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Review

Reflex epileptic mechanisms in humans: Lessons about natural ictogenesis

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ABSTRACT

The definition of reflex epileptic seizures is that specific seizure types can be triggered by certain sensory or cognitive stimuli. Simple triggers are sensory (most often visual, more rarely tactile or proprioceptive; simple audiogenic triggers in humans are practically nonexistent) and act within seconds, whereas complex triggers like praxis, reading and talking, and music are mostly cognitive and work within minutes. The constant relation between a qualitatively, often even quantitatively, well-defined stimulus and a specific epileptic response provides unique possibilities to investigate seizure generation in natural human epilepsies. For several reflex epileptic mechanisms (REMs), this has been done.

Reflex epileptic mechanisms have been reported less often in focal lesional epilepsies than in idiopathic "generalized" epilepsies (IGEs) which are primarily genetically determined. The key syndrome of IGE is juvenile myoclonic epilepsy (JME), where more than half of the patients present reflex epileptic traits (photosensitivity, eye closure sensitivity, praxis induction, and language-induced orofacial reflex myocloni).

Findings with multimodal investigations of cerebral function concur to indicate that ictogenic mechanisms in IGEs largely (ab)use preexisting functional anatomic networks (CNS subsystems) normally serving highly complex physiological functions (e.g., deliberate complex actions and linguistic communication) which supports the concept of system epilepsy. Whereas REMs in IGEs, thus, are primarily function-related, in focal epilepsies, they are primarily localization-related.

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1. Introduction

In reflex epilepsies (REs), an important part of a patient's seizures if not all occur in response to well-defined, often syndrome-specific and individually consistent sensory or cognitive stimuli. According to a recent comprehensive review [1], the sensory-precipitating stimuli most often are visual, more rarely tactile or proprioceptive, whereas simple audiogenic triggers in humans are practically nonexistent. These triggers typically act within seconds. The best known cognitive stimuli work within minutes and relate to visuomotor coordination and praxis, reading and talking, and music. The constant relation between a qualitatively, often even quantitatively, well-defined stimulus and a specific epileptic response provides unique possibilities to investigate seizure generation in natural human epilepsies. The traditional approach is to enrich standard electroencephalography (EEG) diagnostics with specific tests for individually suspected triggers with the aim to provoke interictal epileptiform discharge (ED) or even seizures. Because of the high frequency of photosensitivity (PS), intermittent light stimulation (ILS) has become part of standard EEG. Recently, advanced methods of functional imaging promise novel data about ictogenic mechanisms. For several reflex epileptic mechanisms, these have been applied. They comprise the following:

- photosensitivity
- eye closure sensitivity
- orofacial reflex myocloni
- praxis induction
- musicogenic epilepsy.

The first four on the list are closely related to juvenile myoclonic epilepsy (JME); the fifth, to temporal lobe epilepsy (TLE). They will be discussed here.

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2. Photosensitivity

2.1. Description

Photosensitivity refers to conditions where seizures are precipitated by intermittent light stimuli. Photosensitivity occurs in two animal strains, Senegalese baboons of the species *Papio papio* and Fayoumi chickens [2]. In humans, there exists a rare variant in some progressive myoclonus epilepsies where the reaction is to single light flashes or low-frequency stimulation up to 4 Hz. In common clinical language, PS refers to cases where seizures are precipitated by more rapid ILS, the most sensitive frequency range usually being 14 to 30 Hz. Examples of environmental triggers comprise sunlight glittering on a water surface, television, stroboscopic lights, and others [1]. In the EEG, ILS elicits the "photoparoxysmal response" (PPR) which consists of "generalized" bilateral synchronous 3- to 4-Hz spike-and-wave (SW) discharges that often have occipital preponderance. Precipitated seizure types are myoclonic > generalized tonic–clonic (GTC) > absences > simple focal occipital with visual aura and/or version of eyes and head. Wolf and Goosses [3] described the close syndromatic relation to JME where they found the trait in 30.5% of treated patients 21.9 ± 11.2 years of age (SD). In untreated patients investigated in the typical peak age between 10 and 20 years [4], the rate would be higher. The findings also depend much on the stimulation parameters. In the study of Appleton et al. [5], 55 of 61 patients with untreated JME in the age range of 7–16 years (90%) were photosensitive, but in 18 of these patients, this finding required continuous ILS from a distance of 30 cm lasting more than 4 min. With the same stimulation parameters, no PS was found in 60 healthy controls and 30 patients with benign rolandic epilepsy, but it was found in four of 30 patients (13%) with childhood absence epilepsy. Pure PS, i.e., cases with no spontaneous seizures, accounts for up to 40% of all patients with seizures and PS [6] and 8 of 53 cases (15%) in another study [7]. However, pure PS is not recognized as a syndrome of its own.

Apart from idiopathic generalized epilepsies (IGEs), PS is a frequent feature of Dravet syndrome [8]. Its relation to some other epilepsy syndromes was recently reviewed by Kasteleijn-Nolst Trenité et al. [4].

In several respects, the photosensitive response is quantitative. It depends on light intensity, both absolute and in relation to background illumination, and on the amount of retina stimulated. Monocular stimulation is much less effective than binocular stimulation. Usually, there is an individual core range of flicker frequency with the highest triggering effect which diminishes with lower and higher frequencies. The stimuli need to be repetitive and usually last several seconds before the PPR is elicited. The PPR is also quantitative, occurring more or less rapidly and involving less or more leads, and seizures may be elicited more or less easily. Photosensitivity shows circadian fluctuation, and even during one EEG investigation, the responses to stimuli with the same characteristics are often variable.

The PPR outlasts the stimulation but only briefly, usually by <1 s. A buildup towards a seizure after termination of the ILS may occur, but it is very rare.

2.2. Advanced investigations

Photosensitivity poses the problem of understanding in what way the brain of these patients processes stimuli received in the visual cortex different from normal and why the most typical epileptic response is bilateral motor. To get some insight into this question, Parra et al. [9] investigated ten photosensitive patients with magnetencephalography (MEG) and compared them with five healthy controls and three nonphotosensitive subjects with epilepsy. They discovered that the PPR was preceded by an enhancement of phase synchrony in the γ band harmonically related to the stimulation frequency. Whereas synchronized harmonic fast-frequency oscillations seem to be part of the natural perceptional processes, the findings preceding PPR differed from those of the controls both by a significantly higher synchrony and by a wider spatial distribution beyond the occipital region. In a patient with myoclonic seizures, this involved, particularly, the frontal and central regions; in a patient with absences, the parietal sensor positions were mostly affected.

Subsequently, important new insight was gained by Moeller et al. [10] who studied the PPR in six photosensitive subjects with EEG-triggered functional magnetic resonance imaging (fMRI) and found that, in contrast to spontaneous SW discharge where the thalamus plays a pivotal role, PPR is a merely cortical phenomenon involving the frontal and parietal cortices. In agreement with Parra et al. [9], the response started before the appearance of SW, with an activation of the cortical areas which 3 s later at PPR onset were deactivated. The thalamus only became involved later when in one patient the PPR further evolved into a clinical seizure [11].

Together with the data of Appleton et al. [5], these findings could indicate that PS represents an upregulation of occipitofrontal pathways common to JME which could provide a basis also for the other reflex epileptic traits (RETs) of this syndrome.

3. Eye closure sensitivity

During ILS, the PPR is usually best seen at eye closure, but eye closure sensitivity (ECS), even if it overlaps with PS, also exists as an independent reflex epileptic mechanism [1].

3.1. Description

Eye closure sensitivity is defined by seizures or SW activity appearing within 2 s after eye closure, most often as a brief subclinical volley. The provoked seizures usually are eyelid myocloni with or without absence. Eye closure sensitivity is pathognomonic in Jeavons syndrome or eyelid myoclonia with absence (EMA), a rare pediatric epilepsy syndrome [12]. Eye closure sensitivity is found in ca. 20% of patients with JME [13], whereas its frequency in other types of IGE has not been systematically investigated.

The EEG feature can be easily discovered because repeated opening and closing of the eyes during the EEG is routine. However, the feature for unexplained reasons is rarely mentioned in EEG reports. Like in PS, the SW discharges in ECS mostly have an occipital preponderance.

Self-stimulation by blinking has been reported but is not generally accepted as others believe that the eye blinking supposed to be a consciously or semiconsciously applied trigger is already part of the seizure.

In the vast majority of cases, ECS is only seen with lights on, and it has, therefore, been suggested that the response is generated in the visual cortex, supported by the EEG [14]. However, the eyelid myocloni of ECS are not invariably accompanied by SW discharges [15]. In addition, ECS is only provoked by (voluntary or involuntary) slow eye closure which is generated in the supplementary motor area (SMA) and never by physiological blinking or by nociceptive reflex blinks in response to visual threats which are generated in the brain stem. Therefore, the SMA has, certainly, a central role in the ictogenesis, and its interaction with the visual system still remains to be clarified [15].

3.2. Advanced investigations

Eye closure sensitivity in 15 patients with EMA has recently been investigated with EEG-triggered fMRI and MR morphometry in comparison with healthy controls and with patients with IGE not presenting ECS [16]. The authors conclude that EMA with ECS is generated in the visual cortex but do not discuss the possibility that their findings are related to PS rather than to ECS which is likely because all their patients with EMA but none of their control patients with IGE were photosensitive. Their finding of increased blood oxygenation level-dependent (BOLD) signal increase in parts of the systems for oculomotor control in EMA was not integrated into their concept of ECS generation. They also fail to comment on the fundamentally different networks related to physiological, nonprovocative blinks and to voluntary eye closure which they report. Patients with JME with ECS, unfortunately, were not included for comparison. This investigation leaves, thus, more questions open than it answers. Decreased gray matter density in the SMA as well as the