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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Increased photosensitivity following short sleep in sleep deprived patients

Augmentation de la photosensibilité après un court sommeil chez des patients privés de sommeil

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Summary
Introduction. — We aimed to determine the effect of short day-time sleep on photoparoxysmal epileptic activity in sleep-deprived patients.
Methods. — We retrospectively reviewed video-EEG recordings performed between 2003 and 2015. All recordings following at least four hours of sleep deprivation, including intermittent photic stimulation (IPS) both before and after sleep with any form of epileptiform activity were included. The study group was divided into four subgroups: (1) no photoparoxysmal response (PPR) group, with epileptiform activities other than PPRs; (2) increment group, with PPR duration increased by $\geq$200% after vs. before sleep; (3) no significant change group, with PPR duration increased between 50% and 200% after vs. before sleep; (4) decrement group, with PPR duration increased $\leq$50% after vs. before sleep.
Results. — A total number of 5805 EEG recordings from 459 patients was analyzed. Photosensitivity was present in 98 patients (21.4%). The PPRs after sleep were increased in 70% of the photosensitive patients, did not change in 23%, and were decreased in 7%. The increase in duration of PPRs was statistically significant ($P < 0.001$). In our cohort, photosensitivity would have been detected in 67 patients if IPS was applied only before sleep and in 91 patients if IPS was applied only after awakening ($P < 0.05$).

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Conclusions. — This study demonstrates that photosensitivity is enhanced after awakening from a short sleep following sleep deprivation. Thus, we recommend performing IPS after awakening to increase sensitivity to detect photoparoxysmal epileptiform discharges.

MOTS CLÉS
EEG ;
Privation de sommeil ;
Réponses photoparoxystiques ;
Réveil après sommeil ;
Stimulation lumineuse intermittente

Résumé
Introduction. — Nous avons cherché à déterminer l'effet d'un sommeil de jour de courte durée sur l'activité épileptique photoparoxystique chez des patients privés de sommeil.
Méthodes. — Nous avons examiné rétrospectivement des enregistrements vidéo-EEG effectués entre 2003 et 2015. Tous les enregistrements effectués après au moins quatre heures de privation de sommeil, comprenant une stimulation lumineuse intermittente (SLI) réalisée avant et après le sommeil, et caractérisés par une activité épileptiforme quelle qu'en soit le type, ont été inclus. La population étudiée a été divisée en quatre sous-groupes : (1) groupe sans réponse photoparoxystique (RPP), incluant des activités épileptiformes autres que des RPP ; (2) groupe incrémental, avec une durée des RPP augmentée de 200 % ou plus entre après et avant le sommeil ; (3) groupe sans changement significatif, avec une durée des RPP augmentée de 50 % à 200 % entre après et avant le sommeil ; (4) groupe décrémental, avec une durée des RPP augmentée de 50 % ou moins entre après et avant le sommeil.
Résultats. — Un total de 5805 enregistrements EEG correspondant à 459 patients a été analysé. La photosensibilité était présente chez 98 patients (21,4 %). Les RPP étaient augmentées après le sommeil chez 70 % des patients photosensibles, inchangées chez 23 % et diminuées chez 7 %. L'augmentation de la durée des RPP était statistiquement significative ($p < 0{,}001$). Dans notre cohorte, la photosensibilité aurait été détectée chez 67 patients si la SLI avait été appliquée seulement avant le sommeil et chez 91 patients s'il avait été appliquée seulement après le réveil ($p < 0{,}05$).
Conclusions. — Cette étude démontre que la photosensibilité est augmentée au réveil d'un sommeil de courte durée suivant une privation de sommeil. Ainsi, nous recommandons d'effectuer des SLI après le réveil pour augmenter la sensibilité à détecter des décharges épileptiformes photoparoxystiques.

Introduction

Photoparoxysmal responses

Intermittent photic stimulation (IPS) is a way of simulating, under controlled conditions, the flashing lights of daily life such as sunlight, television, and video games, which may trigger epileptiform discharges and sometimes seizures, particularly in photosensitive epilepsies. These discharges are called photoparoxysmal responses (PPRs). They were first defined by Bickford in 1952 and this provocation technique has been used over half a century as a routine part of the EEG recording process [3].

Photoparoxysmal responses may emerge in the form of spike, spike-wave and slow waves which may be focal or generalized. PPRs do not generally indicate increased risk of epilepsy if they are found incidentally in patients without epilepsy, with the exception of type 4 discharges which are regarded as epileptiform in nature. In addition, their presence does not constitute a specific epilepsy syndrome, as PPRs can be found in many kinds of epileptic disorder [6].

Factors modulating epileptiform discharge detection

Epileptiform discharges are dynamic processes and can be affected by many variables. Sleep deprivation and sleep itself can increase the detection of epileptiform discharges. These conditions change the seizure threshold dynamically by means of increased cortical excitability and by changing thalamic modulatory effects [14]. Photoparoxysmal responses are not an exception. They are also affected by not only technical parameters such as frequency and wavelength of the stimulus, but also patient factors such as vigilance and eye closure [10].

In 1974, Scollo-Lavizzari et al. showed that sleep deprivation potentiates PPRs, and that short sleep following this sleep deprivation does not diminish, but possibly even potentiating these pathological responses [16]. In our study, we aimed to determine whether short sleep in sleep-deprived patients can precipitate photosensitivity.

Methods

We reviewed video-EEG recordings performed between the years 2003 to 2015 in our clinic in a retrospective manner. A total number of 5805 EEG recordings were reviewed within this timeframe.

All video-EEGs were recorded following sleep deprivation of at least four hours. All examinations included a minimum of 20 minutes of awake recording both before and after sleep, and at least 60 minutes of spontaneous sleep. Video-EEGs were performed according to a standard

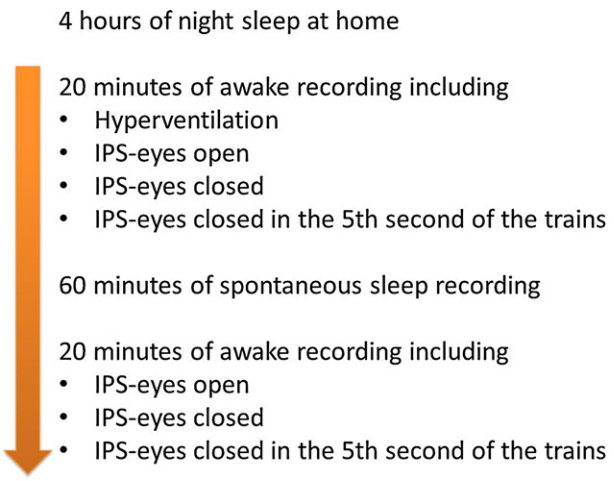

Figure 1 Description of the standard EEG protocol.

protocol (Fig. 1). Scalp electrodes were placed according to the 10/20 international system. Time constant was set to 0.3 sec and high-frequency filter was 70 Hz. We applied IPS in 10-second trains of flashes, between the frequencies of 1 Hz to 60 Hz, while the patients' eyes were closed, open and during eye closure in the 5th second of the same frequency stimulation. Each train was separated by an interval of minimum 7 seconds. The same flash frequencies and durations were used for all patients regardless of their sensitivity. This protocol was applied before and after sleep recordings. Total PPR durations were calculated as the summation of all PPRs occurring during IPS, before or after sleep. The distance of the photic stimulator to the nasion was 30 cm.

Video EEG recordings were independently evaluated by two neurologists. EEG recordings meeting both of the following requirements were included;

- epileptiform activity (focal or generalized spikes, spike and waves, multiple spikes and multiple spike and waves) at any period of the record;
- IPS both before and after sleep.

We identified 459 recordings meeting these requirements. Following this, EEG recordings including PPR were evaluated in more detail (as illustrated in Fig. 2). The total duration of PPRs before and after sleep was calculated. Recordings were then divided into four groups:

- no PPR group (NPG): epileptiform activities other than PPRs;
- increment group (IG): PPR duration following sleep $\geq$ 200% of the PPRs before sleep;
- no significant change group (NCG): PPR duration following sleep between 200% and 50% of the PPRs before sleep;
- decrement group (DG): PPR duration following sleep $\leq$ 50% of the PPRs before sleep.

Increment group was further stratified into two subgroups:

- the recordings with no PPR before sleep, showing PPRs only after sleep;
- the recordings with PPRs before sleep, more than 2-fold increase after sleep.

Photoparoxysmal responses were classified into 4 groups as defined by Waltz et al. [20]. Patients' diagnoses were coded as in ILAE proposal for revised terminology of seizures and epilepsies [2].

Statistical analysis was performed with SPSS 21st edition. To compare categorical values, we used Chi^2 test. For numerical values between two groups, we used student *t*-test and Mann-Whitney U tests. For tests including more than

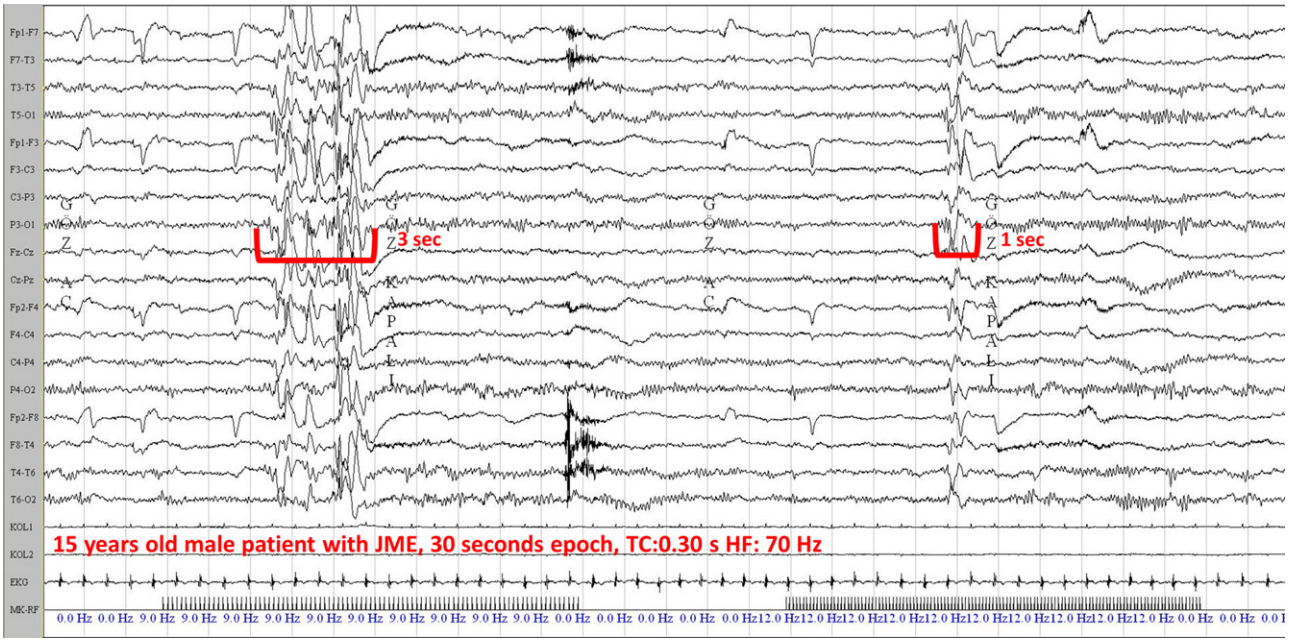

Figure 2 An illustration of photoparoxysmal response.

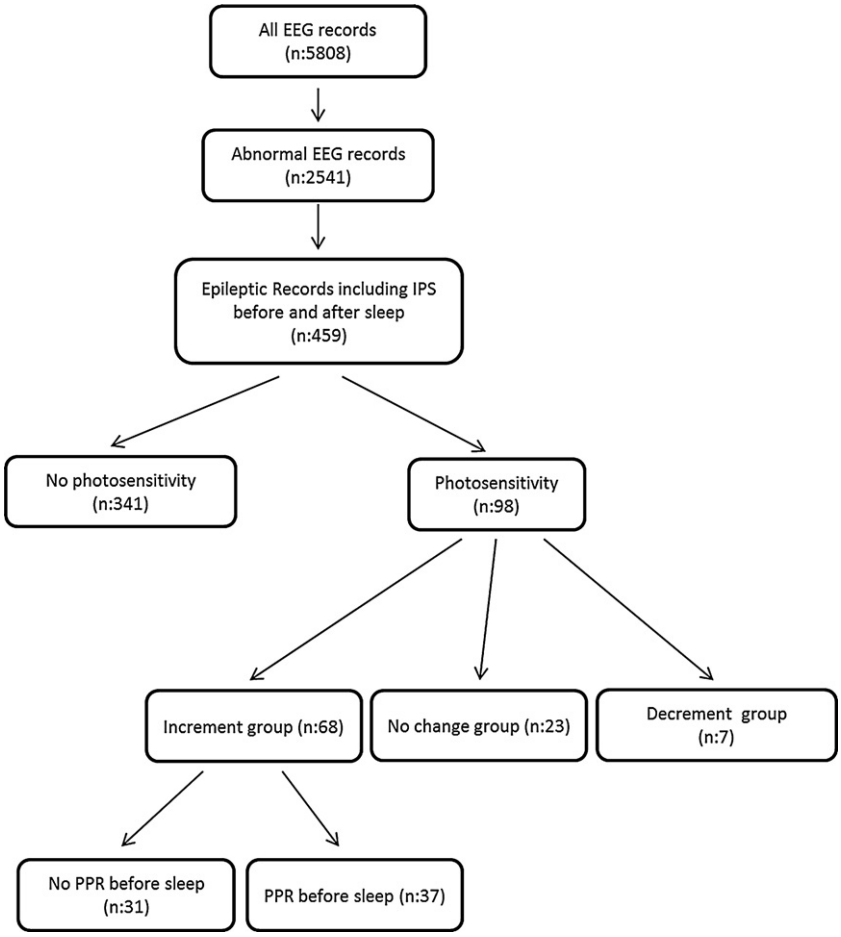

Figure 3 Flowchart of the results provided by inclusion and analysis criteria.

Table 1 Demographic features of the study group.

	NPG (n:361)	IG (n:68)	NCG (n:23)	DG (n:7)	*P*
Age (median)	10.6	12	11.9	7.5	< 0.001
Gender (M/F)	1:1	2:3	2:3	2:3	> 0.05
Epilepsy diagnosis (%)	88.1	88.2	95.7	71.4	> 0.05

DG: decrement group; IG: increment group; NCG: no significant change group; NPG: no PPR group; M/F: male to female ratio.

two valuables, we used one-way Anova and logistic regression models. The significance level was defined as $P \leq 0.05$.

Results

Out of 5808 EEG recordings, 2541 (43.8%) were abnormal and 459 (8%) met inclusion criteria. (Fig. 3). Demographic data of the patients is summarized in Table 1. Eighty-eight percent ($n = 405$) of the patients were diagnosed with epilepsy. Syndromic classification of included patients is shown in Fig. 4.

Ninety-one patients had PPRs either only after sleep, or both before and after sleep. Seven patients had PPRs only before sleep and PPRs diminished after sleep. PPRs were thus present in 98 patients (21.4% of the study group), either before or after sleep or both, the remaining 361 patients (78.6%) consituting the no-PPR group (NPG).

Out of 98 photosensitive patients, 87 were formerly diagnosed with epilepsy, while 11 were referred with conditions other than epilepsy (5 attention deficit hyperactivity disorder, 2 febrile convulsions, 1 abdominal pain, 1 speech disorder, 1 migraine, 1 pseudoseizure). Male to female ratio of the photosensitive group was 2/3. Syndromic diagnoses found in the subgroups are presented in Fig. 5.

Comparison of photoparoxysmal activity before and after sleep revealed that 70% of the photosensitive patients were more sensitive to IPS after sleep (IG). Within this group, 45.7% showed no PPR before sleep. No change group (NCG) was 23% of the photosensitive patients and 7% showed decreased activity.

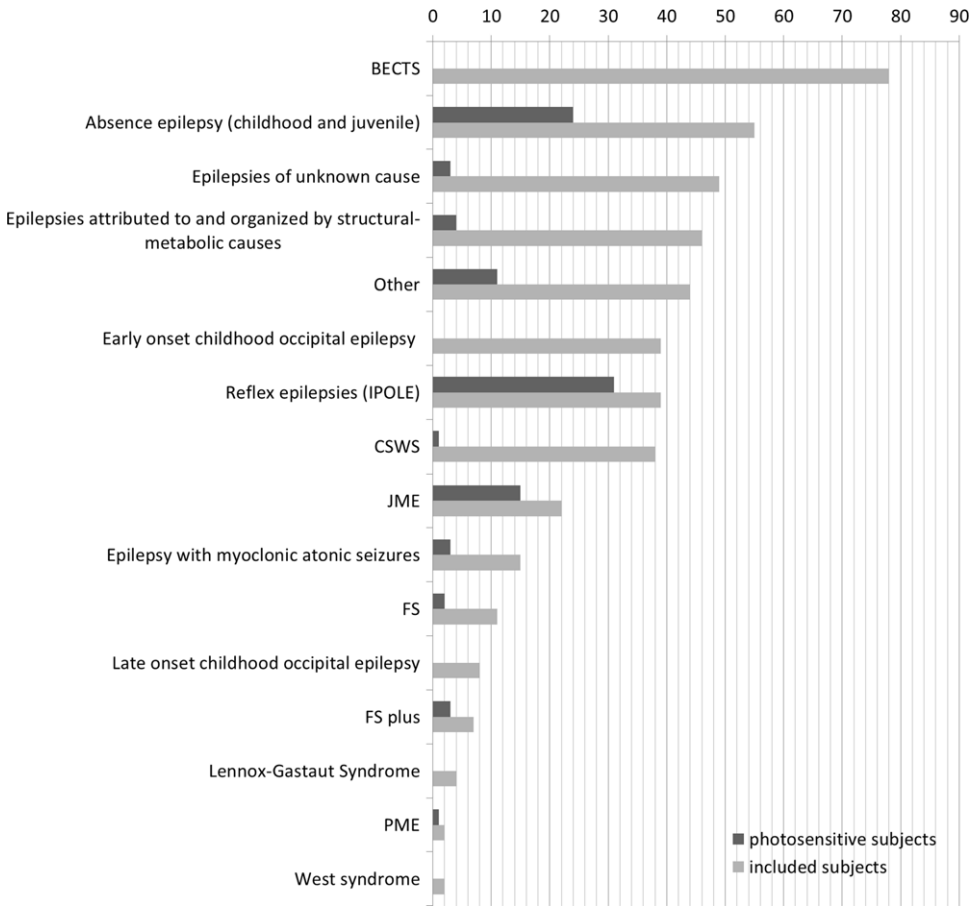

Figure 4 Syndromic classification of included patients.

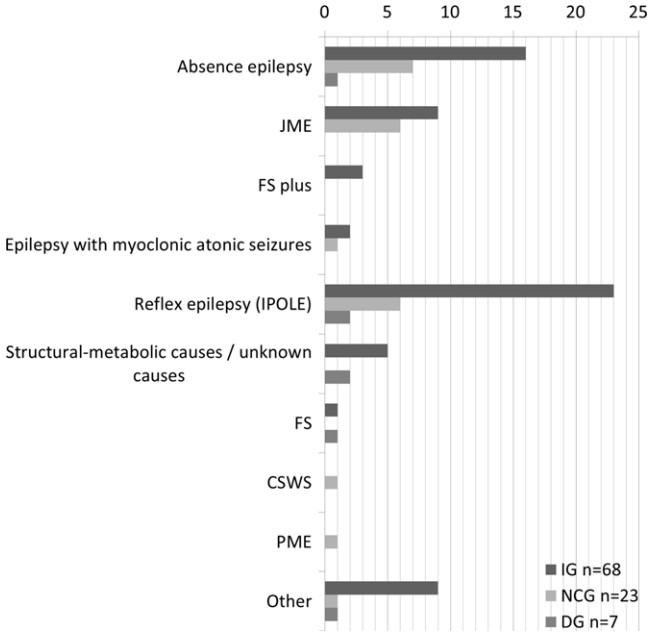

Figure 5 Syndromic diagnoses of the photosensitive patients, according to the subgroups of patients with PPRs. DG: decrement group; IG: increment group; NCG: no significant change group.

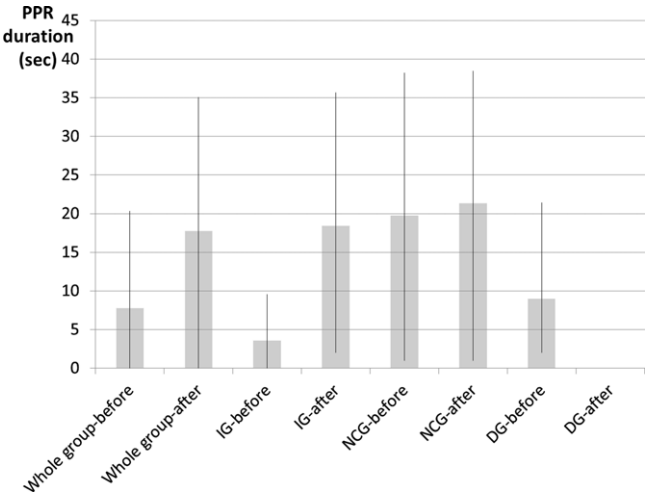

Figure 6 Photoparoxysmal response (PPR) duration means and standard deviations in each subgroup of patients with PPRs. IG: increment group; NCG: no significant change group; DG: decrement group.

Table 2 JME, IPOLE and absence patients according to the groups.

	JME	Absence	IPOLE	Total number of patients in this group
NPG	7	30	7	361
IG	9 (7)	16 (8)	23 (8)	68
NCG	6	7	6	23
DG	0	1	2	7
Total	22	54	38	459

DG: decrement group; IG: increment group; NCG: no significant change group; NPG: no PPR group; JME: juvenile myoclonic epilepsy; IPOLE: idiopathic photosensitive occipital lobe epilepsy; PPR: photoparoxysmal response. The numbers within parentheses are the number of patients with no PPR before sleep, showing PPRs only after sleep.

Mean duration of PPRs was 3.60 sec before and 18.40 sec after sleep in IG; 19.40 sec before and 21.35 sec after sleep in NCG; 9.00 sec before and 0.00 sec after sleep in DG (Fig. 6). The increased duration of PPRs following awakening was statistically significant ($P < 0.001$). Further stratification according to the epilepsy diagnosis did not diminish this significance ($P < 0.001$ in epilepsy patients and $P = 0.016$ in patients with a diagnosis other than epilepsy).

If IPS was applied only before sleep, it would be possible to detect photosensitivity in 67 patients (68% of the photosensitive patients). If it was applied only after awakening, the rate would increase to 91 patients (92% of the photosensitive patients) ($P < 0.05$ in total). This difference was more significant for patients with photosensitivity ($P < 0.001$). Statistical analysis of patients with epilepsy ($P < 0.05$) and with both epilepsy and photosensitivity ($P < 0.001$) revealed similar results. Seven patients showed photosensitive responses only before sleep.

In the whole study group, there were 22 patients with juvenile myoclonic epilepsy (JME), 54 with absence epilepsy (both childhood and juvenile) and 38 with idiopathic photosensitive occipital lobe epilepsy (IPOLE) [1,11]. Prevalence of JME, IPOLE and absence epilepsies was significantly higher in the photosensitive group as expected ($P < 0.001$). Relevant results are summarized in Table 2.

A closer look at the photosensitive patients with those 3 diagnoses revealed:

- sixty percent ($n = 9$) of the photosensitive JME patients were in IG. Seven of these patients were PPR-free before sleep and PPRs emerged only after awakening;
- seventy percent ($n = 16$) of the photosensitive absence epilepsy patients were in IG. Eight of these patients were PPR-free before sleep and PPRs emerged after awakening;
- seventy-two percent ($n = 23$) of the photosensitive IPOLE patients were in IG. Eight of these patients were PPR-free before sleep and PPRs emerged after awakening.

Discussion

Intermittent photic stimulation is an efficient and safe tool to reveal photosensitivity. Taken together with signs and symptoms of a given patient, EEG evidence of photosensitivity may suggest specific diagnoses. Existence of PPRs can also affect therapeutic approach, such as the necessity for daily life modifications. Quantification of PPRs can be used to evaluate the efficacy of the treatment. Therefore, IPS plays a critical role in diagnosing and monitoring epileptic syndromes.

In this study, we found that the likelihood of PPR detection was increased if IPS was performed after short-term sleep in sleep-deprived subjects. In our cohort, performing IPS only before sleep would have led to the detection of 68% of the photosensitive patients. If IPS was performed only after awakening, the rate would raise to 92%, preventing 24% from being missed. Therefore, if IPS were to be performed only once during a recording, we suggest that it should be done after sleep to enhance its sensitivity.

The interaction between photosensitivity and sleep is rather interesting. Sleep is a dynamic process. The likelihood of the epileptiform discharges differs in each phase of the sleep. While non-REM sleep facilitates the generation of epileptiform discharges, REM sleep is almost resistant to such discharges. Sleep also modulates the emergence of the PPRs. It has been showed that PPRs significantly decrease during drowsiness, vanish during deep non-REM sleep and then re-emerge during REM sleep, similar to wakefulness. However, later studies displayed inconsistent results; some researchers supported those findings [4,21] and some claimed that PPRs diminish in all phases of sleep [5,12,15].

Sleep deprivation facilitates the emergence of epileptiform discharges and has commonly been used as an activation procedure for EEG recordings. Sleep deprivation also increases the likelihood of photosensitivity [16]. The underlying mechanism was suggested to be increased susceptibility due to sleepiness. After all, decreased vigilance is known to facilitate the spontaneous paroxysms [13]; however, sleepiness or level of vigilance alone is not sufficient to explain the whole picture.

Transitional periods and arousals are known to be strong activators. Arousing stimuli, indeed, precipitate both epileptic discharges and clinical seizures. Halász has proposed a critical zone of vigilance where spike-wave discharges (SWD) are most likely to occur. He mentioned that if a stimulus wakes the subject just to a critical level of vigilance where SWDs can emerge, and not further to the point of being wide-awake, paroxysms may appear. Additionally, SWDs themselves may cause an instability of vigilance, which could lead to a vicious cycle; ''a prolonged fluctuation around the critical level and long transitional periods, full of SWD'' [9].

High IPS sensitivity rates (38%) are demonstrated in JME patients during the induced awakening period [7]. Indeed, induced awakenings are shown to provoke epileptiform discharges more prominently than spontaneous ones [18]. Also, arousals from slow-wave sleep increase visual system responsiveness, but this effect lasts only for a few seconds in feline models [19].

Short sleep following sleep deprivation increases discharges in all vigilance levels including the awake state [9]. Additionally, evoked potential studies in feline models revealed that sleep deprivation increased thalamocortical excitability and this effect is more prominent in drowsiness state after awakening from slow wave sleep, especially

following sleep deprivation [17]. The thalamocortical network plays an important role in the generation of epileptic activity in the idiopathic generalized epilepsies such as JME and absence epilepsy. Since the mode of function is burst-firing, it has been speculated that the generation of slow wave sleep and SWDs might have a similar mechanism. Therefore, facilitation of the thalamocortical network might be the main mechanism underlying this increase in PPRs after sleep.

Another contributing mechanism might be a relative REM deprivation. The patients are allowed to sleep the first half of their night sleep, which is scant in REM phase, leading to partial deprivation of REM sleep before the EEG recording. None of our patients were observed to enter the REM phase during sleep recordings. REM deprivation in kindled rats is shown to lead to a reduced seizure threshold, but in a somewhat delayed timeframe. The effect was not obvious right after the deprivation, but became prominent 24 hours after sleep deprivation has ended, and lasted up to 72 hours [8]. It is noted that this delay might point to a necessity of some ''recovery sleep'' before the seizure threshold could decrease.

The main limitations of the study are its retrospective nature and lack of correlations of the data with the antiepileptic treatment. Another limitation concerns the normal EEG traces. Since normal EEG recordings are not archived, it was not possible to determine the exact number of normal EEG traces including IPS procedure both before and after. Over eighty percent of the abnormal EEG traces did not meet inclusion criteria due to lack of evaluable IPS periods both before and after sleep. The main underlying reasons were: unevaluable trace during IPS due to artifacts, subjects falling to sleep rapidly, sleeping throughout the IPS, recording including only sleep or awake period, subject being younger than 6 months old, intolerance of the subject to the IPS and lack of cooperation of the subject.

An important point is that the ratio of photosensitivity in epilepsy patients was slightly higher than that reported in the literature, which was 10—20% in children and 5—10% in adults, compared to 21.4% in our study group [22]. This difference points out a possible selection bias, as the study was retrospective and only EEG recordings with epileptiform activities were included.

In conclusion, this study demonstrates that photosensitivity is increased after a short sleep following sleep deprivation. We recommend performing IPS after sleep to increase its sensitivity in triggering photoparoxysmal epileptiform discharges.

Disclosure of interest

The authors declare that they have no competing interest.

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