND *vs.* IGE *vs.* PS) on the six blocks (within-subjects factor: block 1 to block 6) for each PR-VEP measure. Univariate results were analysed whenever Wilks' Lambda multivariate criterion achieved statistical significance. The homogeneity of covariance was examined with Mauchley Sphericity Test. In the case of nonsphericity, Greenhouse-Geisser epsilon adjustment was used. As a measure of habituation we computed the slope of the linear regression line (as expressed by the formula: $y = mx + b$) of peak-to-peak amplitude values (N75-P100, P100-N145) and peak latencies (N75, P100, N145) for each subject over the six blocks (see Figures 2.8 and 2.9). This measure has the advantage of being relatively insensitive to individual variability. A negative slope of the regression line was indicative of habituation, whereas a positive slope was taken as an index of lack of habituation. Differences in slope among groups (ND *vs.* IGE *vs.* PS) were assessed using a one-way ANOVA, for amplitude and latency indices. Post hoc tests were performed with Bonferroni's confidence interval adjustment for multiple comparisons to define which variables contributed to the major effects. Statistical significance was set at $p < 0.05$.

Figure 2.8. PR-VEP from a ND subject



Notes: Left-hand box = first block; right-hand box = sixth block.
Source: Author

Figure 2.9. PR-VEP from a PS subject



Notes: Left-hand box = first block; right-hand box = sixth block.
Source: Author

2.5 Results

2.5.1 Basic statistics

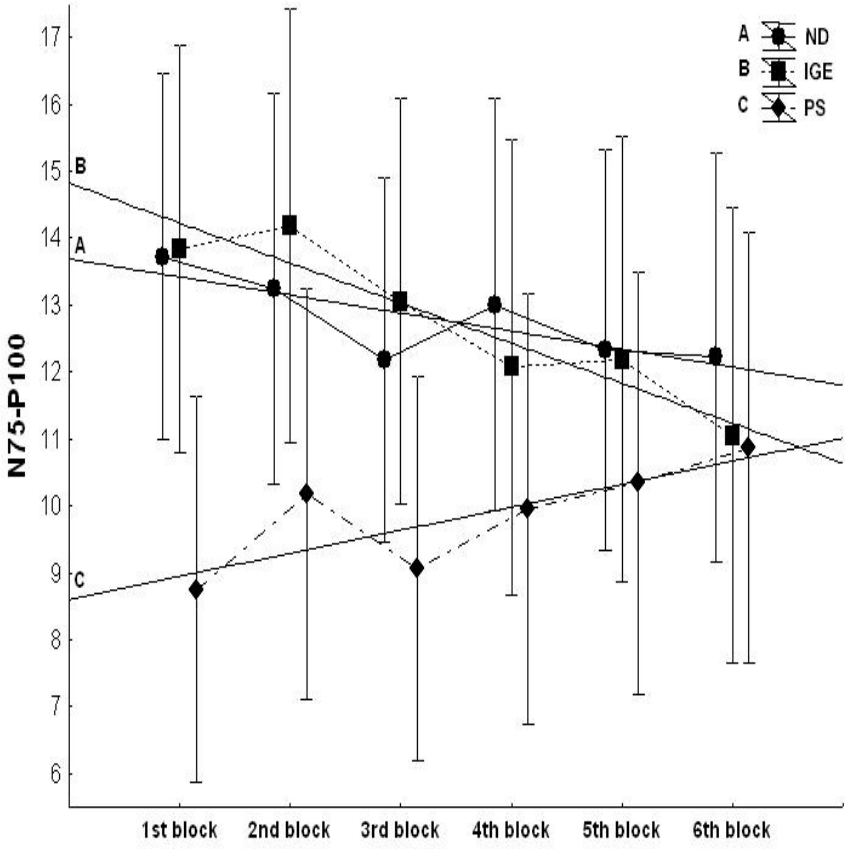
No significant difference between ND, IGE and PS was observed in gender (Chi-Square Test, two-tailed: $\chi^2 = 0.544$, df = 2, p = 0.76) and age (one-way ANOVA: $F_{2,54} = 0.333$, p = 0.72); IGE and PS did not differ significantly in drug use (Fisher's Exact Test, two-tailed: p = 0.08). No significant difference was found in the mean N75-P100 and P100- N145 peak-to-peak amplitudes (*t*-test, N75-P100: $t_{34} = -0.835$, p = 0.41; P100-N145: $t_{34} = -0.936$, p = 0.36) and slope indices (N75-P100 slope: $t_{34} = 0.159$, p = 0.87; P100-N145 slope: $t_{34} = -0.687$, p = 0.50) of the first block between the 24 patients (14 IGE and 10 PS) taking antiepileptic drugs at the time of recording and the 12 unmedicated patients (3 IGE and 9 PS).

2.5.2 Repeated measure ANOVA

Results of multivariate and univariate analyses on latencies and amplitudes of the PR-VEPs are summarised in Table 2.4. Repeated measure ANOVA model for N75-P100 revealed significant "Block" and "Block × Group" effects (Wilks' Lambda = 0.774, $F_{5,50}$ = 2.917, p = 0.02; Wilks' Lambda = 0.682, $F_{10,100}$ = 2.113, p = 0.03 respectively). Univariate repeated measure analyses showed non-significant "Block" effect ($F_{5,270}$ = 1.960, p < 0.09, ε = 0.807) and a significant "Block × Group" effect ($F_{10,270}$ = 2.926, p < 0.002, ε = 0.807). Univariate ANOVA on single blocks revealed significant differences between the three groups only in the first block of stimulation ($F_{2,54}$ = 4.395, p < 0.02), in which PS had lower N75-P100 amplitude than ND and IGE (post hoc tests: PS *vs.* ND, p < 0.04; PS *vs.* IGE, p = 0.04) (Figure 2.10).

In all other rm-ANOVA models, neither multivariate nor univariate tests for repeated measures reached the significance threshold.

Figure 2.10: Trend, means and standard deviations (in microvolts) of the N75-P100 amplitude of the pattern reversal VEP across the six blocks.



Notes: ND: normally developing; IGE: idiopathic generalised epilepsy; PS: photosensitive epilepsy.
Source: Author

Table 2.4. Results of repeated measure ANOVA models.

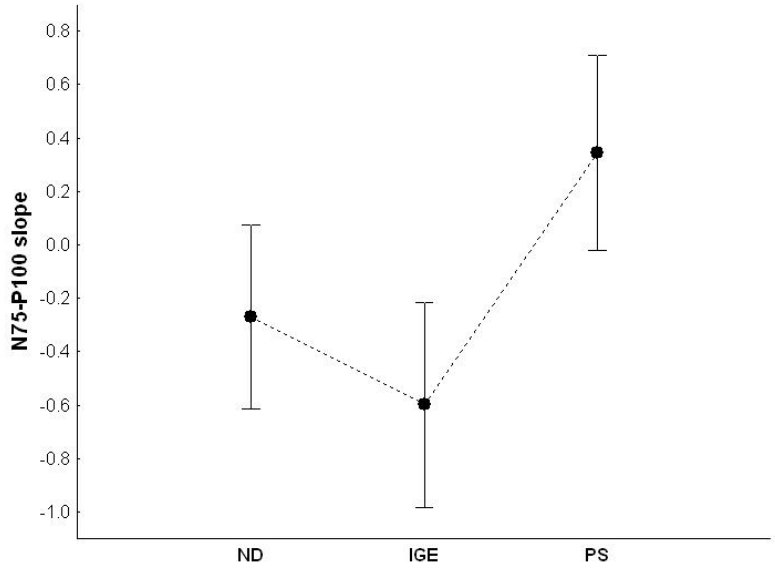
	Multivariate tests for repeated measures								Univariate tests for repeated measures					
	Block effect				Block x Group effect				Group effect			Block effect			Block x Group effect		
Measure	Wilks'λ	F	df	p	Wilks'λ	F	df	p	F	df	p	F	df	p	F	df	p
N75-P100 Amp	**0.774**	**2.917**	**5,50**	**0.02**	**0.682**	**2.113**	**10,100**	**0.03**	**1.244**	**2,54**	**0.30**	**1.960**	**5,270**	**0.09**	**2.926**	**10,270**	**<0.002**
P100-N145 Amp	0.935	0.691	5,50	0.63	0.882	0.654	10,100	0.76	2.232	2,54	0.12	1.555	5,270	0.17	0.658	10,270	0.76
N75 Lat	0.918	0.895	5,50	0.49	0.782	1.311	10,100	0.24	0.869	2,54	0.43	1.385	5,270	0.23	1.479	10,270	0.15
P100 Lat	0.903	1.075	5,50	0.39	0.863	0.763	10,100	0.66	1.288	2,54	0.28	1.222	5,270	0.30	0.971	10,270	0.47
N145 Lat	0.868	1.516	5,50	0.20	0.811	1.107	10,100	0.36	1.532	2,54	0.23	0.697	5,270	0.63	1.341	10,270	0.21

Note: Significant effects ($p<.05$) presented in bold.
Source: Author

2.5.3 Slope

One-way ANOVA revealed differences between the three groups (Figure 2.11) in the N75-P100 amplitude slope index ($F_{2,54} = 6.691$, $p < 0.003$) with PS presenting higher slope values than ND and IGE (post hoc tests: PS *vs.* ND, $p < 0.05$; PS *vs.* IGE, $p < 0.002$; ND *vs.* IGE, $p = 0.62$). Tests for all other slope measures were not significant (P100-N175 amplitude: $F_{2,54} = 0.881$, $p = 0.42$; N75 latency: $F_{2,54} = 1.485$, $p = 0.24$; P100 latency: $F_{2,54} = 0.192$, $p = 0.83$; N145 latency: $F_{2,54} = 0.022$, $p = 0.978$).

Figure 2.11: Slope of the interpeak amplitude N75-P100 for the three groups.



Notes: ND: normally developing; IGE: idiopathic generalised epilepsy; PS: photosensitive epilepsy.
Source: Author

2.6 Discussion

In recent years there has been an increasing interest in understanding the molecular mechanisms of photosensitivity. Two susceptibility loci have been reported on chromosomes 7q32 and 16p13 encoding Gamma Aminobutyric Acid (GABA) receptor subunits (Stephani et al., 2004; Pinto et al., 2007); this finding has been used to suggest that the photosensitivity could be an expression of GABA-mediated changes in cortical excitability. However, previous studies have suggested that a range of pathophysiological mechanisms might underpin the electro-clinical correlates of the photo-paroxysmal response (Harding and Fylan, 1999; Takahashi et al., 1999). This would suggest that sub-typing based on physiologically meaningful measures – intermediate phenotypes – might be desirable to increase the yield of future genetic studies. In this respect, visual habituation is a reliable and easily obtainable measure of excitability of the visual cortex; in the normally developing child its neural mechanisms emerge during the first months of life and can be delayed in neurological conditions (González-Frankenberger et al., 2008). Our study suggests that photosensitivity is associated with changes in cortical excitability and these changes are not present in patients with idiopathic epilepsies without photosensitivity. This might imply that, in spite the strong phenotypic association in specific epileptic syndromes, the two traits are the expression of separate genetic substrate, as hypothesised in accordance to early genetic evidence from familial studies (Doose and Gerken, 1973).

The only available study with comparable paradigm in adult patients (Siniatchkin et al., 2007), on subjects with a rather different phenotypic expression of visual sensitivity and no history of overt seizures, reported a stronger habituation in subjects with propagating PPR compared to subjects with a non-propagating PPR and healthy controls. However, a direct comparison with this study is inappropriate, as our sample presents salient differences in terms of case definition and age.

The reduced N75–P100 inter-peak amplitude of the first block of 100 stimuli in the PS compared to the other two groups, independent of drug treatment, is a novel finding. Its interpretation must take into account factors like the wide variability of PR-VEP amplitude in normative studies (Cigànek, 1969; Sokol and Jones, 1979). Data on young patients with epilepsy are equally controversial, some studies reporting normal amplitude (Lucking et al., 1970; Martinovic et al., 1990; Verrotti et al., 2000), others increased amplitude (Faught and Lee, 1984; Genç et al., 2005). In IPOE, an increased steady state VEPs amplitude was detected (Porciatti et al., 2000). In adults with propagating PPR, increased PR-VEP amplitudes in N75-P100 and P100-N145 components were found (Siniatchkin et al., 2007). Paradigms comparable to the one used in this study have been used in migraine research and have shown impaired visual gating control in migraineurs (Schoenen et al., 2003) but findings are still contradictory. Some authors have demonstrated that the higher the excitatory drive to the cortex, the larger the VEP amplitudes in the first block of recording, and the more pronounced the VEP habituation

(Schoenen, 1996; Afra et al., 1998; Bohotin et al., 2002). In this sense, a measure of amplitude change relative to baseline such as the slope of the VEP amplitude over time used in our study has the theoretical advantage of being a more robust indicator of the underlying cortical processes. From a pathophysiological point of view, and in analogy with previous findings on migraineurs patients, we could postulate that high-amplitude PR-VEP can be attributed to hyperexcitability of the occipital cortex with increased neuronal synchronisation and habituation to a mechanism to compensate the baseline level of hyperexcitability. In analogy with data reported in patients with migraine (Fumal et al., 2006) the baseline hypoexcitability we found in photosensitive patients, expressed by lower N75-P100 VEP amplitudes in the first block of stimulation, can itself play a role in the habituation deficit. A further study (Afra et al., 2000) noticed that VEP potentiation was negatively correlated with amplitude in the first block of averaged responses, suggesting that the lack of habituation in migraine might be due to a decreased cortical preactivation level. Although habituation of visually evoked potentials is a complex neurobiological phenomenon, it might be connected to preactivation excitability levels. As suggested by Schoenen et al. (2003) in agreement with the 'ceiling theory' (Knott and Irwin, 1973) a low preactivation level of sensory pathways allows a wider range of suprathreshold activation before reaching the 'ceiling' and initiating a 'reducing' response, i.e. habituation. This theory applied to the VEP findings in our study would explain both the low first block amplitude and the lack of

habituation on trial repetition. There is evidence that loci on chromosomes 7q32 and 16p13, which encode GABA receptor subunits, are involved in photosensitivity (Stephani et al., 2004; Pinto et al., 2007). If we assume that the preactivation level of cortical excitability depends on the activity of inhibitory circuits, such GABA level, serotonin and noradrenalin, a dysregulation of these transmitters could lead to an alteration of the cortical excitability and explain the observed electrophysiological abnormalities. More plausible would be to interpret the reduced amplitude of the first block in light of the extensive electrophysiological evidence of increased inhibitory activity in epileptic cortex, both at a synaptic and non-synaptic level (De Curtis and Avanzini, 2001). The reduced amplitude of the VEP to the first 100 stimuli in our PS sample could be explained considering two alternative hypotheses. Intracranial studies in human epilepsy have suggested that interictal epileptiform activity is associated with inhibition in the cortical region of ictal onset and in the surrounding areas (Gumnit and Takahashi, 1965; De Curtis et al., 2005). Neuroimaging data of reduced activation of the occipital cortex to visual stimuli both in animal models of photosensitivity (Szabó et al., 2007) and in epileptic patients (Masuoka et al., 1999) support the notion of a reduced pre-activation level of occipital cortex and could better account for the apparent discordance between reduced amplitude of the first block and lack of habituation in subsequent blocks. A further possible explanation involves a disruption of the physiological thalamic regulation of cortico-cortical synchronisation.

According to this model, reduced cortico-thalamic input can produce excess inhibition or disfacilitation, generating thalamic cell membrane hyperpolarisation and low-frequency oscillations (Llinás et al., 1999). The possible role of altered thalamocortical mechanisms in photosensitivity is indirectly supported by evidence of bilateral grey matter volume reduction in the thalamus and occipital cortex in photosensitive patients with JME, not seen in JME without photosensitivity (Lin et al., 2009).

Understanding whether the suppression of PR-VEP might be considered an endo-phenotype of photosensitivity or the expression of the insult produced by repetitive epileptiform discharges during the natural history of the condition would require longitudinal studies involving also family members. However, cross-sectional studies in migraine have shown age-dependent reduction in visual habituation, interpreted as the result of disturbed maturational processes, and lack of habituation not correlated with duration or severity of the disease. This has been interpreted as indicative that the deficient visual habituation is a congenital feature (Oelkers-Ax et al., 2005). In analogy with these findings, and taking into account the relatively young age of our cohort and short time between identification of clinical symptoms of photosensitivity and the neurophysiological measures, we have some grounds to hypothesise that the observed changes are likely to reflect the underlying biological substrate rather than being secondary to duration of the electro-clinical abnormalities

Regarding latencies, we found increased latency of the N75 VEP component, which however did not reach statistical significance. In previous literature, prolonged PR-VEP peak latencies were reported in treated patients with progressive myoclonus epilepsy (Mervaala et al., 1986), focal and generalised seizures (Drake et al., 1989), complex partial seizures (Mervaala et al., 1989), and other types of epilepsy (Mervaala et al., 1986; Cosi et al., 1989). In the photosensitive population, findings from other studies (Porciatti et al., 2000; Siniatchkin et al., 2007) seem to suggest no remarkable differences in latencies in photosensitive patients compared to healthy controls. At this moment there is no agreement about VEP latencies in epilepsy.

2.7 Conclusions

In conclusion, our findings have provided supportive evidence to the notion that photosensitivity is associated with altered balance between excitatory and inhibitory cortical processes. Even if a strong association exists between specific epilepsy syndromes and visual sensitivity, the photosensitivity trait seems to be the expression of specific pathophysiological mechanisms, of which the habituation of PR-VEP is one of the intermediate phenotypes.

Chapter 3

Pre-stimulus alpha power, VEP amplitude and cortical excitability

3.1 Abstract

Purpose: Based on the findings of the first study, a second study was designed to further explore mechanisms underlying the reduced amplitude of the N75-P100 VEP component in the first block of stimulation in PS group. We focussed on the relationship between measures of visual habituation, VEP amplitude and spectral properties of pre-stimulus ongoing brain activity.

Background: research on human visual cortex has extensively investigated the relationship between pre-stimulus alpha activity and the subsequent event-related potential (ERP). The phase reset model suggests that ERP is generated as a result of stimulus-triggered alpha-phase realignment and that a positive correlation exists between the pre-stimulus alpha power and the magnitude of early visual-evoked response (Makeig et al., 2002; Hanslmayr et al., 2007). Furthermore, studies which explored the relationship between oscillatory activity in the alpha band and visual brain function have suggested that decreased alpha power reflects a state of enhanced cortical excitability, while an increased alpha power reflects a state of reduced cortical excitability (Pfurtscheller, 1992; 2001; Ploner et al., 2006).

Materials and methods: EEG data collected during the first study were utilised to perform spectral analysis of the resting period immediately preceding the onset of visual stimulation. Each 4 sec pre-stimulus EEG epoch was Fast Fourier Transformed (FFT) and the power

spectrum was computed. Relative power in each of the traditional EEG bands was then calculated as the ratio of the absolute power in each band over the absolute power in the interval 1-40 Hz (delta, theta, alpha, beta, and gamma). The frequency bands used were delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-12 Hz; beta: 12-20 Hz and gamma: 20-40 Hz. Correlation and multiple regression analyses were performed to investigate the relationship between absolute and relative power of the frequency bands, in particular alpha, and the amplitude of the first block of stimulation.

Results: the results of this study indicate a positive relationship between both absolute and relative pre-stimulus relative alpha power and N75-P100 VEP amplitude in the first block of stimulation; such relationship appears to be significant both in correlation and in multiple regression analysis (where all frequency bands, subjects' group membership and drug treatment are controlled for).

Conclusions: this finding supports previous literature and provides supplementary evidence of an alteration of excitatory and inhibitory mechanisms in photosensitive occipital cortex.

3.2 Objectives

The aim of the present study is to shed light on the mechanisms underlying reduced amplitude of the visual evoked potential in patients with photosensitivity, and to examine whether this amplitudes correlates with prestimulus ongoing brain activity.

3.3 Background

3.3.1 Posterior alpha oscillations

The posterior alpha oscillations (8-12 Hz) are the most prominent oscillation activity during wakeful rest. Although they are believed to originate from occipito-parietal areas (Berger, 1929; Adrian and Matthews, 1934; Hari et al., 1997) and to reflect the spontaneous rhythm of visual areas, a general agreement regarding their genesis is still lacking. Early research on the origin of posterior oscillatory activity was focussed on the pacemaking role of the thalamus. In the eyes-closed condition, healthy subjects show a correlation between alpha power in posterior regions and relative cerebral blood flow (rCBF). Posterior alpha oscillations have been associated with an increase of rCBF in the right thalamic regions, limbic system and frontal cortex and also with a decrease of rCBF in primary and associative visual areas, as well as the dorsomedial prefrontal cortex (Sadato et al.,, 1998). Animal and human data have supported the involvement of thalamus and parieto-occipital regions in the generation of alpha rhythm (Lopes Da Silva and Storm Van Leeuwen, 1977; Lopes da Silva et al., 1980). Subsequent studies have suggested a cortical origin of alpha oscillations. More recently, primate data supported multiple local cortical generators of alpha oscillations in the V2-V4 extrastriate areas, with a primary local pacemaker at the level of layer 5 and demonstrated that the activity of the generators is highly synchronised (Bollimunta et al., 2008).

In human visual cortex the relationship between pre-stimulus alpha activity and the subsequent event-related potential (ERP) has been subject to extensive investigation. The phase reset model hypothesises that the ERP is generated as a result of stimulus-triggered alpha-phase realignment, and predicts a positive correlation between the pre-stimulus alpha power and the magnitude of early visual-evoked response (Makeig et al, 2002; Hanslmayr et al., 2007). Correlations between the pre-stimulus alpha power and the amplitude and latency of the following evoked response have also been described. In particular, alpha power was found to correlate with he overall VEP peak-to-peak amplitude within the first 250 msec post stimulus (Rodin et al., 1965); subsequently several authors (Basar, 1983; Brandt et al., 1991; Brandt and Jansen, 1991; Jansen and Brandt, 1991; Basar and Schurmann, 1994) identified a positive correlation between pre-stimulus EEG amplitude and evoked potential amplitude. These results are interpreted as a reflection of the neural energy state existing prior to the presentation of the external stimulus. In the auditory domain both direct (Rahn and Basar, 1993; Brandt, 1997) and inverse (Romani et al., 1988) relationships between pre-stimulus EEG activity and evoked responses have also been reported. These contradictory findings have been interpreted as due to differences in methodologies; in many cases, in fact, the background EEG and the Evoked Response were recorded at different times. Furthermore, studies on relationship between oscillatory activity in the alpha band and visual brain function have also suggested that reduced alpha activity reflects a

state of enhanced cortical excitability, while increased alpha power a state in which cortical excitability is reduced (Pfurtscheller, 2001; 1992; Ploner et al., 2006). Even though available data come from studies on healthy adults, pre-stimulus spectral measures seem suitable as a further probe of excitation/inhibition imbalance in clinical settings.

3.4 Materials and methods

3.4.1 Subjects

Of the 57 children recruited in the previously reported study, data from 52 participants (31 males, mean age = 12.9 years, SD = 2.28, range 7–17 years) were included in the analysis; 5 cases were thus excluded because artefacts in the pre-stimulus epoch could not be reliably removed. Seventeen subjects (8 males; mean age = 13.1, SD = 1.93) had visually induced seizures plus PPR or PPR only; the association with spontaneous seizures was not an exclusion criterion. Sixteen participants (10 males; mean age = 13.3, SD = 2.20) had idiopathic generalised epilepsy without photosensitivity. Nineteen normally developing (ND) children (9 males; mean age = 12.4 years, SD = 2.65) matched for age and gender, with no personal or family history of epileptic seizures, migraine (with or without aura) or other neurological disorder were recruited as controls. Participants in the idiopathic generalised epilepsy (IGE) group received a syndromic diagnosis according to the International Classification and Terminology of Epileptic Syndromes (Engel, 2006). Eight of them presented idiopathic generalised epilepsy with absences, 8 were diagnosed with other idiopathic generalised

epilepsy syndromes. Four were taking Valproate, 1 Lamotrigine, and 1 Ethosuximide at the time of recording. Participants in the photosensitive (PS) group presented a history of photo-paroxysmal response and clinical photosensitivity but no clinical manifestations in the week prior to recording or during the procedure. Photoparoxysmal response was classified according to Waltz criteria (Waltz et al., 1992). In 8 subjects the PPR was of type I and II, 9 subjects presented a propagating PPR type III and IV; 10 subjects were taking Valproate at the time of the recording. Informed consent was obtained from both the patients and their parents. The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the respective Institutions.

3.4.2 Data acquisition

The EEG recordings were performed using 21 Ag/AgCl disk electrodes attached to the scalp in the standard locations according to the international 10–20 system, including Oz and Fpz. A cephalic ground electrode was placed half-way between Fz and Cz. Impedances were kept below 5 KOhm for the duration of the recording. Two electro-oculographic channels were used to monitor eye movement. Data was acquired using a Micromed digital polygraphic system and stored on hard-disk for off-line analysis. IPS was performed at least 15’ prior to the pattern reversal visual evoked potential (PR-VEP) recordings using a Grass PS 22 stimulator. The protocol consisted of 10 sec stimulus trains at 5, 10, 12, 15, 18, 20, 25, 50 flashes/s. In accordance with

recommended guidelines, subjects had their eyes opened during the first 5 sec of each period of visual stimulation at a particular frequency, and were then asked to close their eyes for the remaining 5 sec (Kasteleijn-Nolst Trenité et al., 1999).

Stimulus consisted of a full-field black-and-white checkerboard pattern subtending 15' of arc, reversing at 3 reversal/s with 100% contrast. Stimulus was generated using a VSG 2–5 graphic stimulator (Cambridge Research Systems) and presented binocularly on a high-resolution CRT screen with a 120 Hz refresh rate. Participants were seated at a distance of 1 m and instructed to fix a 1 cm^2 dot placed in the centre of the screen. Eye movements were monitored by technical staff through a video camera positioned behind the video screen. For each patient 10 sec of rest EEG was recorded before starting the visual stimulation.

3.4.3 Data processing for pre-stimulus analysis

Digital data was exported to EDF, converted into the NPX data format (Neurophysiological signals in Extensible Markup Language) and analysed in the NPXLab environment (Bianchi et al., 2007). NPXLab is a software tool for the processing and analysis of physiological data stored using the XML format: it allows performing spectral analysis, to extract ERP from EEG data, to perform statistical analysis and the Independent Component Analysis. Data were digitally band-pass filtered between 1 and 100 Hz and segmented into 300 ms epochs (from 50 ms pre- to 250 ms post-stimulus). The 50 ms pre stimulus was used as baseline. Trials

were averaged off-line in six sequential blocks of 100 responses and analysed separately. Peak latencies of the N75, P100 and N145 components of the PR-VEP and N75–P100, P100–N145 inter-peak amplitudes were measured at Oz position of the international 10–20 system. Peaks were defined as maximum negative or positive deflections in the following time ranges: 60–110 ms for N75, 90–160 ms for P100, 130–210 ms for N145. A qualified neurophysiologist detected peaks manually. Each four-second pre-stimulus EEG epoch was Fast Fourier Transformed (FFT) and the power spectrum was computed. The frequency bands used were delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-12 Hz; beta: 12-20 Hz, and gamma: 20-40 Hz. Relative power in the occipital derivations in each of the EEG bands was then computed as the ratio of the absolute power in each band over the total power in all the bands (delta, theta, alpha, beta, gamma).

3.4.4 Statistical analysis

Correlation analysis and multiple regression analysis were performed to asses the relationship between the relative power of the selected EEG frequency bands and the N75-P100 VEP inter-peak amplitude of the first block of 100 stimuli. The amplitude of the N75-P100 interpeak amplitude was used as the dependent variable and was regressed on absolute and relative pre stimulus spectral power in the following frequency intervals: Delta (1-4 Hz); Theta (4-8 Hz); Alpha (8-12 Hz); Beta (12-20 Hz); Gamma (20-40 Hz). Prior to the analysis, an outlier inspection indicated the presence of 5 outliers – or extreme cases –

whose values fell outside ± 3 SD from the variable mean; following guidelines on multivariate analysis (Cohen and Cohen, 1983), these values were removed from the dataset. The effects of drug intake (antiepileptic drug and VPA), and group membership (IGE and PS) were also controlled for by including four additional dummy variables in the regression models. The antiepileptic drug dummy variable was coded 1 for patients treated with the drug and 0 otherwise; the VPA dummy variable was coded 1 for patients assuming VPA or 0 otherwise; the dummy variable for IGE group was coded 1 for patients with IGE or 0 otherwise; the dummy variable for PS was coded 1 for patients with PS or 0 otherwise. The two baselines for drug intake and group membership were patients who did not assume any drug and members of the ND group, respectively. Statistical significance was accepted at $p < 0.05$.

3.5 Results

Table 3.1 reports the correlation matrix involving absolute frequency band powers. Most notably, a significant positive correlation ($r = 0.410$; $p= 0.004$) is found between the N75-P100 PR-VEP amplitude of the first block of stimulation and the absolute pre-stimulus power in the spectrum of alpha band (8-12 Hz); no significant correlations appear to be present between N75-P100 PR-VEP amplitude and the absolute bands' power delta ($r = 0.077$; $p=0.608$); theta ($r = 0.233$; $p= 0.115$), beta ($r = 0.122$; $p= 0.416$), and gamma ($r = 0.133$; $p= 0.373$). Significant inter-band correlations also emerged as follows: theta-delta ($r = 0.481$; $p= 0.001$),

theta-alpha (r = 0.326; p= 0.026), theta-beta (r = 0.323; p= 0.027), theta-gamma (r = 0.301; p= 0.040), and beta-gamma (r = 0.532; p= 0.000).

Table 3.2 reports the correlation matrix involving relative frequency band power. Once again, there is a positive correlation (r = 0.277) between pre-stimulus alpha and N75-P100 PR-VEP amplitude, though only marginally significant (p = .058); no significant correlations appear to be present between N75-P100 PR-VEP amplitude and the relative bands' power delta (r = 0.027; p=0.859); theta (r = -0.164; p= 0.269), beta (r = -0.087; p= 0.559), and gamma (r = -0.210; p= 0.158). Significant inter-band correlations also emerged as follows: theta-delta (r = -0.499; p= 0.000), delta-alpha (r = -0.560; p= 0.000), delta-beta (r = -0.654; p= 0.000), delta-gamma (r = -0.452; p= 0.001), and beta-gamma (r = 0.404; p= 0.005).

Table 3.3 reports the results of regression analysis using N75-P100 PR-VEP amplitude of the first block as dependent variable. Model 1 in Table 3.3 reports results for the absolute band powers model, which explains 34.9% of the variance in the dependent variable (F = 2.200, p = 0.045). In this model, alpha absolute power shows a positive and significant relationship with N75-P100 PR-VEP amplitude (standardised beta = 0.357, p= 0.019). Notably, none of the other variables included in Model 1 shows a statistically significant relationship with the dependent variable. Model 2 in Table 3.3 reports results for the relative band powers model, which explains 30.9% of the variance in the dependent variable (F = 2.121, p = 0.058). In this model, alpha relative power shows a

positive and significant relationship with N75-P100 PR-VEP amplitude (standardised beta = 0.295, p= 0.045). In this case, a further significant relationship is present between PS group and the dependent variable (standardised beta = -0.407, p = .0050). In summary, correlation analysis and multiple regression analysis converge in indicating that both the absolute and relative power of pre-stimulus alpha are positively and significantly related to the N75-P100 PR-VEP amplitude of the first block of stimulation.

Table 3.1. Matrix of correlations involving absolute band powers

			1	2	3	4	5	6	7	8	9	10
1	N75-P100 VEP Amplitde	Pearson Correlation	1									
		Sig. (2-tailed)										
2	Delta Absolute Power	Pearson Correlation	0.077	1								
		Sig. (2-tailed)	0.608									
3	Theta Absolute Power	Pearson Correlation	0.233	**0.481**	1							
		Sig. (2-tailed)	0.115	**0.001**								
4	Alpha Absolute Power	Pearson Correlation	**0.410**	0.105	**0.326**	1						
		Sig. (2-tailed)	**0.004**	0.481	**0.026**							
5	Beta Absolute Power	Pearson Correlation	0.122	-0.029	**0.323**	0.220	1					
		Sig. (2-tailed)	0.416	0.846	**0.027**	0.137						
6	Gamma Absolute Power	Pearson Correlation	0.133	-0.008	**0.301**	0.178	**0.532**	1				
		Sig. (2-tailed)	0.373	0.956	**0.040**	0.231	**0.000**					
7	Antiepileptic drug	Pearson Correlation	-0.039	-0.010	-0.213	-0.242	-0.117	-0.159	1			
		Sig. (2-tailed)	0.794	0.948	0.150	0.101	0.435	0.286				
8	VPA	Pearson Correlation	-0.060	0.157	-0.011	-0.121	-0.023	-0.100	**0.624**	1		
		Sig. (2-tailed)	0.687	0.292	0.940	0.419	0.876	0.504	**0.000**			
9	IGE group	Pearson Correlation	0.243	-0.129	-0.116	-0.124	-0.050	-0.065	**0.455**	-0.087	1	
		Sig. (2-tailed)	0.100	0.387	0.439	0.406	0.737	0.664	**0.001**	0.562		
10	PS group	Pearson Correlation	**-0.409**	0.030	-0.067	-0.148	-0.160	-0.088	0.181	**0.473**	**-0.515**	1
		Sig. (2-tailed)	**0.004**	0.844	0.655	0.320	0.284	0.556	0.223	**0.001**	**0.000**	

Notes: Significant correlations ($p<.05$) marked in bold; N = 47. Source: Author

Table 3.2. Matrix of correlations involving relative band powers.

			1	2	3	4	5	6	7	8	9	10
1	N75-P100 VEP Amplitde	Pearson Correlation	1									
		Sig. (2-tailed)										
2	Delta Relative Power	Pearson Correlation	0.027	1								
		Sig. (2-tailed)	0.859									
3	Theta Relative Power	Pearson Correlation	-0.164	**-0.499**	1							
		Sig. (2-tailed)	0.269	**0.000**								
4	Alpha Relative Power	Pearson Correlation	0.277	**-0.560**	-0.171	1						
		Sig. (2-tailed)	0.060	**0.000**	0.249							
5	Beta Relative Power	Pearson Correlation	-0.087	**-0.654**	0.105	0.151	1					
		Sig. (2-tailed)	0.559	**0.000**	0.482	0.310						
6	Gamma Relative Power	Pearson Correlation	-0.210	**-0.452**	-0.035	0.031	**0.404**	1				
		Sig. (2-tailed)	0.157	**0.001**	0.813	0.835	**0.005**					
7	Antiepileptic drug	Pearson Correlation	-0.039	0.026	0.019	-0.117	0.057	0.037	1			
		Sig. (2-tailed)	0.794	0.864	0.900	0.432	0.703	0.806				
8	VPA	Pearson Correlation	-0.060	0.159	-0.034	-0.173	-0.016	-0.105	**0.624**	1		
		Sig. (2-tailed)	0.687	0.285	0.819	0.244	0.915	0.482	**0.000**			
9	IGE group	Pearson Correlation	0.243	-0.018	0.047	-0.023	0.026	-0.015	**0.455**	-0.087	1	
		Sig. (2-tailed)	0.100	0.902	0.753	0.875	0.861	0.918	**0.001**	0.562		
10	PS group	Pearson Correlation	**-0.409**	-0.068	0.096	-0.049	-0.007	0.151	0.181	**0.473**	**-0.515**	1
		Sig. (2-tailed)	**0.004**	0.648	0.519	0.744	0.964	0.312	0.223	**0.001**	**0.000**	

Notes: Significant correlations ($p<.05$) marked in bold; N = 47. Source: Author

Table 3.3. Results of regression analysis with absolute and relative band powers.

Dependent Variable = N75-P100 PR-VEP amplitude for the first block of stimulation									
	Model 1 (Absolute Band Power)					Model 2 (Relative Band Power)			
Independent variables ↓	Std. beta	t	Sig.	VIF	Independent variables ↓	Std. beta	t	Sig.	VIF
(Constant)		5.833	0.000		(Constant)		5.413	0.000	
Drug	-0.083	-0.342	0.734	3.318	Drug	-0.168	-0.696	0.491	3.204
VPA	0.230	1.097	0.280	2.499	VPA	0.288	1.322	0.194	2.609
IGE	0.169	0.766	0.448	2.759	IGE	0.146	0.658	0.515	2.703
PS	-0.362	-1.855	0.072	2.168	**PS**	**-0.407**	**-2.022**	**0.050**	**2.223**
Delta Absolute Power	-0.022	-0.137	0.892	1.461	Delta Relative Power	-	-	-	-
Theta Absolute Power	0.114	0.650	0.520	1.750	Theta Relative Power	-0.063	-0.441	0.662	1.123
Beta Absolute Power	-0.084	-0.508	0.615	1.570	Beta Relative Power	-0.082	-0.536	0.595	1.292
Gamma Absolute Power	0.069	0.428	0.671	1.459	Gamma Relative Power	-0.088	-0.559	0.580	1.362
Alpha Absolute Power	**0.357**	**2.453**	**0.019**	**1.200**	**Alpha Relative Power**	**0.295**	**2.072**	**0.045**	**1.113**
R^2				0.349					.309
F				2.200					2.121
Sig. F				**0.045**					0.058
N				47					47

Notes: i) standardised beta coefficients reported; ii) significant effects ($p<.05$) marked in bold; iii) in Model 2, Theta relative power is excluded from the analysis due to multicollinearity induced by the high correlation of this variable with the other independent variables (see Table 3.2). Additional analyses showed that results concerning prestimulus alpha are stable even after Theta relative power is excluded; also, Theta relative power has a non significant correlation with the dependent variable (see Table 3.2), and therefore its exclusion is not likely to affect the direction of our results. Source: Author

3.6 Discussion

The results of the present study demonstrate a positive relationship between the pre-stimulus alpha power and N75-P100 PR-VEP amplitude in the first block of stimulation, once group affiliation, assumption of medications and power of the other frequency bands (delta, theta, beta, and gamma) are controlled for. This finding goes in the same direction as the previous literature (Basar, 1983; Brandt et al., 1991; Brandt and Jansen, 1991; Jansen and Brandt, 1991; Basar and Schurmann, 1994) and adds further insight to the findings of the first study of this thesis. The previous finding of reduced amplitude of N75-P100 PR-VEP in the first block of stimulation in the PS group (see Chapter II for details) was earlier interpreted taking into account two alternative hypotheses. The first one explained the phenomenon considering that the interictal epileptiform activity is associated with inhibition in the cortical region of ictal onset and in the surrounding areas (Gumnit and Takahashi, 1965; De Curtis et al., 2005). Further possible explanations involve a disruption of the physiological thalamic regulation of cortico-cortical synchronisation. According to this theory, reduced cortico-thalamic input can produce excess inhibition or disfacilitation, generating thalamic cell membrane hyperpolarization and low-frequency oscillation (Llinás et al., 1999). The positive relationship between VEP amplitude and pre-stimulus alpha in our sample can be a further explanation to the reduced N75-P100 VEP amplitude in the PS group. Furthermore, studies that explore the relationship between oscillatory activity in the alpha band

and neurophysiological measures of visual brain function have demonstrated that a decreased alpha activity reflects a state of enhanced cortical excitability and increased alpha activity a state in which cortical excitability is reduced (Pfurtscheller, 1992; 2001). Variations in the level of posterior, pre-stimulus alpha-band activity have been found to predict whether a forthcoming visual sub-threshold stimulus will be detected or not as well as the size of the evoked brain response (Ergenoglu et al., 2004). Moreover, behavioural studies (Rahn and Basar, 1993; Hanslmayr et al., 2005) and, more recently, transcranial magnetic stimulation studies have suggested that alpha power inversely relates to visual cortex excitability (Romei et al, 2008a; 2010). The available body of evidence suggests that low pre-stimulus alpha power can be interpreted as an indicator of greater excitability of the visual cortex. Therefore, the lower pre-stimulus alpha power in the PS group can be seen as an indicator of increased cortical excitability. Of difficult interpretation is the finding of a correlation between theta band (4-8 Hz) activity with the other oscillations of the ongoing pre-stimulus EEG. At a neurophysiological level EEG power bands cannot be directly related to specific neurophysiological phenomena as little is known about neuronal networks underlying different frequency components of the human EEG (Steriade et al., 1990; Silberstein, 1995) and about the pathophysiology of EEG background activity in general (Schaul, 1990).

3.7 Conclusions

In conclusion, the present study establishes a positive relationship between the N75-P100 PR-VEP amplitude and low pre-stimulus alpha power and offers further elements to suggest that altered occipital cortical excitability can account for the pathophysiological substrate of epileptic photosensitivity.

Chapter 4

Thalamocortical dysrhythmia in photosensitive epilepsy

4.1 Abstract

Purpose: we proposed thalamocortical dysrhythmia theory to explain the lack of habituation and reduced amplitude of the N75-P100 VEP component in the first block of stimulation in PS group. According to this model, reduced cortico-thalamic input can produce excess inhibition or disfacilitation, generating thalamic cell membrane hyperpolarization and low-frequency oscillation (Llinás et al., 1999). The third experiment was designed to provide experimental support to the possible disruption in the physiological thalamic regulation of cortico-cortical synchronization in photosensitive epilepsy. We set out to measure changes in induced oscillatory EEG activity following the presentation of spatially structured static visual stimuli .

Materials and methods: horizontally oriented stationary sinusoidal gratings with a spatial frequency of 3 cycles per degree (cpd) were presented to a group of 8 subjects with photosensitive epilepsy; data was compared to that of a control group of 8 healthy volunteers matched for age and gender. Stimuli were presented for a 4 sec “on” period, followed by a 4 sec “off” period during which a full field screen of the same luminance was shown. The gratings were generated using a Cambridge Research System VSG 2/3 grating generator and displayed on a Sony screen at a refresh rate of 210 Hz. This paradigm was designed to offer a long enough analysis window and allow recording both evoked and induced oscillatory activity, a condition not satisfied by the PR-VEP paradigm used in study 1. The spatial frequency and contrast of the

stimulus were as previously reported in magnetoencephalographic study (Hall et al., 2005) to optimase gamma oscillations in human primary visual cortex. Independent Component Analysis (ICA) preceded by Principle Component Analysis for dimensionality reduction of component (from 128 to 64) was firstly performed. This was followed by time-frequency analysis of the components accounting for the largest contribution in terms of 10 Hz activity at Oz. Finally, to determine which independent components were common across subjects, we performed cluster analysis on the component maps and activity spectra

Results: five clusters of independent components of the post-stimulus single-trial EEG data, derived by ICA analysis, accounted for most of the grand mean ERP. Each cluster contained components among the top three contributors to the VEP response for each subjects. Three clusters of occipital components exhibited the following features: firstly, the presence of evoked and induced gamma band in both PS and control groups, without statistically significant differences between the two groups; secondly, the presence of an important and sustained desynchronisation in the alpha- beta bands only in the control group; thirdly, a significant phase locked and sustained synchronisation (power increase) in the theta band only in the PS group. The two groups did not show statistically significant differences in the other two clusters.

Conclusions: these findings, taken together, seem to corroborate the existence of a disruption in the connection between thalamus and

occipital cortex as suggested in thalamocortical dysrhythmia only in the PS group.

4.2 Objectives

In the first study we suggested that the thalamocortical dysrhythmia model could have explained the lack of habituation to visual stimuli and the reduced amplitude of the N75-P1000 VEP component in the first stimulus block in the group of PS patients. According to this model, reduced cortico-thalamic input can produce excess inhibition or disfacilitation, generating thalamic cell membrane hyperpolarization and low-frequency oscillation (Llinás et al., 1999). To support this hypothesis, in the second study, we evaluated whether the low VEP amplitude could be related to a low pre-activation level of the ongoing activity of the occipital cortex. In this experimental study we used a visual paradigm consisting of horizontally oriented stationary sinusoidal gratings with a spatial frequency of 3 cycles per degree (cpd) and measure induced and evokek changes in oscillatory activity in patients with photosensitive epilepsy and compared the findings to those recorded from a control group of healthy volunteers. The aim was to provide with electrophysiological evidence which might support the previous speculation regarding a potential involvement of mechanism of thalamo-cortical dysrhythmia advanced to explain the results of the first experiment.

4.3 Background

4.3.1 Theta oscillations

Oscillations in theta frequency band (4-8 Hz) have been extensively studied in rat model animal experiments, especially during spatial exploration (Skaggs et al., 1996). These oscillations can be detected in the local field potentials (LFP) and in the potentials recorded from individual pyramidal cells (Kamondi et al., 1998). It has been demonstrated that hippocampal cells systematically change their phase of firing in relation with theta oscillation as a rat moves through a place field (Jensen and Lissman, 2000). Still a matter of controversy is whether theta oscillations in rats are specialised for the organisation of spatial information or generally involved in other functions. Theta oscillations in humans have been mainly investigated using MEG and EEG methods in resting condition or during memory and spatial tasks. Due to its favourable signal/noise ratio, intracranial EEG has also been used. Mirroring animal experiments research on stimulus-induced changes in oscillatory activity in the theta band has recently become a topic of interest, in relation with spatial task (Kahana et al., 1999), mirroring animal experiments, and working memory tasks (Sarnthein et al., 1998; Klimesch, 1999). The role of theta oscillations in task that lacked a spatial component has been recently investigated and results suggested that human theta oscillations are not uniquely specialised for spatial computations (Raghavachari et al., 2010). Studies in neurological or psychiatric conditions have been relatively sparse (Basar-Eroglu et al.,

2008). In epilepsy, 4–8 Hz pathological thalamo-cortical EEG oscillations and their relation to the low threshold Ca++ currents have been studied in the context of absence seizures and their animal models (Gloor et al., 1990; Huguenard, 1999; McCormick and Contreras, 2001). Two studies have suggested that patients with generalised epilepsy present significantly higher absolute spectral power in the delta, theta, and alpha range than healthy individuals (Mirsky and Grady, 1988; Clemens et al., 2000). In particular, spectral analysis of EEG background activity disclosed pathologically enhanced synchronisation mainly in the delta–theta range in patients with absence epilepsy (Mirsky and Grady, 1988), and in patients with genetically related generalised epilepsy syndromes with a strong genetic component such as juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalised tonic–clonic seizures on awakening (Clemens et al., 2000). These findings have been subsequently interpreted in light of the thalamocortical dysrhythmia model (Clemens, 2004).

4.3.2 Gamma oscillations

Fast EEG oscillatory activity in the gamma band from different cortical areas has been recorded during in vivo and in vitro experiments. Three main functionally distinct gamma band oscillations have been described: (1) activity which is phase-locked to the onset of a particular stimulus and is directly related to it; (2) steady-state evoked activity in the 40Hz range, that is usually provoked by visual, auditory or somatosensory stimuli and can be interpreted as a natural resonance

frequency of the brain involved in primary sensory processing; (3) induced oscillation which proceed from continuous sensory stimulation, not time or phase locked to a specific stimulus but increased during meaningful information processing (Tallon-Baudry et al, 1997).

A modulation in the degree of synchrony seems to play a role in information processing in the brain. Recent studies have documented the existence of synchronous gamma band oscillations in tasks involving higher cognitive functions such as memory, attention and perception. Gamma band activity has also been described in the local field potentials (LFP) from the visual cortex of cats and monkeys and also reported in the human visual system. Visual stimuli with a wide range of physical properties are able to elicit responses in the gamma band. Consensus on standardised protocols to induce this activity is still lacking. Herrmann (2001) showed that stimulating humans with flickering light at frequencies between 1 and 100 Hz resulted in EEG power increase around 10, 20, 40 and 80 Hz. Lopez and Sannita (1997) recorded high-frequency (100±110 Hz) magnetic oscillatory fields in human's occipital cortex in response to monocular transient full field-flash stimulation at frequencies of 0.6 Hz. A linear relationship between stimulus contrast and gamma band power in the visual cortex has been reported Hall et al. (2005). Using similar stimuli to Hall et al. (2005), Adjamian et al. (2008) suggested that gamma oscillations in primary visual cortex are preferentially generated in response to very low luminance and contrast stimuli. Several theories on the significance and the pathogenesis of

gamma band activity have been proposed. Some experiments showed that gamma band is generated by intrinsically oscillating neurons, the so called ”chattering cells” (Gray and McCormick, 1996), whose interactions with large populations of neurons establish the phase synchrony necessary to make the changes detectable in EEG and MEG recordings. There is evidence of dependence of gamma band activity on the interconnection of subsets of inhibitory interneurons and excitatory pyramidal cells (Brunel and Wang, 2003). In the hippocampus (Banks and Pearce, 2000), one such subset seems to be responsible for the generation of GABA(A)-mediated inhibitory post-synaptic potentials (IPSPs), with fast kinetics on the soma of the pyramidal neurons, while a separate subset produces GABA(A)-mediated IPSPs with slow kinetics on the dendrites of the pyramidal neurons. Recently, two independent research groups (Buchner et al., 1999; Carozzo et al., 2004) identified two components of gamma band oscillations in the visual cortex: the first probably generated in subcortical structures, and the second one originating in the occipital cortex itself, probably in area V1.

Regarding the pathogenesis of gamma band activity in epilepsy there are indications that the dendritic GABA(A)ergic slow IPSPs would be decreased in some experimental models of epilepsy (Cossart et al., 2001), resulting in disinhibition of fast interneurons and abnormal enhancement of beta/gamma oscillations from IPSPs with fast kinetics. Studies on high frequency oscillation in intracranial recordings of epileptic patients have revealed high oscillation activity at the onset of some forms of epileptic

seizures, especially focal seizures (Allen et al., 1992; Fisher et al., 1992; Traub et al., 2001). In patients with photosensitive epilepsy, enhanced synchrony in the gamma band harmonically related to the frequency of stimulation precedes the stimulation trials that evolve into PPR and not those not followed by PPR, or those recorded in healthy controls (Parra et al., 2003). This finding in patients with photosensitive epilepsy has been interpreted as the expression of abnormal control of gamma band oscillations that may deviate from the normal dynamic range under the influence of intermittent photic stimulation.

4.3.3 Thalamocortical dysrhythmia

In its original description, thalamocortical dysrhythmia has been attributed to changes in intrinsic, voltage-gated ionic conductances at the level of thalamic relay cells, which provoke de-activation of T channels by cell membrane hyperpolarisation. In this model, dysrhythmia would be generated by membrane hyperpolarisation or its functional equivalent (T-type Ca^{++}channel deactivation) in the affected thalamus. Thus, protracted hyperpolarisation of a specific nucleus can result in low-frequency oscillations in the theta frequency range (4-8 Hz). Such oscillations activate return cortico-thalamic pathways through the reticular nucleus or by direct thalamic activation. The result is the promotion of large scale low frequency oscillation coherence. At a cortical level, the reduction of lateral inhibition promotes coherent gamma frequency oscillation and positive symptoms. This theory was firstly suggested to explain the MEG findings of thalamo-cortical

oscillations in the theta band frequency (4-8 Hz) in awake human patients affected by a wide variety of neurological and psychiatric conditions (Llinás at al., 1999). This low frequency thalamo-cortical activity has two features that distinguish it from the theta activity present under normal waking conditions: firstly it is a persistent low frequency thalamocortical resonance during the awake state; secondly it shows a wide coherence over the recorded channels. As previously suggested, this low frequency activity is not pathological itself, in fact it occurs as thalamocortical synchronisation continuously during theta sleep (Contreras et al., 1996) and transiently during wakefulness under specific conditions such as mental and emotional activity (Lisman et al., 1995; Schacket al., 1999). Furthermore, in healthy individuals, such low and high frequency oscillations are not temporally coherent and represent different thalamo-cortical functional states. Therefore it is reasonable to expect that if some thalamic structures are continuously hyperpolarised by over-inhibition or deafferentation, ongoing rhythmic low threshold spike burst activity would be present. Recent studies have indicated that thalamocortical dysrhythmia is present in disorders such as Parkinson's disease (Sarnthein and Jeanmonod, 2007), chronic pain (Jones, 2010), tinnitus (De Ridder et al., 2007), migraine (Coppola et al., 2007), Tourette syndrome and attention-deficit/hyperactivity disorder (Sukhodolsky et al., 2007) and schizophrenia (Bish et al., 2004). The alteration of cortico-thalamic interconnections has been also suggested in epilepsy studying the function of T-type calcium channels and their role in childhood

absence epilepsy (Nelson et al., 2006). These conditions have been classed under the term “thalamocortical dysrhythmia syndrome” or TCDS (Llinás et al., 1999). The role of thalamic structures in Parkinsonian tremor has been confirmed by evidence that surgical thalamectomy can alleviate this symptom. More recently, low-frequency thalamic oscillations have been recorded in humans with Parkinson’s disease (Jeanmonod et al., 1996; Schnitzler and Gross 2005). In Parkinsonism hyperactive pallidal drive to the motor thalamus produces hyperpolarisation of thalamic relay cells and the consequent de-activation of T-channels, the appearance of low threshold calcium spiking and low frequency oscillation (Llinás et al., 1999). Clinically, Parkinson’s disease is characterized by the presence of both negative and positive symptoms; in the most severe cases bradykinesia can make patients functionally paralysed but still presenting tremors. Negative symptoms are thought to be associated with low-frequency oscillatory activity, and positive symptoms with a persistent and usually not present abnormal gamma band activity, an “edge effect“ probably due to lateral disinhibition resulting from asymmetrical inhibitory interneuronal activity at cortical level (Llinás et al., 2005). This phenomenon may be compared to the positive and negative symptoms of migraine, where areas of blindness (scotoma) are often surrounded by bright halos. This proposal suggests that dysrhythmia of particular cortical regions underlies the generation of corresponding symptoms. Tremor would result from dysfunction of lateral motor and premotor cortex, whereas the

anterior supplementary motor area is proposed to be dysrhythmic in Parkinsonian akinesia. This model has been proposed for conditions such as tinnitus, peripheral neurogenic pain and some neuropsychiatric disorders of striatal origin, in which the dysrhythmic mechanism is triggered from the thalamus toward the cortex in a so called “bottom-up” process. In epilepsy, central cortical neurogenic pain and other neuropsychiatric conditions of cortical origin, the mechanism is triggered from the cortex to the thalamus in a so called “top-down” process. Similarly, molecular alterations that enhance low-frequency thalamic rhythmicity have been demonstrated to produce conditions such as absence epilepsy in rats (Talley et al., 2000; Song et al., 2004). These findings show that a reduction of T channels excitability by pharmacological procedures results in a reduction of such dysrhythmic phenomena (Coulter et al., 1990). Furthermore, mutations that suppress T-channel expression also prevent the generation of absence epilepsy (Kim et al., 2001) and produce phenotypes with reduced sleep behaviour.

4.3.3.1 Thalamic neurons

The study of the electrophysiological properties of thalamic neurons began in the early 1960s with in vivo intracellular recordings using feline preparations (Purpura, 1970). In these studies, thalamic neurons were considered as simple relay elements between sensory inputs and the cerebral cortex. Subsequently also electrophysiological studies of thalamic relay functions supported this basic assumption. However, with the development of in vitro recording, it became clear that the intrinsic

electrophysiological properties of thalamic neurons went beyond a simple relay function (Llinás, 1988; Trimmer and Rhodes, 2004; Traub et al., 2005). In the early 1980s, in the attempt to understand the electrical characteristics of thalamic activity, in vivo (Deschenes et al., 1982, 1984; Steriade and Deschenes, 1984) and in vitro experiments (Llinás and Jahnsen, 1982; Jahnsen and Llinás, 1984) were undertaken, which led to a fundamental revision of the accepted dogma at the time. Rather than mere relays, thalamic neurons were viewed as having *sui generis* intrinsic electrical properties that gave them specific functional dynamics (Steriade and Llinás, 1988). Both in vivo and in vitro studies suggested that thalamic neurons were not simple links in a connectivity chain but were rather the fundamental arbiters for global brain states. When depolarised from positive resting potential levels to -55 mV, thalamic neurons fire tonically both under in vivo and in vitro conditions. Such tonic firing was shown to last for the whole duration of the membrane depolarisation. Thalamic activity can be continuously regulated by sensory or cortical synaptic input, the latter being the more powerful. When these neurons are sufficiently depolarised, they generate subthreshold oscillations at frequencies near 40 Hz (gamma band). This activity supports thalamic cells resonance and is the functional antithesis of the rhythmicity that supports the slow wave sleep.

4.4 Materials and methods

4.4.1 Subjects

Fourteen participants (5 males, mean age = 23.5 years, SD = 10.61, range 11-43 years) were recruited from the Birmingham Children Hospital NHS Foundation Trust and the Neurophysiology Department of Aston University in Birmingham between July 2009 and June 2010. Seven subjects (2 males; mean age = 18 years, SD = : 9.46, range 11-39 years) had clinical photosensitivity and PPR on EEG; 7 subjects (3 males; mean age = 29 years; SD: 9.16; range: 18-43 years) matched for age and gender, with no personal or family history of epileptic seizures, migraine (with or without aura) or other neurological disorder were recruited as controls. Participants in the photosensitive (PS) group presented a history of photoparoxysmal response and clinical photosensitivity but no clinical manifestations at the time of recording. All presented idiopathic generalised epilepsy with photosensitivity; 3 of them had a diagnosis of idiopathic generalised epilepsy with absences, 3 had pure photosensitive epilepsy and 1 presented eyelid myoclonia with absences according to the International Classification and Terminology of Epileptic Syndromes (Engel, 2006). Two were taking Valproate and one Levetiracetam. The other 4 patients were drug-free at the time of recordings. All the patients presented a propagating PPR type III-IV according to Waltz criteria (Waltz et al., 1992). Clinical and EEG features are presented in Table 4.1. Informed consent was obtained from both the subject and their parents if appropriate. The study was

conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Aston University.

Table 4.1: Subjects characteristics

Variable	**PS (n=7)**	**CTR (n=7)**
Gender (F/M)	5/2	4/3
Mean (SD) age in years	18 (9.46)	29 (9.16)
Photosensitivity	100%	0%
Antiepileptic drugs		
None	57%	100%
One	43%	0%
Two or more	0%	0%
PPR		
I-II Type	0%	0%
III-IV Type	100%	0%

Source: Author

4.4.2 Data acquisition

4.4.2.1 Dense array EEG

A 128-channel Hydrocel Geodesic Sensor Net was applied to each person for the recording (see Figure 4.1), requiring an average of 40 min for application and impedence checks. The EEG-amplifier characteristics included a bandpass filter of 0.1 to 400 Hz and sampling rate of 1 KHz. The 128-channel EEG was recorded with a common vertex reference and re-referenced digitally to standard clinical montages for inspection, including the average reference. Because of the improved coverage of the inferior head surface of the 128-channel Geodesic Sensor Net, the average reference allows the potential at each index electrode to be examined with reference to a close approximation to the zero potential of the head. The average-referenced EEG waveforms were examined with topographic waveform plots, a technique that allows for the inspection of the geometric distribution of the potential fields. In addition, topographic maps were created using spherical line interpolation. Photic stimulation was performed at least 15' prior to VEP recordings using a Grass PS 22 stimulator and consisted of ten-second periods of regular frequencies at 5, 10, 12, 15, 18, 20, 25, 50, 60 Hz. In accordance with recommended guidelines, subjects had their eyes opened during the first 5 seconds of each period of visual stimulation at a particular frequency and were asked to close their eyes for the following 5 seconds (Kasteleijn-Nolst Trenité et al., 1999b).

Figure 4.1: Dense Array EEG recording

Source: Aston University Website; Subject: Author

4.4.3 Visual paradigm

Appropriate selection of spatial patterns and contrast levels are critical for the generation of visual gamma oscillations. The best stimulation for eliciting a sustained gamma band response is represented by horizontal gratings. The spatial frequency and contrast were chosen to be optimal for generating gamma oscillations in human primary visual cortex as previously demonstrated with MEG (Adjamian et al., 2004). The protocol consists of horizontally oriented stimuli, in the form of stationary sinusoidal gratings at 3 cycles per degree (cpd), presented for a 4 second “on” period (experimental condition referred as ‘pattern’ in the spectral plot) followed by a 4 second “off” period in a full field screen of the same luminance (control condition or passive period, referred to as ‘blank’ in the spectral plots). Gratings were presented at a viewing

distance of 1.5 m, and 80% contrast; each “on-off” cycle was repeated 60 times. The gratings were generated using a Cambridge Research System VSG 2/3 grating generator and were displayed on Sony screen with a refresh rate of 210. Given the passive nature of the viewing paradigm, subjects were not required to make any response.

4.4.4 Data analysis

Dense array EEG data were analysed in the EEGLAB environment (Delorme and Makeig, 2004), an open-source toolbox (http://sccn.ucsd.edu/eeglab/) under Matlab 7.5.0 R2007b (Mathworks Inc.). Data were filtered using a digital high-pass filter of 1 Hz and low-pass filter of 100 Hz, re-referenced as average reference and segmented into epochs of 8000 ms (from 4000 ms pre- to 4000 ms post-stimulus). The 1000 ms pre stimulus EEG was used as baseline. This temporal segmentation allowed averaging of the responses and the extraction of an event related potential (ERP) as well as time-frequency analysis of the event related spectral perturbations (ERSP).

4.4.4.1 ICA analysis

The ICA algorithm used in this study was an ‘informax’ neural network algorithm (Linsker, 1992; Nadal and Parga, 1994) that uses stochastic gradient ascent to find a square ‘unmixing’ matrix that maximises the joint entropy (Cover and Thomas 1991) of a non-linearly transformed ensemble of zero-mean input vectors. Informax ICA is one of a family of algorithms that exploit temporal independence to perform the blind separation of linear mixtures of source signals. Four main

assumptions underlie ICA decomposition of EEG data: (1) signal conduction times are equal, and summation of currents at the scalp electrodes is linear, both reasonable assumptions for currents carried to the scalp electrodes by volume conduction at EEG frequencies (Nunez, 1981); (2) spatial projections of components are fixed across time and conditions; (3) source activations are temporally independent of one another across the input data; and (4) statistical distributions of the component activation values are not Gaussian. The suitability of this ICA decomposition for EEG analysis is discussed in Makeig et al. (1999). The ICA decomposition with dimensionality reduction of component (from 128 to 64) was performed using FastICA (the algorithm is based on a fixed-point iteration scheme maximizing non-Gaussianity as a measure of statistical independence).

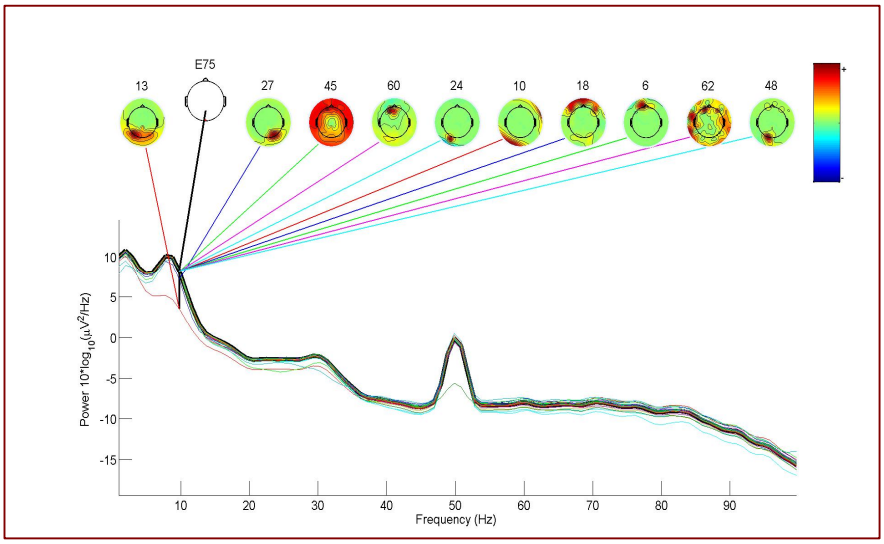
After visual inspection of the scalp maps and of the time-course of their activation, we selected the components accounting for artefacts. One of these components was clearly related to eye-blinks and therefore it was subtracted from the on-going EEG data. The EEG data were back-projected to the subset of the remaining components. All the analyses we reported in the following sections refer to this 'cleaned' dataset.

ICA linearly decomposed each subject's EEG data into 64 maximally independent components. Each of these is characterised by a different and time-invariant scalp map, which represents the spatial projection of the component to each scalp channel, and a time course of activation in each trial.

For each subject the baseline or epoch-mean power spectrum (ERP) was analysed, along with two event-related time/frequency measures: (1) the event-related spectral perturbation (ERSP), measuring mean event-related changes in the power spectrum at a data channel or component (Makeig, 1993); and (2) inter-trial coherence (ITC magnitude and phase, also called phase-locking factor) at single channels or components. ITC is a frequency-domain measure of the partial or exact synchronisation of activity at a particular latency and frequency to a set of experimental events to which EEG data trials are time locked. The measure was introduced by Tallon-Baudry et al. (1996) and termed 'phase locking factor.' The ITC measure ranges between 0 and 1. A value of 0 represents absence of synchronisation between EEG data and the timelocking events; a value of 1 indicates their perfect synchronisation.

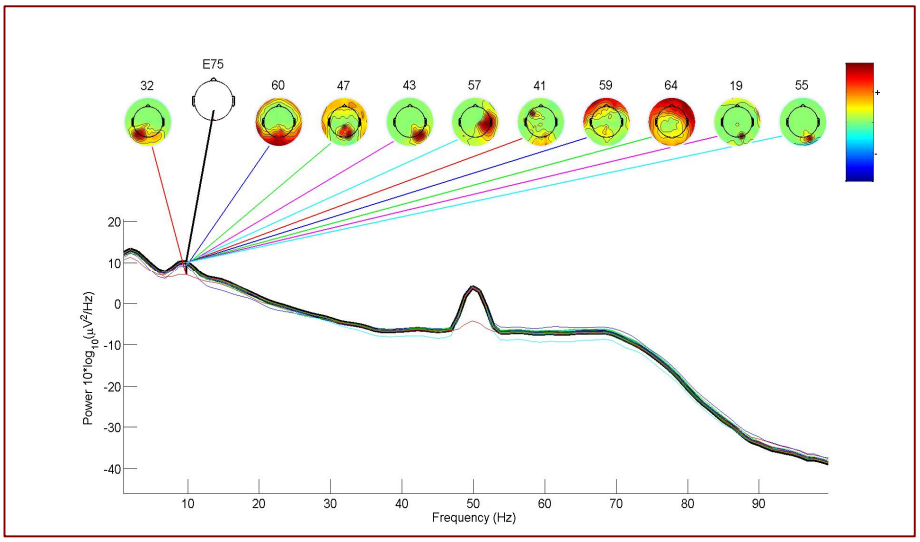
The time course of the ERP activity at the Oz scalp location, where activity was expected to be maximum was used as one of the selection criteria for the components of interest. For each subject an EEGLAB *spectopo*, showing the components accounting for the largest portions of 10 Hz activity at electrode POz (middle scalp map) corresponding to channel 75, has been performed (see Figure 4.2 and Figure 4.3). In addition and an EEGLAB *envtopo* showing the envelopes (i.e., the min and max values, across all channels, at each time point) of the 10 independent components making the largest potential contributions to the ERP, has been calculated.

Figure 4.2. EEGLAB *spectopo* plot for subject 9 (control group).



Note: The figure shows the power spectrum of the selected channel (top black trace), the activity spectra of the projection to that channel of each of the 64 components (lower traces), and the scalp power maps of the 10 largest-contributing components. Source: Author.

Figure 4.3. EEGLAB *spectopo* plot for subject 1 (PS group).

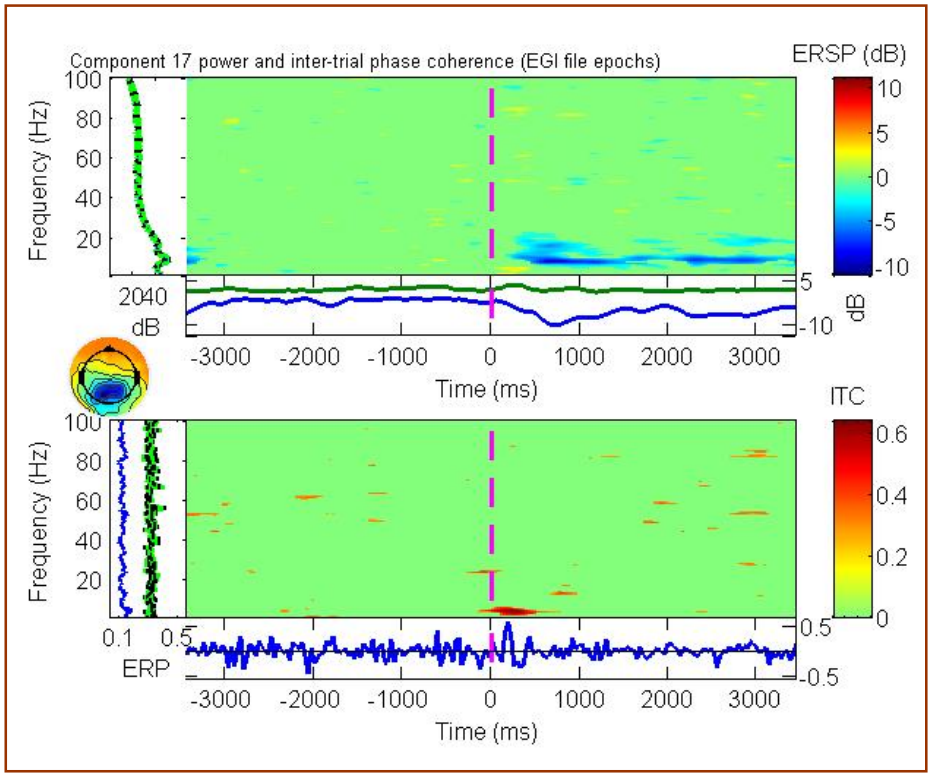


Note: The figure shows the power spectrum of the selected channel (top black trace), the activity spectra of the projection to that channel of each of the 64 components (lower traces), and the scalp power maps of the 10 largest-contributing components. Source: Author.

As a next step, a time-frequency analysis of the component accounting for the largest contribution in terms of 10 Hz activity at Oz has been performed. Figures 4.4 and 4.5 represent ERSP and ITC of two components of interest in subject 8 belonging to CONTROL group. An important power decrease in the 8- 12 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period and an increase in 20-40 Hz activity are respectively represented. The analysis was conducted on the entire 8 s by comparing the active (black-white gratings) and passive (isoluminant grey) periods.

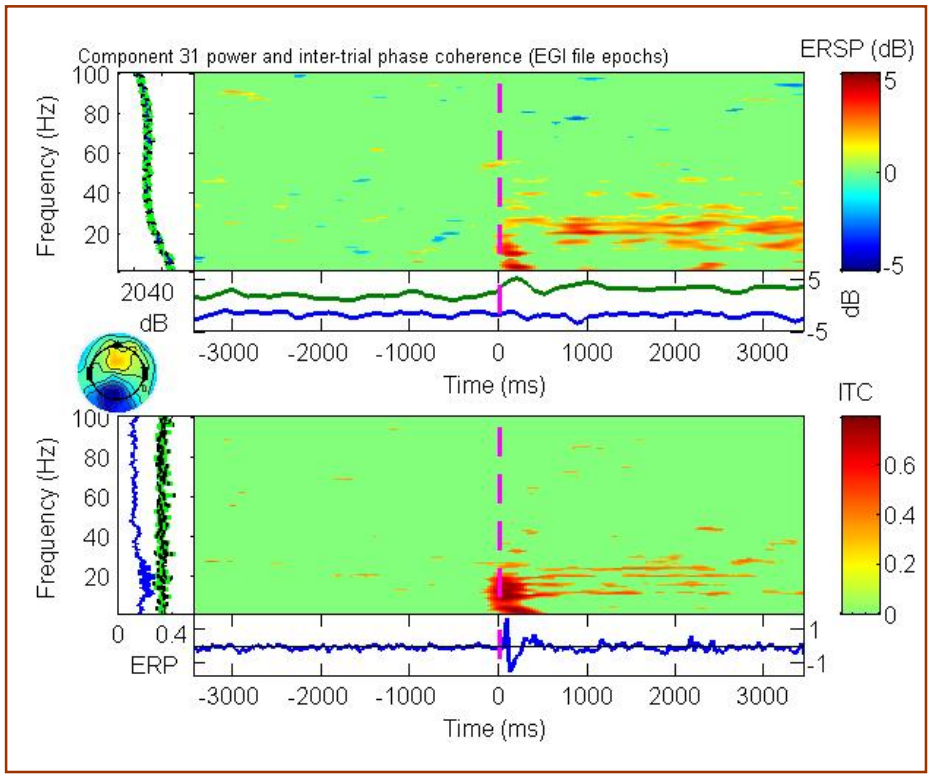
Figures 4.6, 4.7 and 4.8 represent ERSP and ITC of three components of interest in subject 2 belonging to PS group are represented. In Figure 4.7 a power decrease in the 8- 12 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period is represented. Figure 4.8 shows a power increase in the induced and evoked gamma band (range between 20-60 Hz), and Figure 4.9 shows a power increase in the theta band (3-8 Hz). The analysis was conducted on the entire 8 s active versus passive periods (black/white gratings).

Figure 4.4. ERPS and ITC of component 17 in subject 8 (CONTROL group).



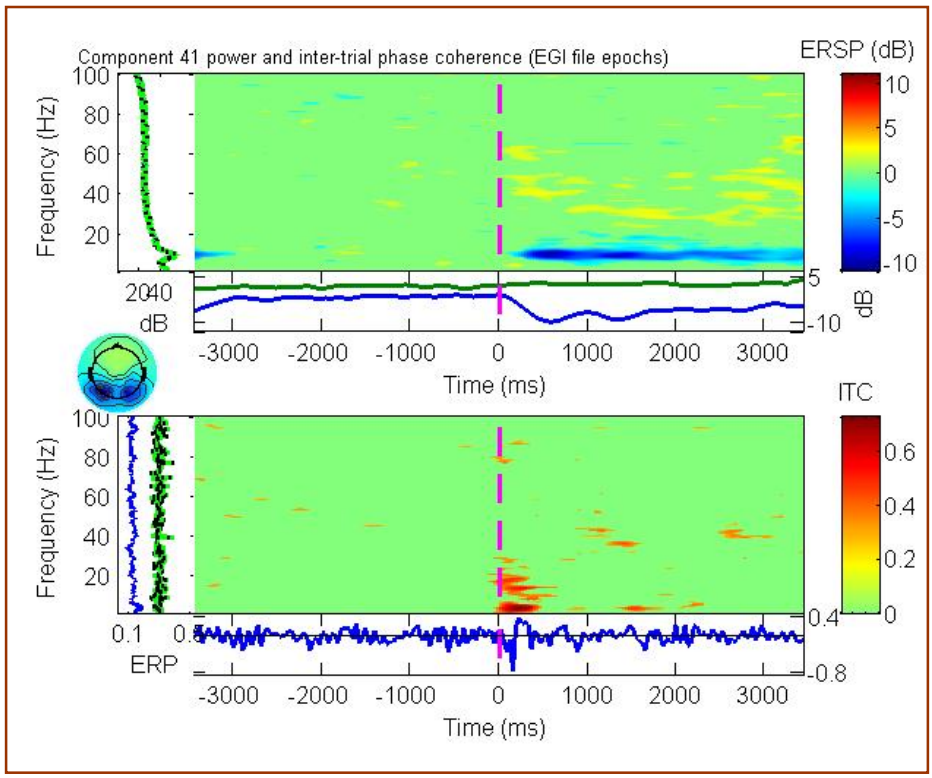
Notes: The component explains the 43% of variance. Image on the top shows power decrease in the 8- 12 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period. Blue and red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

Figure 4.5: ERSP and ITC of component 31 in subject 8 (CONTROL group).



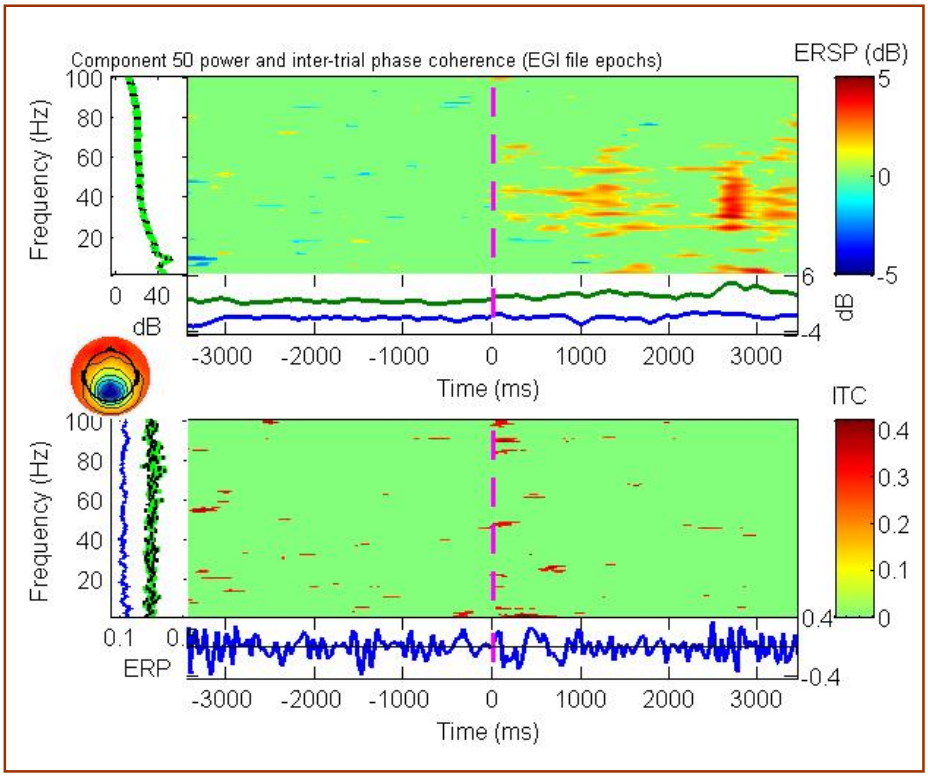
Notes: The component explaind 23% of variance. Image on the top shows significant power increase in the 20- 30 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period. Blue and red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

Figure 4.6: ERSP and ITC of component 41 in subject 2 (PS group).



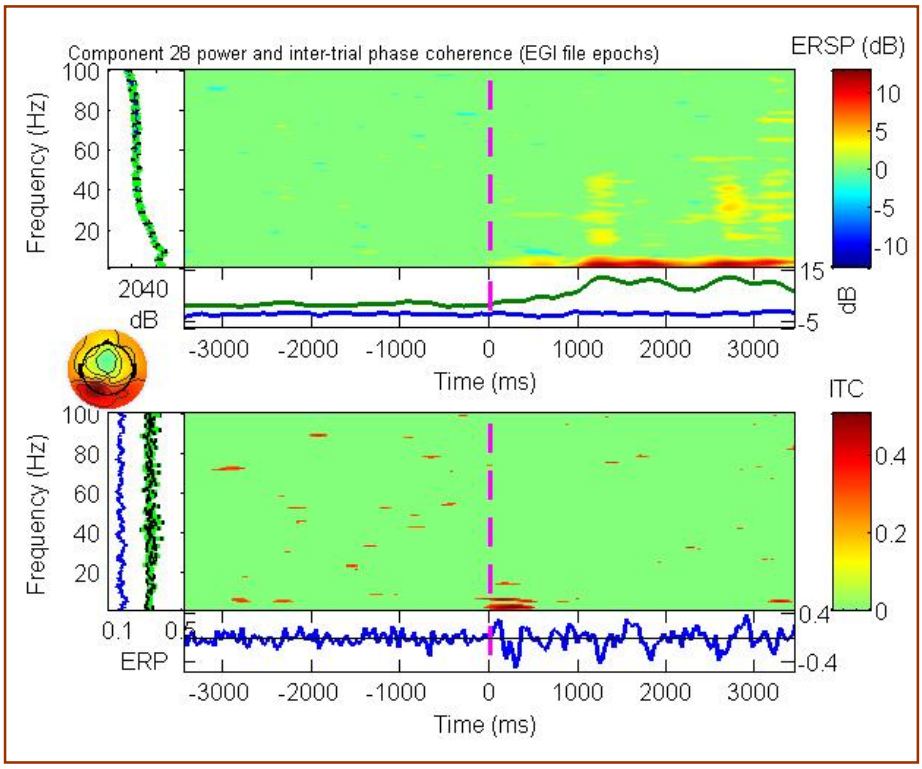
Notes: The component explains 40% of variance. Image on the top shows significant power decrease in the 8- 12 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period. Blue and red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

Figure 4.7: ERSP and ITC of component 50 in subject 2 (PS group).



Notes: The component explains 23% of variance. Image on the top shows a power increase in the induced gamma band at the frequency of 20-50 Hz band induced. Blue and red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

Figure 4.8: ERSP and ITC of component 28 in subject 2 (PS group).



Notes: The component explains 33% of variance. Image on the top shows important power increase in the 3-8 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period. The blue and the red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

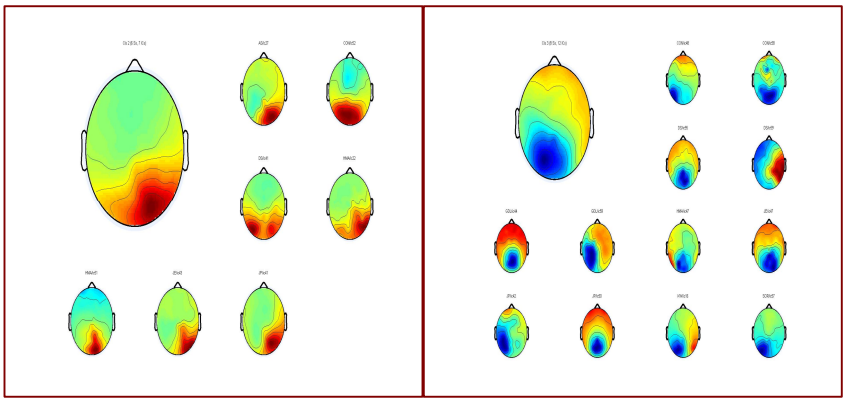
To determine which independent components were common across subjects, we performed cluster analysis on the component maps and activity spectra. Statistical analysis of the components of interests was then performed using a K-means cluster analysis. Clusters of interest within and between subjects were identified. Component clusters were further analysed in terms of ERSP, inter-trial coherence and topographic maps. Time-frequency analysis was performed in the 1-100 Hz interval, which included the major frequency bands of interests, in particular theta band (4-8 Hz), low gamma band (25-40 Hz), and high gamma band (>40

Hz). The time frequency parameters were the following: cycles 1 .01, frequency: 1-100, winsize: -2000- 3999.

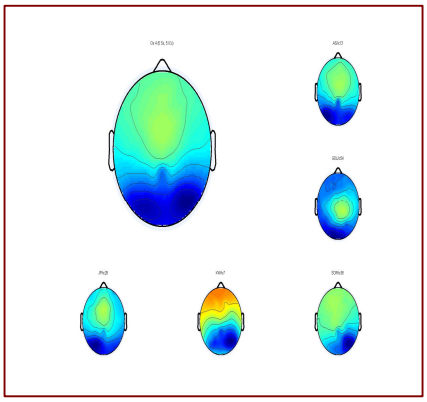
4.5 Results

Three clusters of independent components of the post-stimulus single-trial EEG data, derived by ICA analysis, accounted for most of the grand mean ERP. Each cluster contained components among the top three contributors to the VEP response for each subjects. The three occipital clusters (Figure 4.9) exhibited the following features: (1) they present an important and sustained desynchronisation in the alpha-beta band in both groups; (2) the presence of evoked and induced gamma band in the PS and CONTROL groups, without statistically significant differences between the two groups; and (3) a massive phase locked and sustained synchronisation in the theta band only in the PS group.

Figure 4.9: Clusters of independent components of the post-stimulus single-trial EEG data.



Cluster 1 Cluster 2



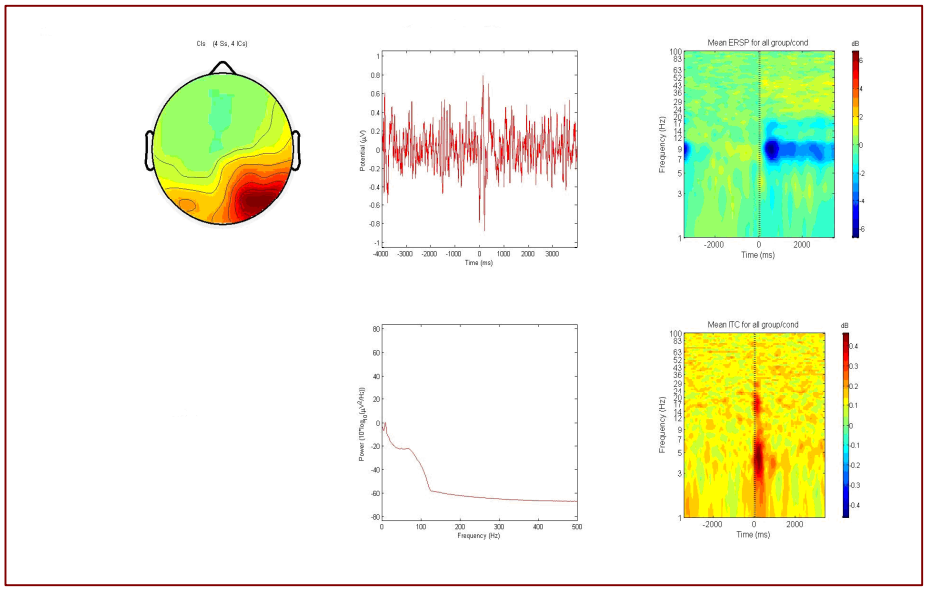
Cluster 3

Notes: Clusters accounting for most of the grand mean ERP. Each cluster comprised from 4 to 12 independent components from all the 14 subjects. Together, the three clusters comprised 24 independent EEG components drawn from all 14 subjects. Source: Author

Components in Cluster 1 (Cluster 1, Figure. 4.10) accounted for the sustained desynchronisation in the high alpha- beta band in both PS and CONTROL group. Their scalp maps were consistent with single equivalent current dipoles in occipital mesial cortex. Rhythmic, central-posterior components found in twelve subjects, contributed significantly to induced and sustained gamma activity in both PS and CONTROL

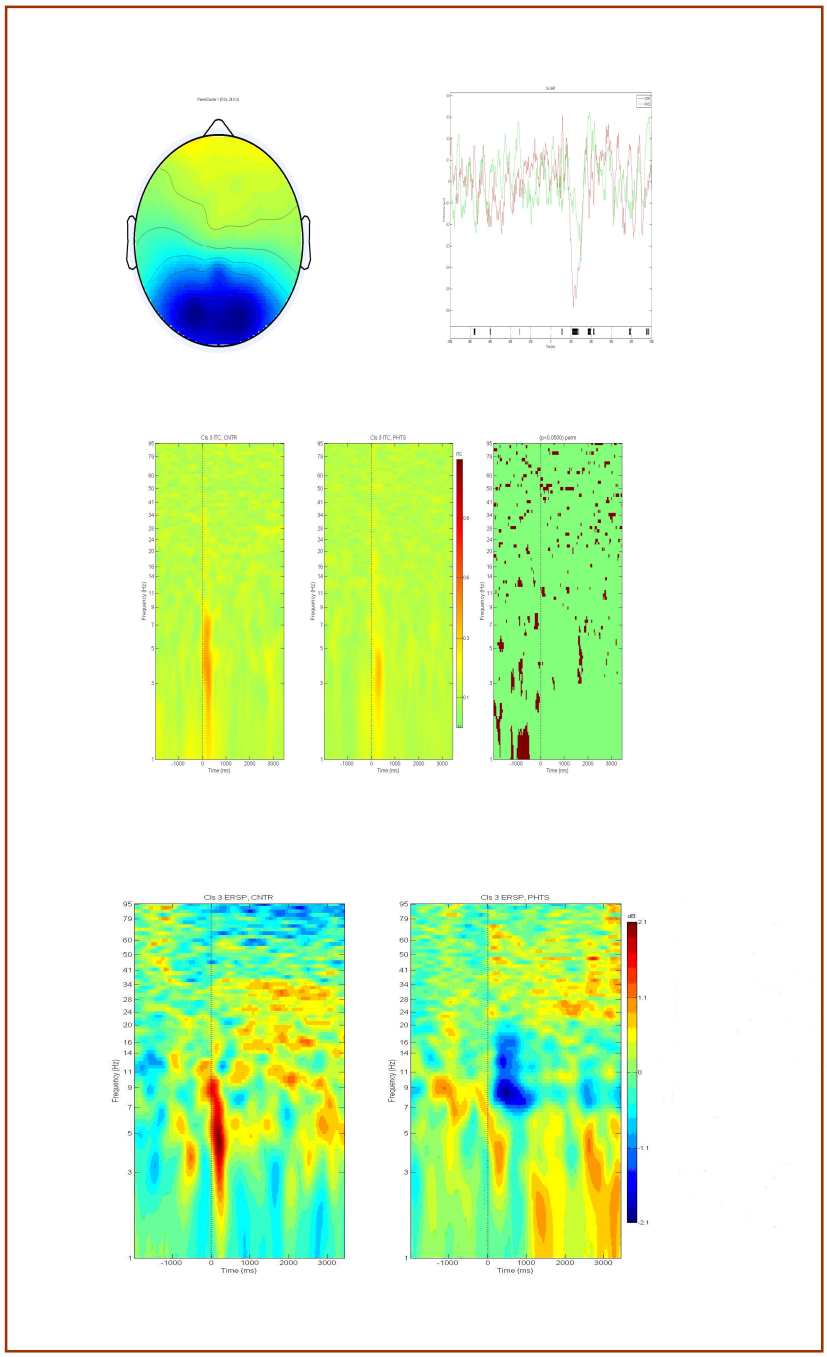
group (Cluster 2, Figure 4.11). In the CONTROL group the peak frequency is settled around 25-40 Hz, in the PS group the peak frequency appears slightly higher, being around 25-60 Hz. One more component cluster (Cluster 3, Figure 4.12) with posterior scalp maxima representation and 1-6 Hz spectral peak accounted for separate posterior delta-theta activation. This cluster is mainly constituted by components belonging to the PS group. No post-stimulus ITC has been demonstrated Cluster 3. Together, the three component clusters accounted for 77% of variance in the grand-mean ERP.

Figure 4.10. Cluster 1 mean scalp map, average ERP and spectrum and average ERSP and ITC



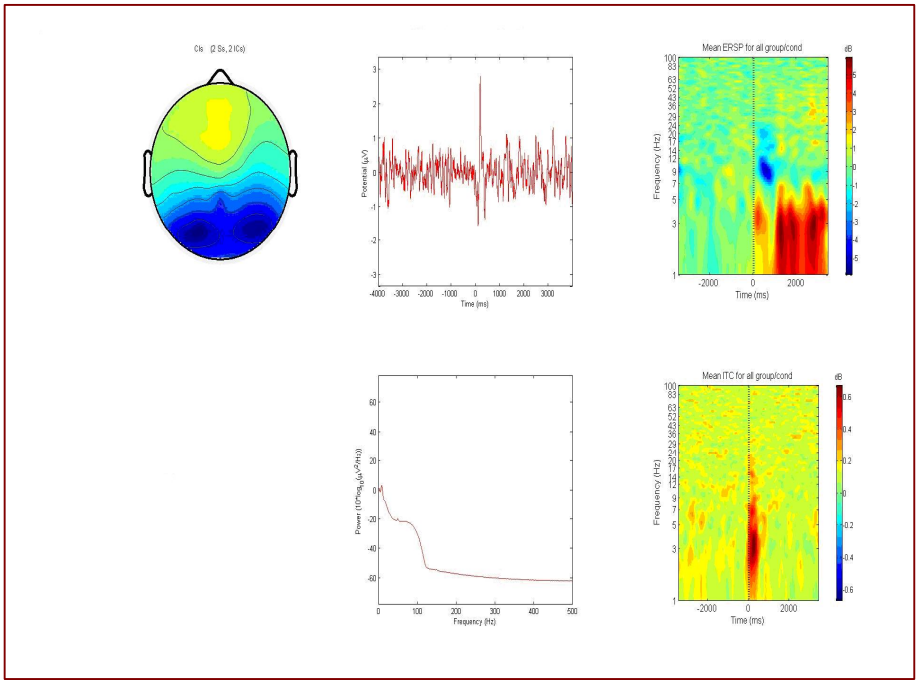
Source: Author

Figure 4.11. Cluster 2 mean scalp map, average ERP and spectrum for both groups and average ERSP and ITC for PS and CONTROL groups



Notes: The bottom left box shows the average ERPS for the component belonging to CONTROL group; the bottom right box shows the average ERP for the component belonging PS group. Source: Author

Figure 4.12. Cluster 3 mean scalp map, average ERP and spectrum and average ERSP and ITC



Source: Author

4.6 Discussion

This study was designed to characterise spatio-temporal and frequency-domain properties of the response of the visual cortex to static stimuli in patients with visual sensitivity. We hypothesised a possible disruption in the physiological thalamic regulation of cortico-cortical synchronisation. Results include three main findings: (1) a significant and sustained post-stimulus desynchronisation in the alpha- beta band (8-20 Hz) in PS and CONTROL groups; (2) an increased evoked and induced gamma band activity power (25-60 Hz) in the PS and CONTROL group, without statistically significant differences between the two groups but a slightly higher peak frequency in the PS group (40-

60 Hz); and (3) a consistent phase locked and sustained synchronisation (increase in spectral power) in the theta band (4-8 Hz) only in the PS group.

The first finding of this study was the presence of an important and sustained desynchronisation in the alpha-beta band in both experimental groups (Figure 4.10). Event related desynchronisation (ERD) can be viewed as generated by changes in one or more parameters that control oscillations in neuronal networks (Pfurtscheller and Lopes da Silva, 1999). Therefore, ERD can be interpreted as an electrophysiological correlate of activated cortical areas involved in processing of sensory or cognitive information or production of motor behaviour (Pfurtscheller, 1992). As widely recognised, an increased and more widespread ERD could be the result of the involvement of a larger neural network or more cell assemblies in information processing. Factors contributing to such enhancement of the ERD are increased task complexity, more efficient task performance (Boiten et al., 1992; Sterman et al., 1996) and/or more effort and attention (Defebvre et al., 1996). A visual input can result not only in a desynchronisation of occipital alpha rhythms but also in an enhancement or synchronisation of central mu rhythms. Brechet and Lecasble (1965) reported on an enhanced mu rhythm during flicker stimulation, Koshino and Niedermeyer (1975) on enhanced (synchronized) rolandic rhythms during pattern vision and Pfurtscheller (1992) on a central alpha power increase in a reading task.

Another finding of this third study is the presence of an induced and evoked gamma band activity, low gamma (25-60 Hz) oscillations, in both PS and CONTROL groups, with a slightly higher frequency in the PS group (Figure 4.11). This result needs to be explained taking into account the role of gamma oscillations in epileptic networks and the few available paper on transition to PPR in photosensitive epilepsy. Gamma band oscillations have been related to the activity of inhibitory interneurons in cortical/subcortical structures (Whittington et al., 1995), to synchronized thalamocortical discharges (Steriade et al., 1996; Llinás and Steriade, 2006), and to the activity of cortical fast rhythmic bursting cells, so-called "chattering" cells (Gray and McCormick, 1996). 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; Alarcon et al., 1995; Traub et al., 2001). Since the presence of gamma band activity seems to be related to the interconnection between subsets of inhibitory interneurons and epileptic activity due to a decrease activity of dendritic GABA(A)ergic slow IPSPs, epilepsy should result in an abnormal enhancement of beta/gamma oscillations. In photosensitive epilepsy, Parra and co-workers (2007) hypothesised 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 (Tallon-Baudry et al., 1997; von Stein et al., 1999). Thus, the critical systems controlling gamma band

oscillations are disrupted in patients with photosensitive epilepsy and may deviate from the normal dynamical range under the influence of intermittent photic stimulation.

The abnormal theta synchronisation can be interpreted as the electrophysiological correlate of disordered connection between thalamus and occipital cortex, in line with the thalamo-cortical dysrhythmia model. The role of theta oscillations in healthy individuals has been investigated mainly in relation with cognitive tasks such as working memory and visuo-spatial paradigms (Raghavachari et al., 2010). Few studies have been conducted to investigate the role of low-frequency oscillations in short latency visual evoked responses and perceptual tasks (Perfetti et al., 2007; Basar-Eroglu et al., 2008). One study on migraineurs (Coppola et al., 2007) reported increase amplitude of gamma band oscillations in PR-VEP and lack of habituation in patients suffering from migraine with aura between attacks compared to healthy volunteers and migraineurs without aura. In line with the thalamocortical dysrhythmia theory, the authors hypothesised that hypofunctioning serotonergic pathways caused a functional disconnection of the thalamus and leading to decreased intra-cortical lateral inhibition. Moreover, the occurrence of low frequency oscillations has been also detected in patients with idiopathic generalised epilepsy (Clemens, 2004) with a study of the interictal spectral power and inter and intra hemispheric coherence of the EEG. The increased theta band oscillations (4-8 Hz) in the PS group (Figure 4.12) observed in our data is in line with the previous literature on thalamocortical

dysrhythmia and with findings of an increased low frequency oscillation in generalised epilepsy (Clemens, 2000). Our study compared photosensitive patients with healthy subjects. Patients with generalised epilepsy without photosensitivity were not analysed. The results seem to suggest a specific role of low frequency activity in determining epileptic photosensitivity. Based on these data, no speculation is possible regarding the role of epilepsy itself. At the anecdotal level, only three subjects belonging to PS group presented PPR and reflex-only seizures. They showed the same sustained theta power increase in the occipital cortex throughout the duration of the visual stimulation as the other PS subjects with a diagnosis of generalised epilepsy. If confirmed on a larger cohort of patients with IGE and photosensitivity vs. reflex epilepsies, this finding would suggest a specific role of theta oscillation in photosensitivity, rather than a mere reflection of an "epileptic phenotype". In conclusion, a change of thalamocortical activity, due for instance to an anatomical or functional disconnection of the thalamus, can indeed favour low frequency activity which at the cortical level will reduce lateral inhibition and enhance high-frequency phase-locked discharges in cortical networks of inhibitory interneurons. The so-called thalamocortical dysrhythmia (TCD), rather than a syndrome as proposed in several studies (Llinás et al., 1999; Llinás and Steriade, 2006) could be a shared mechanism of a number of pathological conditions including photosensitive epilepsy.

4.7 Conclusions

This third experiment provides supporting evidence to the existence of a disordered connection between thalamus and occipital cortex in photosensitive epilepsy. To the best of our knowledge, this is the first study to explore the mechanism of thalamocortical dysrhythmia in photosensitive epilepsy.

Chapter 5

Thesis conclusions

5.1 Conclusions

The complementary findings of the three studies on which the present doctoral dissertation is based, provide further evidence that photosensitivity is associated with altered balance between excitatory and inhibitory cortical processes. Although a strong association exists between specific epileptic syndromes and visual sensitivity, we put forward the hypothesis that photosensitivity - at least from a neurophysiological point of view - might be the expression of specific mechanisms of which the habituation of PR-VEP represents one of the intermediate phenotypes. Further studies, investigating the relationship between indices of cortical excitability and specific polymorphisms of genes involved in inhibitory neurotransmission, would further clarify whether suppression of the PR-VEP and some features of thalamocortical dysrhythmia might represent an endo-phenotype of photosensitivity. The impaired habituation, as found in the first study, and the dysfunction of thalamocortical connections, as demonstrated in this last study, have been recently reported in adults with migraine with aura (Coppola et al., 2007). The relationship between headache/migraine and epilepsy has been widely studied in terms of clinical manifestations (Panayiotopoulos, 1999), neurophysiological correlates (Parisi et al., 2008) and possible pathophysiological mechanisms (Kasteleijn-Nolst Trenité et al., 2010). A core of neuronal alteration of cortical excitability has been reported for both conditions (Lauritzen, 1987). Epileptic seizures such as migraine attacks seem to be triggered by excessive neocortical excitability;

however, the hyper-excitability is believed to produce a characteristic hypersynchronous activity in epileptic seizures, and cortical spreading depression in migraine. In addition, the presence of a shared biological substrate (Piccioli et al., 2009) is supported by the higher percentage of electroencephalographic abnormalities in patients with migraine with visual aura (MA) than in the other type of headaches, and by the high prevalence of photosensitivity - usually in the form of generalized photoparoxysmal discharges - in patients with MA (Piccinelli et al., 2006). Furthermore, there is evidence that shared genetic risk typically exemplified by the so called channelopathies, contributes to the risk for both migraine and epilepsy (Rogawski, 2008). Shared genetic factor could lead both conditions to the final pathway of cortical excitability, which manifests itself through different clinical signs of migraine and photosensitive epilepsy. In this sense, the two conditions might represent two extremes of the same neurophysiological spectrum. The pathway which leads similar neurophysiological phenomena to translate into apparently distinct clinical conditions remains to be clarified. The fact that visual habituation is preserved in patients with idiopathic generalised epilepsies without photosensitivity seems to exclude that lack of habituation is an expression of an “epilepsy” predisposition.

In conclusion, taking together the evidence from the three studies reported in this thesis, we could attempt a unitary hypothesis. Lack of habituation of PR-VEP, low pre-stimulus alpha band power and the enhanced gamma and theta oscillations in photosensitive patients could

be interpreted as an expression of disrupted thalamo-cortical connections. We are not in a position to establish beyond doubt whether this dysfunction is primarily the result of a top-down disregulation of rather secondary to abnormal afferent drive to the thalamus from a hyperexcitable occipital cortex. In this favourable background substrate, visual stimuli with specific physical characteristic, as postulated by the quantity of light and wavelength dependent theory (Takahashi et al., 1995; Harding and Fylan, 1999), can swing in resonance with the ongoing hypersynchronous activity (Parra et al., 2003) - and lead firstly to an alteration of electroclinical activity as shown in PPR and subsequently to clinical manifestations. In analogy with the theory of thalamocortical dysrhythmia applied to Parkinson disease, the clinical manifestations in photosensitive epilepsy can be interpreted as the positive symptoms of Parkinson. Thus, the protracted hyperpolarisation of occipital cortex will results in excess inhibition, generating thalamic cell membrane hyperpolarisation and thalamic low-frequency oscillations. At a cortical level, the reduction of lateral inhibition produces coherent gamma frequency oscillation and the clinical symptoms. The different clinical manifestation can be interpreted considering the variability of thalamic networks involved.

Following this hypothesis, which combines the previous studies on the nature of the visual stimuli and on the significance of cortical excitability, the role of visual stimuli characteristics is suggested by the fact that a possible treatment measure in photosensitive epilepsy is the

use of lenses of specific filtering frequency; the role of the favourable occipital background is suggested by the use of antiepileptic medications which probably act on the specific epileptic syndrome more than on the peculiar mechanism of photosensitivity.

5.2 Limitations

We are aware that experiments performed in this thesis have intrinsic limitations.

- First of all the sample size of the third study was relatively limited. Whilst the effect size proved to be very large, one has to accept that replicating the findings on a larger sample including a group of patients with idiopathic generalised epilepsy without photosensitivity would give further strength to our findings, which need to be considered as still preliminary;
- A second limitation is represented by the fact that, in all the three experiments, a small subset of subjects in both the IGE and PS groups were medicated at the time of the study. Whilst one would ideally prefer drug-free participants to test the experimental hypothesis without having to deal with drug treatment within the design of statistical analysis, this is often difficult for the ethical dimension of delaying treatment.
- Finally, the poor compliance of some of our paediatric patients in performing visual tasks, such as the ones designed for this thesis, has led to the exclusion of a several data sets at the analysis stage due to excessive motion or difficulties in maintaining constant visual focus on the stimulus.

5.3 Future research

Results of our studies could be taken forward. Further investigation rising from the findings of this preliminary work could include:

- Quantification of resting GABA concentration in visual cortex using magnetic resonance spectroscopy, to compare the three groups of participants, ND, IGE, PS. This future research could allow further pursuing of the idea advanced in the first part of this thesis that an abnormal response to visual habituation in photosensitive epilepsy could be an expression of an altered mechanism of sensory gating control as it might result in neurotransmitter disorders.

- In view of the clinical contiguity between photosensitivity and migraine particularly in paediatric age, an additional line of investigation could pursue the application of the same structured paradigms utilised in this thesis to explore the neurophysiological background of paediatric migraine and to further characterise the possible pathophysiological mechanisms shared by the two conditions.

- Another matter of interest suggested by the results of the first study could be to link the lack of habituation in photosensitive epilepsy and genetic polymorphisms of relevant neurotransmission.

- Finally, an important source for future research could be to pursue systematically the role of thalamocortical dysrhythmia in photosensitive epilepsy, for example by performing additional analyses with techniques such as MEG and simultaneous EEG-fMRI, which have the ability to improve spatiotemporal resolution.

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Appendix 1:

Abdominal *migralepsy* or simple comorbidity between abdominal migraine and photosensitivity? A case of shared neurophysiological background

A.1. Introduction

A.1.1 Abdominal migraine

Under the denomination of childhood periodic syndromes, several recurrent, transient, and otherwise unexplained symptoms and signs have been described as being precursors of migraine: cyclical vomiting, abdominal migraine, fever, parasomnias, motion sickness, benign paroxysmal torticollis, pseudoangina, Tourette syndrome, hyperactivity, and benign paroxysmal vertigo of childhood. Evidence linking some of these symptoms to migraine is robust, but for others the association has been described almost anecdotally (Cuvellier and Lépine, 2010). The International Classification of Headache Disorders, 2nd edition (International Headache Society, 2004) defines the diagnostic criteria for abdominal migraine and for cyclical vomiting as precursors of migraine, but does not mention other potential childhood periodic syndromes. In the HIS-classification ICHD-II abdominal migraine is classified among "childhood periodic syndromes that are commonly precursor of migraine" somewhat implying its classification as a sub-type of migraine. The attacks are characterised by periodic bouts of moderate to severe midline abdominal pain lasting between 1 and 72 hours. The abdominal pain is associated with other vasomotor symptoms such as flushing or pallor, nausea and vomiting. History and physical examination do not show signs of gastrointestinal or renal disease or such disease has been ruled out by appropriate investigations. Pain is severe enough to interfere

with normal daily activities. Most children with abdominal migraine will develop migraine headache later in life. The limited existing literature suggests that the antimigraine drugs pizotifen, propanolol and cyproheptadine can be effective prophylactics drugs. Nasal sumatriptan (although not licensed for paediatric use) may be effective in relieving abdominal migraine attacks (Russel et al., 2002). Prevalence of abdominal migraine was found to be about 2-4% between 3-11 years (Mortimer et al., 1993) and 1-4% between 5-15 years (Abu-Arafeh and Russell, 1995). This condition appears to be much more frequent in females rather than males, age of onset is typically around 7 years old with two distinct peaks at 5 and 10 years old. Studies on abdominal migraine are sparse (Goadsby et. al, 2009) and a clear definition of abdominal migraine's aetiophatogenesis is lacking. Some reports suggest that abdominal migraine could account for paroxysmal abdominal pain in a significant number of adults (Axon et al., 1991; Long et al., 1992). Table A.1.1 summarises diagnostic criteria of abdominal migraine.

Table A.1.1: Diagnostic criteria of abdominal migraine

Diagnostic criteria
A. At least 5 attacks fulfilling criteria B-D
B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)
C. Abdominal pain has all of the following characteristics:
a. midline location, periumbilical or poorly localised
b. dull or "just sore" quality
c. moderate or severe intensità
E. During abdominal pain at least 2 of the following:
▪ anorexia
▪ nausea
▪ vomiting
▪ pallor
F. Not attributed to another disorder

Source: International Headache Society (2004)

A.1.2 Migralepsy

Despite almost two centuries of investigations, the relationship between epilepsy and migraine has not been completely elucidated. A core of neuronal alteration of cortical excitability has been reported for both conditions (Lauritzen, 1987). The term ‘‘migralepsy’’ was first used by Lennox & Lennox (1960) to describe a condition whereby ‘‘ophthalmic migraine with perhaps nausea and vomiting is followed by symptoms characteristic of epilepsy’’. This term has been subject to criticism by several authors and recently considered as too narrow a definition (Sanchez et al., 2010). However, despite this scepticism, migralepsy has been included in the recent International Classification of Headache Disorder II (ICHD-II) (International Headache Society, 2004),

based on the fulfilment of two criteria: (1) migraine fulfilling criteria for 1.2 Migraine with aura (MA); (2) a seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 hour after a migraine aura. This definition does not consider other situations of shared clinical evidence between epilepsy and migraine. To overcome this incomplete classification, some authors have tried to clarify several nuances of the relationships between epilepsy and headache. These authors suggested a revision of the diagnostic criteria of “hemicrania epileptica” in migraine and epilepsy classification, and the introduction of the more specific term of ‘‘ictal epileptic headache’’ (Piccioli et al., 2009). Furthermore, in a recent comment, Parisi and Kastelejin (2010) call for a revision of the definition of migralepsy.

The importance of EEG recording with standardised IPS has been also pointed out in migraine, although contemporary reviewers have criticized most of the EEG studies, emphasizing the frequent abnormal recordings in migraine for various methodological omissions and flaws (Sand, 1991; 2003). The American Academy of Neurology concluded that "EEG is not useful in the routine evaluation of patients with headache (guideline)", admitting, however, that EEG may be used in headache patients with associated symptoms suggesting a seizure disorder.

The present chapter describes a case in which a particular subtype of migraine - abdominal migraine - shows clinical and electroclinical signs of photosensitivity and shares photosensitivity’s neurophisiological background. Additional suggestions of a strong comorbidity between the

two diseases and an improved and wider definition of migralepsy are proposed.

Table A.1.2: Diagnostic criteria for hemicrania epileptica

Diagnostic criteria
A. Headache lasting seconds to minutes, with features of migraine, fulfilling criteria C and D B. Headache develops synchronously with the seizure and is ipsilateral to the ictal discharge C. The patient is having a partial epileptic seizure D. Headache resolves immediately after the seizure

Source: International Headache Society (2004)

Table A.1.3: Diagnostic criteria for migralepsy

Diagnostic criteria
A. Migraine fulfilling criteria for 1.2 Migraine with aura (MA) B. A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 h after a migraine aura.

Source: International Headache Society (2004)

A.2 Case report

An 11-year-old right-handed girl was referred to the Child and Adolescent Psychiatric Department, Birmingham Children Hospital, for a second opinion regarding episodes of recurrent abdominal pain, occasionally associated with vertigo, blurred vision and pallor.

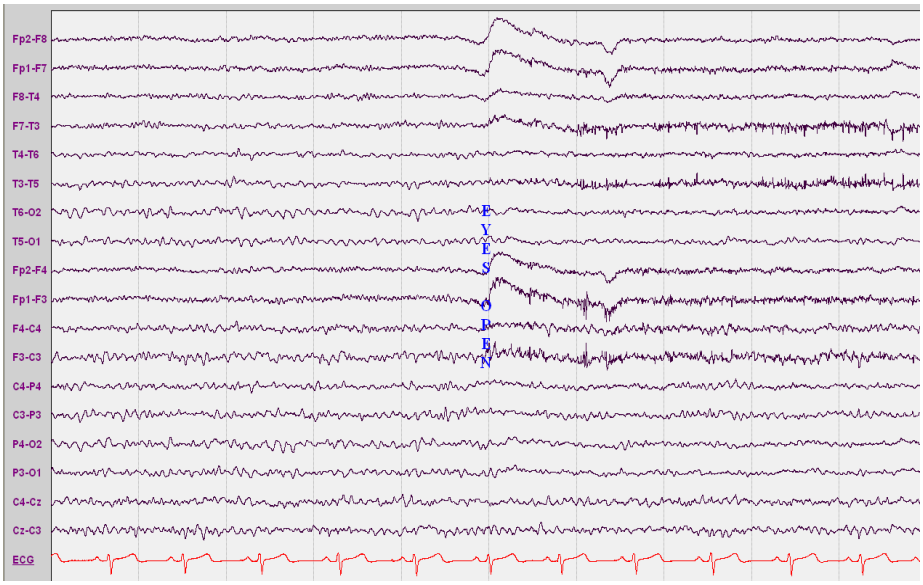
She was born full term with a normal delivery and had normal developmental milestones. Her mother suffered from migraine and maternal grandfather for nocturnal seizure. All the gastroenterological investigations, including endoscopy, carbon breath test and test for porphyria were negative. The onset of the symptoms dates back when she was 3 years old with short-lasting (i.e., a few hours) monthly episodes of abdominal pain associated with pallor; she was diagnosed with mesenteric adenitis and treated with Merbentyl syrup. From the age of 5 the episodes became more prolonged (i.e., up to 2-3 days) and irregular. The child could be asymptomatic for long periods interrupted by periods when episodes were more frequent (i.e. every 2 weeks). The abdominal pain was midline-located and associated with anorexia, nausea, pallor and occasionally with vomiting. During the year prior to our observation the characteristics of the abdominal pain had remained unchanged but other symptoms such as headache, pain in the left eye, colour distortion, blurred vision, tinnitus and dizziness were occasionally referred. She performed a gastroscopy and was treated for gastro-oesophageal reflux and ulcer. Ranitidine, Omeprazole, triple therapy for helicobacter resulted in very slight and time-limited relief. In the beginning of 2010 she came to our attention because of a prolonged cluster of the typical attacks which lasted about a week. She complained of constant abdominal pain and presented with nausea and vomiting. We were asked to evaluate the hypothesis of a psychosomatic disorder. Physical,

neurological and psychiatric examinations, electrocardiography (ECG), gastroscopy, urine and stool porphyrins, and breath test were all normal.

An EEG showed normal background activity in the resting state. During IPS, PPR type 3-4 in the majority of middle frequencies was recorded. Further anamnesis suggested that some episodes of abdominal pain might have been associated with precipitating visual stimuli. A 3-Tesla MRI was performed and reported as normal. We diagnosed abdominal migraine and re-evaluated her at the Clinical Neurophysiology Unit at Aston University for a depth investigation of her photosensitivity. We performed a standard 21- channel EEG and a 128 channel dense array EEG recording, with hyperventilation and intermittent photic stimulation, checking all the frequencies with monocular occlusion and using coloured lenses. Habituation test as described in the first study (Chapter II) and a visual VEP recording, as described in the third study (Chapter IV) were also carried out and analysed accordingly. Photic stimulation was performed at least 15' prior to VEP recordings using a Grass PS 22 stimulator and consisted of ten-second periods of regular frequencies at 5, 10, 12, 15, 18, 20, 25, 50, 60 Hz. In accordance with recommended guidelines, subjects had their eyes open during the first 5 seconds of each period of visual stimulation at a particular frequency and were asked to close their eyes for a period of 5 seconds (Kasteleijn-Nolst Trenité et al., 1999b). Unfortunately, in this occasion we were not able to capture a typical episode during the EEG. She presented a normal background EEG, no changes were noticed during the hyperventilation.

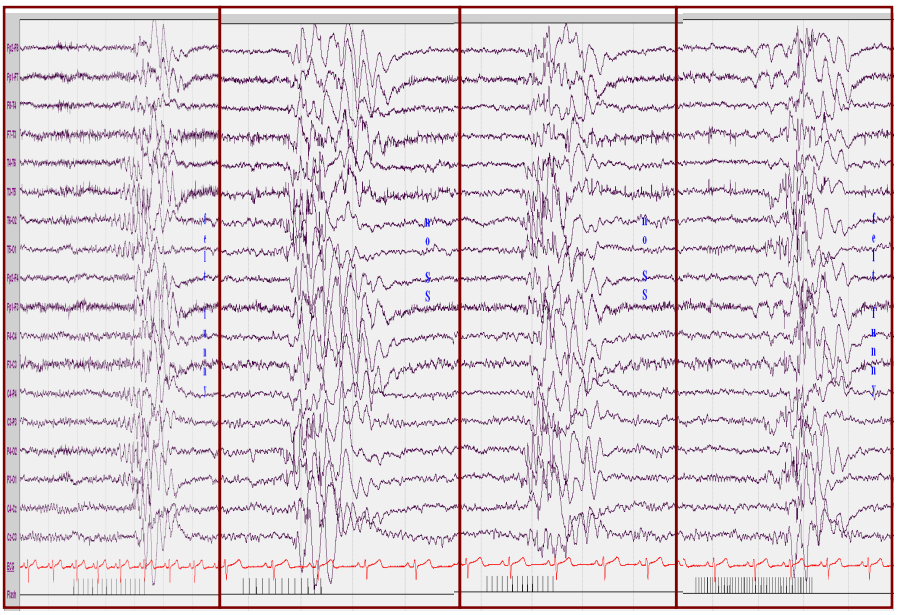
Photic stimulation evoked abnormalities within the range of 5-50 Hz (Waltz PPR response type 3-4) inconsistently associated with a sensation of “funny feeling”. Monocular occlusion offered full protection when either eye was covered (right better that left). Photochromic sunglasses provided by the patient and coloured lenses (Clarlet Z1 Zeiss blue lenses and full range of chromatic filters with 20% transmittance and spectral window across the red and blue wavelength) had no protective effect. Pattern stimulation demonstrated abnormality to a wide range of frequencies. No pure pattern sensitivity was detected; she required a change in luminance together with a change in contrast to evoke abnormality. She presented a clear photosensitivity with generalised PPR at all frequencies between 5-50 Hz, sometimes associated with a funny feeling subjective sensation (Fig. A.1.1; Fig A.1.2).The results were reproducible during the dense array EEG.

Figure A.1.1. Example of PPR response



Source: Author

Figure A.1.2. Example of PPR at respectively 6, 8, 10 and 16 flashes/second.

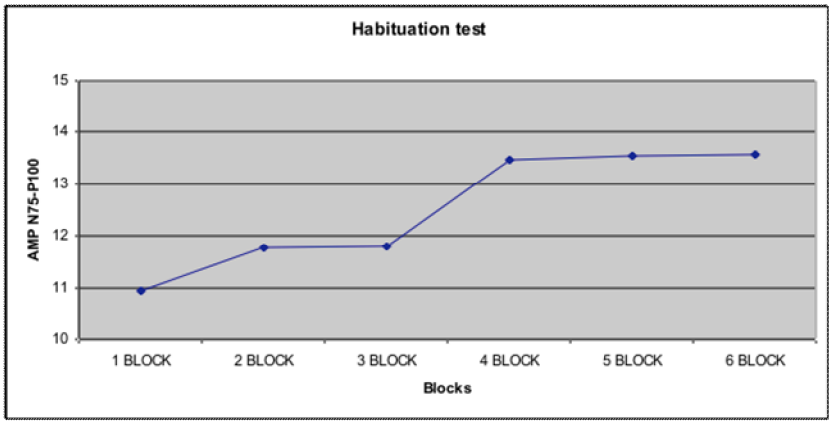


Source: Author

Notes: presence of funny feeling sensation at 6 and 16 flashes/second. No sensations reported at 8 and 10 flashes/second.

Habituation test was well performed and tolerated. She presented a deficit of habituation in PR-VEP (increase of N75-P100 PR-VEP amplitude in the sixth block of stimulation compared to the first one) (Fig. A.1.3).

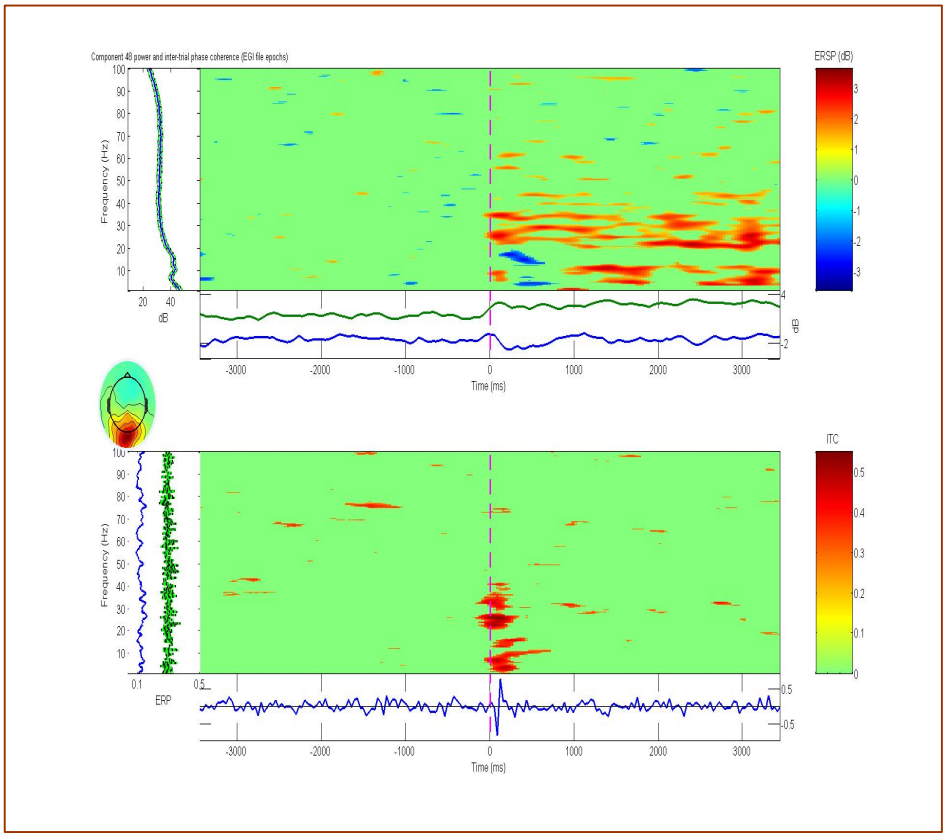
Figure A.1.3. N75-P100 PR-VEP amplitude across the 6 blocks of stimulation.



Source: Author

Visual VEP test was well performed and tolerated as well. A time frequency analysis of the results, as described in Chapter IV, provided evidence of evoked and induced high power gamma band activity in the range of 25-60 Hz and significant phase locked and sustained synchronisation in the theta band (4-8 Hz), as shown in Figure A.1.4. In summary, the patient showed the same electroclinical behaviour previously reported in the group of patients with epilepsy and photosensitivity (PS).

Figure A.1.4. ERPS and ITC representations of component 48.



Notes: The component explains 73% of variance. Image on the top shows power increase in the 1- 4 Hz band induced by the onset of the 3-cpd contrast gratings and sustained during the whole active period and in the gamma band 25-50 Hz. Blue and red colours represent the percentage of significant power decrease and power increase respectively. Source: Author

A.3. Discussion

A series of clinical, neurophysiological and genetic data support the hypothesis of alteration of cortical excitability as a potential mechanism underlying the pathology of both epilepsy and migraine (Gilliam and Perucca, 2008). Although anecdotal, this case presentation of a childhood variant of migraine and photoparoxysmal response on the EEG could be considered as supportive of a possible continuum between some forms of

migraine and epileptic photosensitivity. From a clinical point of view the diagnosis of this young girl created some difficulties in terms of differential diagnosis. However, forms of focal idiopathic epilepsy such as occipital lobe epilepsy or abdominal epilepsy were excluded based on the long duration of the attacks and the apparent normal background. Panayiotopulos syndrome was also excluded due to the high frequency of attacks, the absence of a clear autonomic status at the end of the attacks and for the apparent normal background EEG. The most plausible diagnosis was abdominal migraine as all the diagnostic criteria were fulfilled.

Abdominal migraine is considered a migraine variant with a precise onset during childhood, together with other periodic syndromes. Its precise pathogenetic mechanism is unknown; nevertheless some author suggested the possible involvement of precise age-related brain plasticity conditions, in the contest of other periodic syndromes such as cyclic vomiting. The presence of PPR and interictal EEG abnormalities in patients affected by migraine/ headache is not an unusual finding (Piccinelli et al., 2006). To our knowledge no description of PPR in patients with abdominal migraine is available. The occurrence of photosensitivity in patients with headache as a sole manifestation of epilepsy and in migralepsy has also been widely described (Parisi et al., 2008). In the migrainous paediatric population the risk of epilepsy was estimated to be 3.2 times higher than in tension-type headache, without significant difference between migraine with and without aura; children

with epilepsy have a 4.5 times higher increased risk of developing migraine than children with tension-type headache. However, the risk of photosensitivity is higher only in cases with comorbidity (Toldo et al., 2010). Interestingly, many patients affected by the so-called ‘‘ictal headache’’ presented photosensitive clinical history and a photoparoxysmal electroencephalography (EEG) response, have intermittent photic stimulation (IPS)-evoked headache, and usually a family history of epilepsy and migraine (Walker et al., 1995; Parisi et al., 2007; Piccioli et al., 2009). In a recent paper Parisi et al. (2008) propose the idea that several aetiopathogenetic mechanisms converge into a final pathway represented by membrane hyperexcitability, manifesting as either epilepsy or headache/migraine. The clinical manifestations, time of onset and the spreading of each disorder might depend on anatomo-neurobiological variables. The present report clearly supports this hypothesis, with neurophysiological evidence. Whether the patient described represents a mere case of comorbidity between epilepsy and migraine, or a boundary-spanning case between the two conditions (e.g., migralepsy), is open to debate. However, our patient presented clinical signs of both conditions (a variant of migraine and photosensitivity) and electroclinical behaviour comparable to the one we have described in patients with idiopathic generalised epilepsy and photosensitivity (see Chapter II and IV). In particular the lack of habituation and signs of thalamocortical dysrhythmia, which characterise the neurophysiological background of this patient, have been described in the contest of

paediatric photosensitive patients and also found in previous migraine studies (Schonen et al., 1996; 2003; Coppola et al., 2007). Both this findings have been considered as indirect signs of altered cortical excitability. Furthermore, the present results support the hypothesis of an unbalance in occipital cortex excitatory mechanisms and indicate an overlapping between epilepsy and migraine on the basis of a shared neurophysiological background.

Another interesting topic is the difference in the clinical presentation between adults and children, particularly in the presence of autonomic manifestations. Children display more autonomic manifestations than adults both in the case of headache clinical picture, and in that of early benign focal idiopathic epileptic syndromes, such as Panayiotopoulos syndrome. The argument of a shared neurophysiological background can be applied to investigate the pathogenesis of abdominal migraine. As Panayiotopoulos syndrome, could be the early-onset of rolandic epilepsy, abdominal migraine could be the early onset of migraine and could represent the prototype of a maturational-related disease. Cortical excitability facilitates ictal discharges in Panayiotopoulus syndrome which, irrespective of their location at onset, activate autonomic disturbances and emesis, to which children are particularly vulnerable (Covanis, 2006). Abdominal migraine can be interpreted as an age-related combination of cortical hyperexcitability and unstable autonomic system. When the cortical area exceeds a critical epileptogenic level it will first activate the autonomic system but it may not be strong enough

to activate a cortico-cortical ictal discharge that would generate somatosensory or visual symptoms (Koutroumanidi, 2007). In symptomatic focal epilepsies ictal autonomic manifestations are thought to result from discharge propagation through rich limbic connections to hypothalamus, but also to discrete autonomic cortical centres; this connecting pathway could be applicable to abdominal migraine as well.

A.4 Conclusions

The findings of this case report complement the conclusions reached in the previous three studies. Findings of this case report suggest that alteration of cortical excitability is a phatophysiological background for photosensitivity and migraine; thus, photosensitivity and migraine might share the same neurophysiological mechanism. Reconsideration of the usefulness of EEG recording with IPS is necessary in patients with migraine and migraine variants as well.

Appendix 2:

List of abbreviations

Table A2.1. List of abbreviations used in the thesis

BOLD	Blood Oxigen Dependent Level
CBF	Cerebral Blood Flow
CRT screen	Cathode Ray Tube
EDF	European Digital Format
EEG	Encephalography
ERP	Event Related Potentials
ERSP	Event Related Spectral Perturbation
f-MRI	Functional Magnetic Resonance Imaging
GABA	Gamma Aminobutyric Acid
GAERS	Genetic Absence Epilepsy in Rats from Strasbourg
GMV	Grey Matter Volume
ICA	Independent Component Analysis
ICHD	International Classification of Headache Disorder
IGE	Idiopathic Generalised Epilepsy
IPS	Intermittent Photic Stimulation
IPSP	Inhibitory Postsynaptic Potential
ITC	Inter Trial Coherence
ITPC	Inter Trial Phase Coherence
JME	Juvenile Myoclonic Epilepsy
LCD	Liquid Crystal Display
MA	Migraine with aura
MEG	Magnetoencephalography
LFP	Local Field Potentials
MRS	Magnetic Resonance Spectroscopy
MUA	Multi Unit Activity Analysis
MWA	Migraine without Aura
ND	Normally Developing Children
NTSC	National Television System Committee
OS	Occipital Spikes
PAL	Phase Alternate Line
PET	Positron Emission Tomography
PPR	Photoparoxismal response
PR-VEP	Pattern Reversal Visual Evoked Potentials
PS	Photosensitive Epilepsy
TCDS	Thalamo Cortical Dysrhytmia
VPA	Valproate
VEP	Visual Evoked Potentials
VG	Video-games
VSG	Visual Stimulator System

Source: Author