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Review

Reflex seizure triggering: Learning about seizure producing systems

Anna Szűcs[a,b,*], Beáta Rosdy[c], Anna Kelemen[a], András Horváth[a,b], Péter Halász[a]

[a] National Institute of Clinical Neurosciences, Budapest, Hungary
[b] Semmelweis University Medical School, Heim Pál Children's Hospital, Budapest, Hungary
[c] Heim Pál Children's Hospital

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ABSTRACT

Aim: We aim to study the mechanism of reflex seizure triggering in close link with the system-epilepsy concept.
Method: We use data and theories presented in the literature and scrutinize a few illustrative cases.
Conclusions: The prerequisite of seizure triggering is an epilepsy-prone brain network. When it is activated, it may produce seizures manifesting the function(s) of the same system. Beyond classical reflex seizures triggered by sensory-motor stimuli, we extend the reflex-epilepsy concept to seizures induced by the normal activation of epilepsy-prone systems e.g. praxis-induced seizures and those of sleep/wake system epilepsies elicited by falling asleep (absences) or arousals from NREM sleep (seizures of genetic frontal lobe epilepsy). We suggest that normal functioning of epilepsy-prone systems may trigger seizures in epilepsies in general.

1. Introduction

In this paper we aim to review the ways of reflex seizure (RS) precipitation timely for several reasons. The recently accumulating data on seizure-provoking factors and mechanisms, as well as the high variability of reflex triggering modalities, need new systematization. The emerging concept of system epilepsy [1–4] is a major aspect highlighting seizure-triggering mechanisms. In the vast field of epileptology, we have little knowledge on the mechanism of ictogenesis. We hope to contribute to its understanding with our study on RSs.

RSs used to be defined as curiosities induced by conspicuous 'interesting' stimuli, discriminating them from "normal" epileptic seizures considered spontaneous [5–7]. 'Epilepsies characterised by seizures with specific modes of precipitation' is the description used in the 1989 ILAE classification [8]; and 'reflex' is the term suggested by Engel et al [9,10].

The 2001 ILAE Glossary of descriptive terminology states: RS are "objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by activity of the patient…. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not called reflex seizures; in these seizures and epilepsies the provoking situation is called 'facilitation'" [11].

One way to classify RSs follows the type of the evoking stimuli: sensory or cognitive, simple or complex [7,12–18,23–31]. Another classification follows the supposed focal (unilateral) or generalised (bilateral from the beginning) nature of seizures with some hints that even bilateral RSs might represent secondary and quickly spreading unilateral (focal) ones [1,19,20]. Studying reflex seizures may contribute to the better understanding of epilepsy and seizure-precipitation in general [1,6].

2. Seizure triggers and seizure symptoms in RSs manifest the function of the same brain system

Important progress has occurred in epileptology recently. One step is the blurring of the borders between "focal" and "generalised" epilepsies[43]. In epilepsies considered "generalised", it has been evidenced in several ways that there is a quick secondary generalisation from a primary initiating zone across thalamo-cortical circuits [32]. Some epilepsies traditionally considered "focal", e.g. mesiotemporal epilepsies, typically involve a bilateral system regarding both interictal and ictal phenomena.

The second important step is the emergence of the system approach linking epilepsies to functional brain systems [1]. Functional systems often include bilateral brain regions, e.g. the visual system activated in photosensitive epilepsies involves bilateral visual, cognitive, motor and emotional circuits. The bilateral excitation classifies such epilepsies as "generalised" [20], however, the one system-dependence challenges this classification; calling them "system epilepsies" seems more appropriate.

The third step is the extension of the reflex seizure category. It broadens the group of RS from a bunch of curiosities to large families of

* Corresponding author at: Bakáts str 1-3, 1093 Budapest, Hungary.
E-mail address: szucsan@gmail.com (A. Szűcs).

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Table 1
Illustrative cases (our cases and examples from the literature).

No	Patient, age, gender	Provoking stimulus	First seizure symptom	Epilepsy type, EEG	MRI lesion	Comment
1	20-year-old male	Running	Leg cramp followed by a focal motor seizure	Sparse frontal spikes	None	Carbamazepine has made him seizure free.
2	39-year-old female	Burning or hitting the hand	"Reflex" arm-lift, then jerks and sensory-motor seizure; Jacksonian march.	Frontal? Right frontal spikes and slow activity	Frontal convexity meningioma	Sensory-motor reflex seizures progressed to spontaneous seizures after a few reflex-ones.
3	33-year old male wood hacker	Intensive working with the right arm.	Work-related arm-jerking, then Jacksonian march involving his leg	Focal motor, Jacksonian. Frontal spikes	Left precentral motor strip tumour	His work-related jerking suggested normal muscle-exhaustion before epilepsy-diagnosis was made.
4	48-year-old female	Pressing/ touching the right sole	Leg cramp, right motor seizure	Frontal; Right frontal interictal spikes	Bilateral central focal cortical dysplasia	Focal reflex motor seizures have progressed to spontaneous ones, then right sided epilepsia partialis continua.
5	22-year old female	Touching the right leg	Focal motor seizure involving the right leg, spreading to the upper limb	Frontal; Right frontal and temporal interictal spikes, frontal motor seizures	Right central ganglioglioma	Focal reflex motor seizures in the lower and upper limbs; Hard to treat. After partial removal of the ganglioglioma she has had right sided epilepsia partialis continua for several years now; affecting the hand. Psychosis associated later.
6	O'Brien et al [21], D'Souza et al 2007. [17].	Tooth-brushing	Left facial cramp progressing to more widespread motor seizure	Left facial motor seizures Right-sided epileptiform activity during an induced complex partial seizure.	Right posterior frontal low-grade tumour involving the precentral gyrus. Ictal SPECT: an area of hyper-perfusion consistent with the MRI lesion	
7	Turco et al; Verrotti et al; Zuberi et al. [28–30]	Tapping a circumscribed region of the head or face	Bilateral myocloni	Generalised spike-wave pattern	Infantile reflex epileptic syndromes of variable origin	Quick generalisation from the somatosensory facial and head area.
8	Moeller et al. [26] 14-year old girl	Intermittent photic stimulation	Generalised tonic-clonic seizure	Before seizure onset, photic stimulation induced generalised photo-paroxysmal responses associated with increases of BOLD signal in the visual cortex, thalamus, and both superior colliculi; a decrease in BOLD signal in the fronto-parietal areas. The BOLD signal in the visual cortex increased in magnitude during consecutive epochs of photo-stimulation and photo-paroxysmal responses.		The group of generalised epilepsy; 75-80% of all reflex seizures
9	45 year-old-man	A Nox-band melody and songs from the film "Black cat, white cat" by Emir Kusturica	Hearing melody-fragments, then complex partial seizure with automatisms	Amygdalar? Temporo-lateral?	Left parahippo-campal-amygdalar dysgenesis, enlarged left amygdala	Difficult-to-treat epilepsy, 3-4 seizures/ week Melodies had triggered seizures initially, then spontaneous seizures evolved.
10	28-year-old female	A song by Adele (Laurie Blue Adkins) "Someone like you"	Frequent auras with ear-buzzing, déjà vu, floating sensation; occasional progression to inability to speak, mumbling; arm circling and disturbance of consciousness with amnesia	Temporo-lateral?	none	Under investigation
11	28-year old female	Eating	After finishing meal, feeling a "bash on the stomach" and nausea, evolving to hypermotor seizures with vocalisation	Temporo-frontal? Sparse interictal right frontal spikes, hypermotor seizures with vocalisation, dubious right frontal ictal EEG pattern	Dubious frontal and temporal white matter changes. History of acute myeloid leukaemia	Difficult to treat, frequent seizures, triggered by eating/digestion: complex autonomic network
12	Osei-Lah et al [22] 19-year-old man	Reading	Feeling unwell, unable to read, confused, retching, spitting-partial seizure, generalizing	Temporal lobe; Left temporal ictal pattern; progressing to generalised seizure ativity	None	Focal reading epilepsy

(*continued on next page*)

Table 1 (*continued*)

No	Patient, age, gender	Provoking stimulus	First seizure symptom	Epilepsy type, EEG	MRI lesion	Comment
13	Koutroumanidis et al. [27]; Our 41-year old male patient	Reading	Alexia, masseter twitching progressing to generalised tonic-clonic seizures if continuing reading	Generalised poly-spike-wave activity		Primary, "generalised" reading epilepsy
15	Racicot et al [23] 23-year-old left-handed female	Left-handed tasks requiring visuomotor coordination e.g. pouring juice in a glass, cutting food and, writing. Nocturnal seizures when dreaming of writing.	Vertigo, body stiffening, and laboured breathing. Brief alteration of consciousness was rare, and evolution to a bilateral convulsive seizure occurred once	Right centroparietal interictal epileptiform discharges. Seizures : repetitive preictal polyspike-wave discharges over the right centroparietal leads	Right inferior parietal lobule cortical dysplasia in the depth of the intraparietal sulcus at the junction with the postcentral sulcus. PET: area of hypometabolism over the right parietal lobe.	Practice-induced focal seizures. Dreaming seems to activate the same network.
16	Nevler and Gandelman-Marton. [24] Young man	Thinking	Complex partial seizures	Focal ictal synchronisation	Acute bacterial meningitis, remote head injury in history	High level cognitive network activation underlying focal seizures.
17	Hidetaka Tamune et al [25] 50-year-old female	Emotional stimuli	Temporal lobe seizures;	Interictal low-voltage spikes at F7 and T1. Ictal: 6-Hz bilateral synchronous, more left temporal discharges. Left mesial TLE semiology, gastric aura, automatisms, and dystonic posture of the right upper limb.	amygdala enlargement	Psychogenic non-epileptic seizures suspected initially, then temporal lobe epilepsy recognised.

seizures and epilepsies with most variable types of eliciting stimuli such as cognition, praxis, and sleep/wake changes.

To demonstrate our points in this paper, we discuss some demonstrative cases, ours and those from the literature, in the order of evoking stimuli from simple to more complex.

2.1. Somato-sensory stimuli

In these RSs (Pts 1–7, Table 1), tapping [28–30], rubbing [31] or tooth-brushing [17,21] the ictal semiology may resemble a spinal reflex-loop (Pt 1) [33,34]: the stimulation of the limb, be it light touch, running or tension, evokes motor jerks of the same limb [33].

In our Pt 2, right-sided motor seizures called attention to a benign tumour of her left primary motor area. Initially, a painful burning of her right hand while ironing made her quickly pull it back from the hot iron; then this movement continued in a clonic jerk of the hand and arm. She had similar pain-induced motor seizures several times, spreading occasionally to the lower limb as well, with full awareness. Some months later the same focal motor seizures became spontaneous, not "needing" any stimuli to develop (her motor network may have 'learned' the epileptic working mode).

Similarly, the motor seizures characterised by right arm clonus propagating to the face and leg of our Pt 3 with a left precentral motor strip tumour, were initially triggered by intensive straining of the right arm. This work-related jerking suggested normal muscle-exhaustion, transitorily blurring the epileptic nature of his motor events and making his GP recommend relaxation. Then a brain CT scan revealed his tumour and the diagnosis of epilepsy became clear. He soon developed very similar spontaneous motor seizures in addition to the reflex ones.

A very circumscribed epileptogenic region may be suspected in bilateral reflex myoclonic epilepsies in infancy classified as "generalised", too, where the tapping of just the vertex or perioral region triggers seizures; the stimulation of other facial regions does not evoke them [29–31].

2.2. Photic stimulation

Seizures triggered by intermittent photic stimulation (Pt 8) or by eye closure, reflect the visual system's epileptic involvement [36]. In an epilepsy classified as generalised - eyelid myoclonus with absences - the anatomo-functional changes of the visual system supported the system-link, a "focus" in the visual system [44].

Supporting the epileptic involvement of the visual cortex on the effector's side, photosensitive seizures may start with eye flickering and/or occipital spikes [37,38]. In a 14-year-old bilateral photosensitive epilepsy patient [26], the photo-paroxysmal response to intermittent photic stimulation started with an augmenting activation of the visual cortex shown by functional MRI; this activation spread and generalised shortly after.

A subtype of photosensitive epilepsies, pattern-sensitive epilepsy, presents focal EEG and seizure symptoms [12,46]. In such cases, the specific triggering pattern might affect a tiny circumscribed epilepsy-prone area within the visual cortex [16].

2.3. Music

Musicogenic RSs typically feature temporo-lateral epilepsies, where music in general, or specific melodies evoke focal seizures probably related to a complex hearing-emotional network. In our young female patient (Pt 9) with childhood onset MRI-negative familiar temporal lobe epilepsy, a song by Adele, "Someone like you", provoked auras starting with ear buzzing followed by déja vu and disturbance of consciousness on some occasions. In another patient (Pt 10), certain songs of the band, Nox, and melodies from the film "Black cat, white cat" by Emir Kusturica triggered left temporal seizures underlain by an amygdalo-hippocampal dysgenesis and an enlarged amygdala. He developed

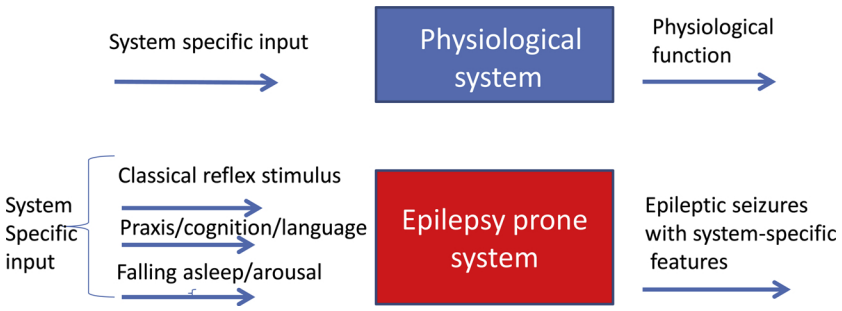

Fig. 1. Epilepsies occur in epilepsy-prone physiological brain networks. System specific stimuli may generate seizures with system specific features.

spontaneous seizures with similar semiology later. It is unclear if he has temporo-lateral epilepsy or the emotional effect of the melodies had a triggering role in an amygdalar epilepsy.

2.4. Eating

The simple focal seizures (auras) of our young female patient (Pt 11) are usually associated with finishing a meal. The spells start with nausea or a sudden unpleasant gastric sensation, which she describes as a "bash on the stomach"; this may progress to a disturbance of consciousness and a hypermotor seizure with vocalisation and amnesia. We suspect her episodes of eating RSs reflect the epileptic readiness of a complex network involved in autonomic control [15].

2.5. High level complex stimuli – "praxis-induced RSs"

RSs triggered by praxis, calculating, reading-writing or language, suggest the epileptic readiness of high-level, complex networks producing bilateral ictal myocloni and EEG patterns in several such cases (Pt 13) [6,7,23,24,27,39–42,45]. These patients' seizure-symptoms - ictal facial twitches or alexia - point to the wide-spread reading-speaking system [6,27]. In an MRI-negative case of mental calculation-induced left arm myocloni, bilateral spike-wave pattern was found. Magneto-encephalography revealed a right prefrontal cortical epileptogenic focus [39].

2.6. Arousal and sleep related epilepsies as "reflex seizures"

The seizures of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) patients are associated with micro-arousals representing cyclic alternating pattern (CAP) A within NREM sleep [4,47–51]. These seizures manifest behaviours of arousal from simple moving, sitting up, turning in bed etc. to violent hyper-motor symptoms that may be looked at as extreme hyper-arousals with "flight-fight "reactions. The activation of the genetically hyper-excitable (epilepsy prone) frontal arousal-system might underlie seizures: whenever the sleep-level shifts towards arousal within phase 2–3 sleep, an arousal-like seizure may occur. Because there is frequent upward fluctuation (arousal) of sleep-depth during NREM sleep, these patients may have up to 60–70 seizures overnight, even manifesting a quasi-periodic occurrence following CAP A periods [51]. In ADNFLE, the frontal lobe is made hyper-sensitive by mutant neuronal nicotinic acid receptor genes and additional candidate genes augmenting prefrontal neocortical cholinergic activity causing fragmented sleep, prefrontal hyper-excitability; and proneness to epilepsy during NREM sleep [52–57].

In absence seizures of idiopathic generalised epilepsy, there is a critical transitional vigilance-zone activating the spike-wave discharges; the EEG hallmark of these epilepsies. These transitional periods occur between wakefulness and NREM-; as well as between REM and NREM sleep. On a sleep microstructural level, absences associate with CAP A1 [58]. NREM sleep promotes, REM sleep inhibits and wakefulness allows their presence [59–63]. The drowsiness-dependence of absences is in accordance with the theory first raised by Gloor: sleep spindles produced by the thalamo-cortical system's burst-firing mode may derail to spike-wave discharges, "same system, same working mode" [64–68]. The switch of sleep spindles to spike-waves has recently been questioned [69], however, the burst-firing mode of the thalamo-cortical system as the origin of spike-waves and absences' association to superficial NREM sleep has remained true [4,69–73].

3. Discussion

The studies on RSs have several conceptual and practical consequences [35,74]. Firstly, the sine qua non of the reflex mechanism is the existence of an epilepsy-prone system (disposed to epileptic activity) able to generate seizures. This epileptic readiness may originate from multiple causes e.g. genetic, lesional, developmental and metabolic, resulting in the epileptic transformation of a functional system. In such cases epilepsy takes over, "hijacks" [75] the affected system distorting its functioning.

We are focusing here on the subsequent step following epileptic transformation. We are looking into the mechanism of actual seizure-generation by the epilepsy-prone system that can easily switch from normal functioning to an epileptic seizure (Fig. 1).

In RSs in a broader sense, there is no external stimulus. It is the normal functional activation of the epilepsy-prone system acting as a seizure-trigger. This might be the case in praxis-, or complex, high level cognition-induced seizures [76–79], probably involving the associative cortex with its thalamic connections, as well as in sleep and arousal related seizures [4,80]. We suppose that also apparently "spontaneous" seizures are ignited by the functional activation of the epileptically transformed system or by a system-specific input.

The system-epilepsy notion is also supported in other ways. In RSs, the trigger and the ictal semiology may be strikingly similar, pointing to the same network. This is well seen in sleep-, and arousal related epilepsies: absences triggered by falling asleep resemble sleep-like states and frontal lobe seizures triggered by arousal are arousal-like episodes.

A remarkable bidirectional system involvement (system-specific input and output) may be seen in other RSs as well: eating triggers ictal gastric sensations; muscle exertion provokes ictal motor phenomena or a painful jerk turns to (sensory)-motor seizures; music triggers an auditory aura etc. The system-dependence of bilateral RSs [6,18] manifests in a one-system onset followed by quick generalization [81]. Occipital symptoms point to the visual cortex in photosensitive epilepsies and the ictal reading-speaking symptoms to the speech network with a dominant-side ictal electric pattern [27].

During the follow-up of RS patients, different types of epileptic "learning" and progression can be seen [26,81,82], as in our patients first producing RSs and progressing to spontaneous seizures later (Pts 2, 3, 9, 10). A three-step epileptic progression, from somato-sensory RSs, across spontaneous motor seizures, to epilepsia partialis continua, was seen in two of our patients (Pt 4 and Pt 5). A third type of kindling-like progression is a development from focal to more widespread focal and

to generalised seizures [81,82].

In summary, adequate afferent sensory imputes or high-level associative cortex stimuli activate the epilepsy prone systems and may ignite a seizure. This mechanism may be an essential part of ictogenesis in general.

Conflict of interest statement

None of the authors has any conflict of interest to declare.

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