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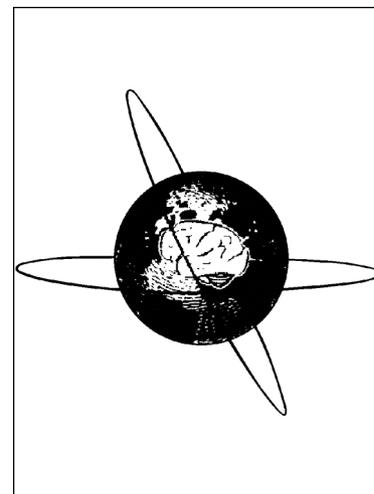
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The topographical distribution of epileptic spikes in juvenile myoclonic epilepsy with and without photosensitivity

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Abstract

Objective: Up to 30% of people with juvenile myoclonic epilepsy (JME) have photoparoxysmal responses (PPR). Recent studies report on structural and pathophysiological differences between people with JME with (JME+PPR) and without PPR (JME-PPR). We investigated whether electrophysiological features outside photic stimulation differ between these subtypes.

Methods: We analysed EEG recordings of people with JME at a tertiary epilepsy centre and an academic hospital. Photosensitivity was assessed in a drug-naïve condition. We compared the occurrence and involvement of posterior electrodes for focal abnormalities and generalised spike-wave activity in the EEG outside photic stimulation between JME+PPR and JME-PPR.

Results: We included EEG recordings of 18 people with JME+PPR and 21 with JME-PPR. People with JME-PPR had less focal abnormalities in the posterior brain regions than people with JME+PPR (19% vs 55%, $p < 0.05$). There was no difference in the distribution of generalised spike-wave activity between people with JME+PPR and JME-PPR.

Conclusion: This study demonstrates electrophysiological correlates of the previously described structural and physiological differences between JME+PPR and JME-PPR.

Significance: Findings support the hypothesis that posterior interictal EEG abnormalities reflect localised cortical hyperexcitability, which makes patients with JME more sensitive to photic stimuli.

Keywords: Juvenile Myoclonic Epilepsy, Photosensitivity, intermittent photic stimulation, interictal discharges, Electroencephalography.

Highlights

- Epileptic spikes in photosensitive juvenile myoclonic epilepsy are prevalent in occipital areas.
- The location of the maximum of generalised abnormalities is not affected by photosensitivity.
- There are likely different epileptic networks in photosensitive and non-photosensitive JME.

Abbreviations:

JME: Juvenile Myoclonic Epilepsy

PPR: Photoparoxysmal response

AED: Anti-epileptic drugs

1. Introduction

Juvenile myoclonic epilepsy (JME) is a type of genetic epilepsy characterised by myoclonic jerks shortly after awakening, and generalised tonic clonic seizures. The diagnosis is based on the clinical presentation and confirmed by 3-6 Hz generalised spike-wave (GSW) or polyspike-wave (PSW) activity on the electroencephalographic (EEG) recording. Over a third of people with JME also have absence seizures. (Beghi *et al.*, 2006) Focal abnormalities such as single spikes, spike-wave complexes and slow waves are seen in 30-45% of cases (Aliberti *et al.*, 1994; Lancman *et al.*, 1994; Seneviratne *et al.*, 2014). At least thirty percent of people with JME also have a photoparoxysmal response (PPR) and myoclonic jerks or generalised tonic clonic seizures triggered by flashing lights (Appleton *et al.*, 2000; Wolf and Goosses, 1986). The PPR is an abnormal response to intermittent photic stimulation. There are four types of PPR: (I) spikes within the occipital rhythm, limited to the occipital regions (II) parieto-occipital spikes with a biphasic slow wave, (III) parieto-occipital spikes with a biphasic slow wave and spread to the frontal region, and (IV) generalised spikes and wave or polyspikes and wave (Waltz *et al.*, 1992). Types (I) and (II) are generally seen as unrelated to epilepsy (Kasteleijn-Nolst Trenité *et al.*, 2001; Waltz *et al.*, 1992). The prevalence of PPR in the general population is estimated around 1.5% (Koeleman *et al.*, 2013). Type (III) and (IV) are considered abnormal. Especially type (IV) appears to be correlated with epilepsy (Kasteleijn-Nolst Trenité *et al.*, 2001). Several recent imaging studies have shown different connectivity patterns in people with JME+PPR and JME-PPR (Bartolini *et al.*, 2014; Vollmar *et al.*, 2012).

We investigated whether the clinical interictal EEG patterns differ between people with JME+PPR type (III) or (IV) and JME-PPR (including PPR type (I) and (II)), by comparing the locations where interictal generalised activity and focal epileptiform abnormalities are seen. We hypothesise that in JME+PPR, there are more interictal EEG abnormalities involving the posterior regions than in JME-PPR.

2. Methods

2.1 EEG selection

We obtained EEG recordings of people with JME, by screening the electronic EEG report databases at Stichting Epilepsie Instellingen Nederland (SEIN), a tertiary referral centre for epilepsy, and at a teaching hospital, University Medical Center Utrecht (UMCU) using the keywords “JME” and the Dutch word for juvenile (“juvenile”). The search encompassed EEG recordings carried out between 1999 and early 2015 at the epilepsy centre and 2010 to 2015 at the teaching hospital. The study was approved by the Medical Ethical Committee of the UMCU, which judged informed consent unnecessary as it pertained a retrospective analysis of data collected for clinical purposes. Data were coded for analysis.

Only recordings of people not taking anti-epileptic drugs (AED) were included. Inclusion criteria were: (a) a confirmed diagnosis of JME (“confirmed JME”) or a confirmed diagnosis of IGE with a strong suspicion for JME (“probable JME”), based on the EEG or clinical presentation; (b) at least one drug naïve EEG recording available; (c) photosensitivity tested using intermittent photic stimulation, either during the EEG recording that was evaluated for the current study or in a previous EEG recording. Exclusion criteria were: (a) incomplete records; (b) any history of neurological comorbidity that could influence the diagnosis of JME; (c) any MRI abnormalities. Duplicates and reports other than EEG reports were excluded. Clinical information was retrieved from the hospital files.

2.2 EEG recordings and photic stimulation

At SEIN, the 32-channel EEG recordings were recorded at 500 Hz using Stellate Harmonie (Stellate inc, Montreal, Canada) and a Grass photic stimulator (PS33+, Grass Products, Quincy, Mass., USA) until 2012 and subsequently at a 512 Hz sample frequency with a SystemPlus Micromed EEG system (Micromed SD 16 DC, Treviso, Italy) and photic stimulator (Micromed, Flash 10S Treviso, Italy). The frequencies used for photic stimulation were 2-5-10-15-20-25-30-40 and 50 Hz, with 6-14-16 and 18 Hz added if necessary to determine exact ranges of photic sensitivity. Participants were asked to close their eyes at the same time that stimulation started. At the UMC Utrecht EEGs were recorded using the Micromed Smart Acquisition Module amplifier (Micromed, Treviso, Italy), at a sample frequency of 512 Hz and intermittent photic stimulation was performed using the Micromed stimulator, and additionally the Grass stimulator in cases in which photosensitivity is suspected. Photic stimulation with eyes open was done with 14-16-18-20-25-15-10-5-2 Hz. For 14-16-18 Hz, participants were asked to close their eyes at the same time that stimulation started. The frequencies 20-15-10-5-2 Hz were tested when the participant had their eyes closed. In both centers, electrodes were placed according to the international 10-20 system, with additional electrodes on the ear lobes (A1 and A2). Conventional 10 mm Ag-AgCl electrodes were used. EEG recording was performed according to the standard clinical protocol, with or without sleep deprivation.

2.3 EEG analysis

After selecting the EEG reports, we retrieved the original EEG recordings. They were re-evaluated by an experienced neurophysiology technician (WS) who was familiar with the reporting style of both centres. The technician was blinded for the research question and assessed the location of focal abnormalities and the location of the maximal amplitude of generalised EEG abnormalities in all EEG recordings. The localised (focal) epileptiform abnormalities outside intermittent photic stimulation or hyperventilation were assessed. Localised abnormalities were defined as paroxysmal focal activity, localised (poly)spike-and-slow-wave activity and (poly)sharp-and-slow-wave complexes. We divided the EEGs into four groups based on the location of the interictal localised abnormalities: No localised abnormalities at all (L-); localised abnormalities present, but not involving the posterior regions

(L_{POST-}), see figure 1a; localised abnormalities present, also in posterior regions (L_{POST+}), see figure 1b; localised abnormalities present only in the posterior regions (L_{IPOSTI}), see figure 1c. The EEGs were also divided in terms of the maximum amplitude of generalised or bilateral synchronous discharges outside intermittent photic stimulation as follows: No generalised abnormalities at all (G-); generalised discharges with maximal amplitudes in the anterior regions (G_{ANT>POST}), see figure 1d; generalised discharges with maximal amplitudes in the posterior regions (G_{POST>ANT}); bilateral synchronous discharges without a clear or alternating maximum (G_{ANT=POST}), see figure 2; bilateral synchronous spike-wave discharges limited to the anterior regions (G_{IANTI}); bilateral synchronous spike-wave discharges limited to the posterior regions (G_{IPOSTI}).

Reports were also divided according to the presence of PPR, defined as an abnormal posterior response spreading to anterior regions (Waltz criteria III or IV)(Waltz *et al.*, 1992). Waltz I and II were included in the JME-PPR group. People were divided into JME-PPR and JME+PPR based on all available EEG reports in which photic sensitivity was tested, so the distinction between JME-PPR and JME+PPR could be based on multiple EEG reports. People with PPR in one report but not in another one were categorised as PPR+.

We compared the number and type of localised discharges (groups L) and the maximum of the generalised SW discharges (groups G) between the JME+PPR and JME-PPR groups.

2.4 Statistical analysis

We compared the clinical characteristics between the people seen at the two centres and between the JME+PPR and JME-PPR groups using Chi² test and Fishers exact test. We compared the number of people with JME+PPR and JME-PPR with discharges not involving the posterior regions (L_{POST-} and G_{IANTI}) to the number of people with JME+PPR and JME-PPR with discharges involving the posterior regions (L_{POST+}, L_{IPOSTI}, and G_{ANT=POST}, G_{ANT>POST}, G_{POST>ANT}, G_{IPOSTI}). We considered a p-value below 0.05 to indicate significance.

3. Results

We retrieved 180 reports mentioning JME from 1999 to April 2015 in SEIN. At the UMCU we found 60 reports from recordings done between 2010 and 2015. Of these, 159 from SEIN and 36 from the UMCU did not meet the inclusion criteria, as for example the EEG was recorded whilst on medication or not suggestive for JME. Three original recordings from each site were unavailable. A total of 39 (21 from UMCU, 18 from SEIN) recordings were included in this study for re-evaluation and statistical analysis.

3.1 Subject characteristics

Age, gender, occurrence of generalised tonic clonic seizures, absence seizures, PPR response, diagnosis and MRI diagnosis did not differ between the sites (table 1). Age of onset of epilepsy was

not available for one person. Myoclonic jerks were described more often in reports from SEIN than those from the UMCU. Neurologists from SEIN more often reported a definite diagnosis of JME than at the UMCU. The prevalence of PPR did not differ between the two centres. The clinical characteristics of the JME+PPR and JME-PPR groups are listed in table 2. Gender, age of onset of epilepsy, age at EEG recording, occurrence of myoclonic jerks, generalised tonic clonic seizures, history of epilepsy in the family and current diagnosis did not differ between JME+PPR and JME-PPR groups.

Table 1: Group characteristics comparison between both centres (UMCU and SEIN).

	UMCU (n=22)	SEIN (n=17)	P value
Female (N)	12 (55%)	10 (59%)	0.79 ¹
Mean age at EEG (years)	17.95 (SD=9.11)	20.35 (SD=5.56)	0.07 ²
Mean age of onset (years)	14.71 (SD=4.16)	16.75 (SD=3.11)	0.26 ²
Myoclonic jerks (N)	14 (64%)	17 (100%)	<0.01 ^{3*}
Generalised seizures (N)	19 (86%)	11 (65%)	0.14 ³
Absences (N)	4 (18%)	4 (24%)	0.71 ³
Confirmed diagnosis JME (N)	8 (36%)	12 (71%)	0.03 ^{1*}
Diagnosis <i>probably</i> JME (N)	14 (63%)	5 (29%)	0.03 ^{1*}
PPR (N)	9 (41%)	9 (53%)	0.46 ¹
Photosensitivity in daily life (N)	3 (14%)	1(6%)	0.62 ³
No MRI done (N)	12 (55%)	11 (65%)	0.74 ³
Negative MRI known (N)	10 (45%)	6 (35%)	0.74 ³
Epilepsy in first degree family (N)	0 (0%)	1 (6%)	0.44 ³
Epilepsy in second degree family (N)	18 (81%)	13(76%)	0.71 ³

PPR= photoparoxysmal response. Percentages are shown in brackets *statistical significance at a level of $p < 0.05$. ¹ χ^2 test. ² Mann-Whitney U test. ³ Fisher's exact test.

Table 2: Group characteristics of people with JME-PPR+ and JME-PPR-.

	PPR+ (n=18)	PPR- (n=21)	P-value
Female (N)	13 (72%)	9 (43%)	0.07 ¹
Mean age at EEG (years)	18.1 (SD=6.5)	19.8 (SD=7.4)	0.51 ²
Mean age of onset (years)	15.9 (SD=3.4)	15.6 (SD=4.3)	0.78 ²
Myoclonic jerks (N)	14 (78%)	17 (80%)	1.00 ³
Generalised seizures (N)	14 (78%)	16 (76%)	1.00 ³
Absences (N)	3 (17%)	5 (24%)	0.70 ³
Confirmed diagnosis JME (N)	10 (56%)	10 (48%)	0.62 ¹
Diagnosis <i>probably</i> JME (N)	8 (44%)	11 (52%)	0.62 ¹

Photosensitivity in daily life (N)	3 (17%)	1 (5%)	0.31 ³
Negative MRI known (N)	6 (33%)	10 (48%)	0.51 ³
No MRI done (N)	12 (67%)	11 (52%)	0.51 ³
Epilepsy in 1 st degree family (N)	1 (6%)	0 (0%)	0.46 ³
Epilepsy in 2 nd degree family (N)	2 (11%)	6 (29%)	0.25 ³

PPR= photoparoxysmal response. Percentages are shown in brackets. ¹ χ^2 test. ² Mann-Whitney U test. ³ Fisher's exact test.

3.2 EEG analysis

The EEG characteristics for the JME+PPR and JME-PPR groups are shown in table 3. All had a normal background pattern. In several cases, intermittent photic stimulation was not performed during the re-evaluated EEG recordings as the presence or absence of PPR had been previously confirmed. In one person, intermittent photic stimulation was not completed due to strong epileptiform reaction and so risked to trigger a convulsive seizure. Localised abnormalities (L+) outside PPR were present in 35 of 39 EEG recordings. The prevalence of localised abnormalities did not significantly differ between people with JME+PPR and people with JME-PPR. In people with JME-PPR, localised abnormalities without posterior involvement (L_{POST-}) were seen more often than in people with JME+PPR (76% vs 22%), while localised abnormalities involving the posterior areas were seen more often in people with JME+PPR (55% vs 19% $p < 0.01$). In four people with JME+PPR but none of the people with JME-PPR, localised abnormalities were limited to the posterior regions (L_{IPOSTI}).

Generalised and bilateral synchronous SWDs were present in 14 of 18 people with JME+PPR and 17 of 21 people with JME-PPR. The distribution of generalised SWDs did not differ between people with JME+PPR and JME-PPR. Most people had generalised SWDs with an anterior maximum (G_{ANT>POST}). In five people with JME+PPR, the onset of the generalised SWDs could be delineated. In all five, it had a clear posterior onset during intermittent photic stimulation. In two of those, there was also a posterior SWD onset outside intermittent photic stimulation, while in the other three the onset could not be discerned.

Table 3: EEG comparison between JME-PPR+ and JME-PPR-.

	PPR+ (n=18)	PPR- (n=21)	P-value
Localised abnormalities outside posterior areas (L_{POST-})	4 (22%)	17 (76%)	<0.01*
Localised involving posterior areas (L_{POST+}, L_{IPOSTI})	10 (55%)	4 (19%)	
No localised abnormalities (L-)	4 (22%)	0 (0%)	
Any localised abnormalities (L _{post-} , L _{post+} , L _{postI})	14 (78%)	21 (100%)	
Localised abnormalities also in posterior areas (L _{post+})	6 (33%)	4 (19%)	
Localised abnormalities only in posterior areas (L _{postI})	4 (22%)	0 (0%)	
Generalised SWD's limited to anterior areas (G_{IANTI})	0 (0%)	3 (14%)	0.23¹

Generalised SWD's involving posterior areas	14 (78%)	14 (67%)
No generalised discharges (G-)	4 (22%)	4 (19%)
Bilateral synchronous generalised SWD's, no max ($G_{ANT=POST}$)	3 (17%)	1 (5%)
Generalised SWD's anterior maximum ($G_{ANT>POST}$)	9 (50%)	13 (62%)
Generalised SWD's posterior maximum ($G_{POST>ANT}$)	2 (11%)	0 (0%)
Generalised SWD's limited to posterior areas (G_{POST})	0 (0%)	0 (0%)

*PPR= photoparoxysmal response. SWD's=spike-wave discharges. Percentages are shown in brackets. The categories in bold are the ones that were contrasted with each other. * statistically significant at a level of $p<0.05$ with χ^2 test. ¹Fisher's exact test.*

4. Discussion

We show that people with JME+PPR and people with JME-PPR have a different distribution of localised interictal EEG abnormalities. The total number of localised abnormalities does not differ significantly between people with JME+PPR and people with JME-PPR, but people with JME-PPR in our sample had significantly less localised abnormalities involving the posterior regions than people with JME+PPR. There was no difference in the distribution of generalised SWDs between people with JME+PPR and JME-PPR. Our findings are in line with several recent suggestions of altered excitability and connectivity between different brain regions in JME. (Brigo *et al.*, 2012; Vollmar *et al.*, 2012)

The exact mechanism underlying PPR is unknown. It was suggested that it is instigated by hyperexcitability of the primary visual cortex. (Brigo *et al.*, 2013; Siniatchkin *et al.*, 2007) Increased connectivity between the occipital areas and the SMA may enable discharges to spread rapidly to other regions of the brain, as an imaging study in people with JME compared to healthy controls showed. (Vollmar *et al.*, 2012). This notion is supported by the fact that intermittent photic stimulation in people with photosensitive epilepsy resulted in temporary increased excitability and reduced inhibition of the motor cortex. (Groppa *et al.*, 2008; Strigaro *et al.*, 2013, 2015) The difference in localisation of focal abnormalities in the EEGs of people with JME+PPR and JME-PPR that we report may be an expression of hyperexcitability of the occipital cortex. Focal abnormalities in JME may reflect areas of increased excitability and/or aberrant connectivity with other parts of the brain. In our sample, focal abnormalities occurred both in JME+PPR and JME-PPR, indicating that there is no *specific* link between the occurrence of focal abnormalities and photosensitivity. Our findings point to a link between the localisation of the focal abnormalities and photosensitivity. A magnetoencephalography (MEG) study in people with idiopathic photosensitive epilepsy and healthy controls showed that there is increased phase clustering in the gamma frequency band at rest and before the onset of PPR in people with photosensitive epilepsy. (Parra *et al.*, 2003) It was hypothesised that in people with epilepsy, but not in controls, intermittent photic stimulation entrains neuronal networks, leading to excessive synchrony, which we suggest may be apparent on the EEG as SWDs. Increased connectivity between the posterior and anterior regions may cause these localised

discharges to develop into GSWs and potentially to seizures. The reason why we find a similar prevalence of an anterior maximum of generalised SWD's' in both groups may lie in the fact that epileptic discharges probably spread along the superior longitudinalis fasciculus, which projects into the frontal lobe.

Photosensitivity is also seen in people without epilepsy and is thought to be a heritable trait, but so far no specific genes have been identified. CHD2 mutations have been linked to photosensitive epilepsy.(Galizia *et al.*, 2015) BRD2 mutations have been linked to both PPR and JME in one study (Pal *et al.*, 2003) but not in others. (Cavalleri *et al.*, 2007; de Kovel *et al.*, 2007; Lorenz *et al.*, 2006) It is possible that both PPR and JME are caused by polygenetic mechanisms and that different combinations of genetic variations can lead to slight variations of the clinical phenotype. (Taylor *et al.*, 2004)

Our study is limited by the relatively small sample size and the fact that clinical EEG recordings offer a limited time window. The recordings are heterogeneous in terms of the duration, the arousal state (awake, sleep or sleep deprived), and the timing at which the recordings were performed. It is possible that photoparoxysmal responses and focal epileptiform discharges, including in the posterior regions, are more likely to be seen in people who had longer recordings or recordings during sleep, especially after sleep deprivation, than in others. Most of our recordings were less than 24 hours. It is therefore possible that characteristics, which only appear at a certain time of the day, have been missed. For example, PPR and focal abnormalities and generalised SWD's in JME may be more prevalent in morning recordings.(Kasteleijn-Nolst Trenité *et al.*, 2007; Labate *et al.*, 2007) Between 1999 and 2015 two different stroboscopes were used for intermittent photic stimulation at SEIN (Grass and Micromed). Some people were tested for photosensitivity with both and some had a PPR only with one of them (usually Grass). Some people may thus erroneously have been classified as JME-PPR since the introduction of the Micromed stroboscope. As this concerns five people, we do not expect that this has a significant impact on the results presented, but should be kept in mind whenever testing for photic sensitivity.(Specchio *et al.*, 2011) There was a female preponderance (72%) in our sample in the JME+PPR group, which did not reach statistical significance. Previous studies showed that women with JME were more often photosensitive than men with JME.(Wolf and Goosses, 1986) There is evidence that female sex hormones modulate cortical excitability in women with and without epilepsy, which could help explain this finding.(Hattemer *et al.*, 2006, 2007) There are other neurological conditions, such as migraine, which are more prevalent in women and that are hypothesised to be related to modulations of cortical excitability by female sex hormones.(Finocchi and Ferrari, 2011) Localised abnormalities were seen in 89% of our sample. This is higher than reported in previous studies, and may have resulted from referral bias. Localised epileptiform abnormalities can complicate the diagnosis of JME, leading to more referrals to specialised centres such as ours.(Aliberti *et al.*, 1994; Lancman *et al.*, 1994) Epileptiform EEG events are dynamic and

can vary considerably within the same person. Perhaps most important is that JME is a clinical diagnosis with a polygenetic aetiology. Our study is based on clinical and EEG assessments and it is likely that our sample is heterogeneous. Several studies have described different clinical presentations of the JME spectrum.(Martínez-Juárez *et al.*, 2006; Taylor *et al.*, 2004) Interestingly, there may be a considerable overlap between idiopathic photosensitive occipital lobe epilepsy and JME in certain cases.(Taylor *et al.*, 2004) Visual aura and conscious head version are classically associated with idiopathic photosensitive occipital lobe epilepsy, but are also reported in JME. It is possible that people with this phenotype have more focal EEG abnormalities in the posterior brain regions.

For successful treatment, it is paramount to differentiate JME from focal epilepsy. Focal EEG abnormalities in JME, in some cases combined with symptoms such as visual auras and conscious head version, may lead to an erroneous diagnosis of focal epilepsy for which sodium channel blockers would be the treatment of choice.(Aliberti *et al.*, 1994; Lancman *et al.*, 1994) This class of drugs, however, may aggravate myoclonic jerks and potentially increases the number of generalised tonic clonic seizures (Thomas *et al.*, 2006).

Our study underlines that localised EEG abnormalities are a common feature in JME, and shows that people with JME-PPR have less localised EEG abnormalities involving the posterior areas than people with JME+PPR. Defective inhibition and increased excitability of the occipital cortex may explain this phenomenon.

Potential conflicts of interest

JWS has been consulted by and received fees for lectures from GSK, Lunbeck, Teva, Eisai and UCB Pharma.

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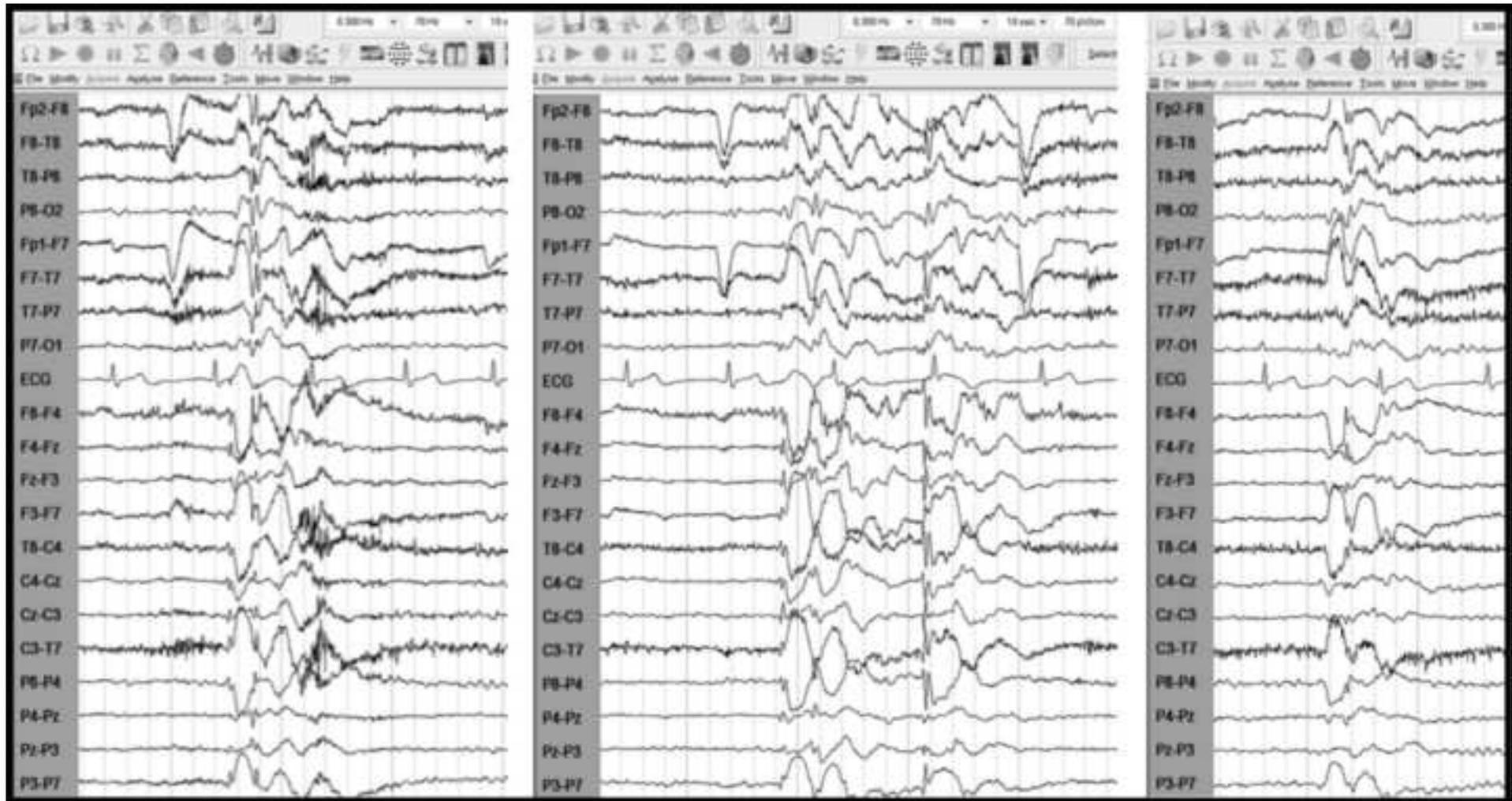
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Figure Legends**Figure 1. Examples of localised and generalised EEG discharges outside intermittent photic stimulation.**

A: L_{POST-} , localised (poly)sharp-and-slow-wave complex not involving the posterior regions (drowsy). Time scale: solid grey vertical lines represent 1s, 9s shown. Filter settings: low pass: 0.160Hz, high pass: 70Hz, scale: 100 μ V/cm. **B:** L_{POST+} localised spike-and-slow-wave activity involving posterior regions (eyes closed). Time scale: solid grey vertical lines represent 1s, 9s shown. Filter settings: low pass: 0.300Hz, high pass: 70Hz, scale: 100 μ V/cm. **C:** L_{POSTI} spike-and-slow-wave complex limited to the posterior regions (eyes open). Time scale: solid grey vertical lines represent 1s, 9s shown. Filter settings: low pass: 0.530 Hz, high pass: 70Hz, scale: 100 μ V/cm. **D:** $G_{ANT>POST-}$ bilateral synchronous (poly)sharp-and-slow-wave discharges with anterior maximum. Time scale: solid grey vertical lines represent 1s, 9s shown. Filter settings: low pass: 0.160Hz, high pass: 70Hz, scale: 150 μ V/cm.

Figure 2. Example of generalised EEG discharges outside intermittent photic stimulation without a clear maximum.

Three events from the same patient, showing bilateral synchronous (poly)sharp-and-slow-wave discharges with an alternating maximum ($G_{ANT=POST}$). Solid grey vertical lines represent 1s. Filter settings: low pass: 0.300Hz, high pass: 70Hz, scale: 70 μ V/cm.



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