



Review

Do reflex seizures and spontaneous seizures form a continuum? – Triggering factors and possible common mechanisms



Friederike Irmen^a, Tim Wehner^{a,b}, Louis Lemieux^{a,*}

^a Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, United Kingdom

^b National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom

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ABSTRACT

Recent changes in the understanding and classification of reflex seizures have fuelled a debate on triggering mechanisms of seizures and their conceptual organization. Previous studies and patient reports have listed extrinsic and intrinsic triggers, albeit their multifactorial and dynamic nature is poorly understood. This paper aims to review literature on extrinsic and intrinsic seizure triggers and to discuss common mechanisms among them. Among self-reported seizure triggers, emotional stress is most frequently named. Reflex seizures are typically associated with extrinsic sensory triggers; however, intrinsic cognitive or proprioceptive triggers have also been assessed. The identification of a trigger underlying a seizure may be more difficult if it is intrinsic and complex, and if triggering mechanisms are multifactorial. Therefore, since observability of triggers varies and triggers are also found in non-reflex seizures, the present concept of reflex seizures may be questioned. We suggest the possibility of a conceptual continuum between reflex and spontaneous seizures rather than a dichotomy and discuss evidence to the notion that to some extent most seizures might be triggered.

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1. Introduction

The recent ILAE report regarding the practical definition of epilepsy includes recurrent reflex seizures that are “associated with an enduring abnormal predisposition to have such seizures” [1]. In his critical appraisal of the ILAE’s 2010 revised classification of the epilepsies [2], Shorvon [3] proposes *provoked* epilepsy as a fourth category next to the “established categories” [4] idiopathic (predominantly genetic), symptomatic (acquired), and cryptogenic (unknown). In this scheme, provoked epilepsies include the subcategory of reflex epilepsies that result from a clearly defined environmental factor inducing seizure occurrence [3]. However, these etiologic categories are not necessary mutually exclusive and integrating recent knowledge on ictiogenesis refines the sharpness of the applied definitions [5]. In a broader sense, it is currently presumed that in all epilepsies an underlying ultimate cause, i.e. a genetic, acquired or cryptogenic aetiology is interacting with several intrinsic and extrinsic proximate *facilitating factors* lowering a seizure threshold, which results in seizure occurrence.

While these facilitating factors may lead to an unspecific alteration of neuronal excitability, seizure *triggers* exhibit a direct and immediate influence on seizure occurrence, the source of which is still poorly understood.

1.1. Triggers in seizures

A broad variety of triggering factors of seizures has been reported. Triggering stimuli may be classified as *extrinsic* such as flashes of light or music and *intrinsic* such as movements or emotion and cognition [6]. If there is an identifiable factor that reproducibly recurrently triggers seizures, the provoked seizures are referred to as reflex seizures. This rare subcategory includes provoked seizures that are “objectively and consistently evoked by a specific afferent stimulus or by activity of the patient” [6], although the degree of reliability of the trigger is not well specified. On a second dimension, the afferent stimuli or triggers may be as *simple* as light stimuli or more *complex* such as music or language (Fig. 1).

In reflex seizures, the most prevalent extrinsic trigger is flashing light. Photosensitivity occurs in approximately 2% of patients with epilepsy [7] and is more frequent in certain syndrome categories such as idiopathic generalized epilepsy (IGE) [8]. Research regarding underlying mechanisms of photosensitivity has received

* Corresponding author at: UCL Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom. Tel.: +44 1494 601361.

E-mail address: louis.lemieux@ucl.ac.uk (L. Lemieux).

growing interest due to the increasing exposure to artificial light and a high number of seizures occurring in response to TV presentation or videogames [9]. Other listed triggers include complex visual stimuli, startle, hot water, verbal-cognitive stimuli such as reading or nonverbal-cognitive stimuli such as mental arithmetic [10–12]. Literature regarding patient reports of triggers name sleep deprivation, emotional stress and fatigue as the most important factors [13]. In children, one of the most commonly reported triggers is fever [14,15]. Patient reports are a valuable source for the assessment of triggering mechanisms albeit ambiguous conceptions of triggers result in a blurred distinction from facilitating factors. Particularly, it could be argued that fever should be considered a *facilitating* rather than a *triggering* factor as it generically lowers the seizure threshold rather than inducing seizure occurrence directly. The same may be true for sleep deprivation [16–18], alcohol withdrawal, exposure to drugs [19], toxins such as heavy metal or carbon monoxide poisoning which have also been associated with seizure occurrence [20,21]. Further reference to triggers can be found in studies assessing the link between hormonal changes during the menstrual cycle [22] or metabolic disturbances such as hypoglycaemia, renal encephalopathy or hepatic failure [9,23] and seizure occurrence.

As becomes apparent with this growing list of factors associated with seizure manifestation, there is an urgent need to classify and distinguish triggers and facilitating factors by their underlying mechanism. Whether or not a seizure is acknowledged as being triggered critically depends on the nature of the triggering factor and the individual patient's report. It is generally accepted that a dynamic and multifactorial presence of facilitating factors and triggers modulate the seizure threshold by interacting with genetically and environmentally determined hyperexcitability.

1.2. The causal mechanism of seizures

The uniqueness of reflex seizures lies in the direct overcoming of the seizure threshold through presentation of the trigger. In reflex seizures, an identified trigger that constantly evokes seizures is thus perceived as the direct cause integrating underlying aetiology and mechanism [24]. When applying this perspective of a “causal mechanism” [25,26] on ictogenesis, all seizures may be considered the result of structural and functional changes in brain networks occurring after an initial event resulting in a lowering of the threshold for synchronized activity, i.e. hyperexcitability of certain brain areas [27]. Such an initial event could result in single

or multifactorial impacts on structural abnormalities, acquired lesions and genetic predispositions. According to our current understanding these could initiate abnormal firing patterns in a neuronal circuit interrupting homeostatic neuronal transmission, cellular transport or cell metabolism. By these means, the hyperexcitable brain region would become more susceptible for epileptic discharges triggered by functional activation of a small area within this system [24]. Specifically, in reflex epilepsies, the hyperexcitable areas may be activated by exposure to particular sensory, cognitive or motor stimuli eliciting epileptic discharges [11]. Thus, reading epilepsy could be described as the result of epileptic discharges within a hyperexcitable brain area involved in language and reading activated by words, letters or language processing [12]. Importantly, the causal mechanisms of ictogenesis in reflex and non-reflex seizures encompass a dynamic interplay of the hyperexcitable predisposed areas, facilitating and triggering factors acting on the seizure threshold. The effect of the triggering stimulus as a switch for epileptic activity in hyperexcitable neuronal circuitries may depend on its level of interference with the multi-layered excitability and inhibition within the neuronal network.

Based on the above considerations on the complexity of triggers, their role in ictogenesis and the assumption of their interplay with a row of facilitating factors, it seems necessary to review the conceptual properties of triggers in seizures. To this end, we review the literature on reflex and non-reflex seizures that have been associated with triggering mechanisms. We conclude that due to the variability of the trigger–seizure relationship and the related varying observability of triggers, a range of yet undiscovered factors that could be categorized as a trigger may be involved in the onset of most if not of all epileptic seizures. We thus suggest that reflex seizures and spontaneous seizures may be the two extremities of a conceptual continuum on which seizures are generated by extrinsic or intrinsic triggers.

2. Methodology: literature search

Defining terminology. There is a wide range of terminology used to describe aetiology and triggers of seizures. On a temporal scale, seizures are induced by an ultimate causative aetiology as well as a row of ‘facilitating factors’ that lower the ictogenic threshold by an unspecific alteration of neuronal excitability. In provoked and reflex seizures a selective stimulus evokes a specific alteration in neuronal excitation that is directly associated with seizure occurrence. In this review, such stimulus will be referred to as ‘trigger’ synonymously for ‘precipitating factor or precipitant’, ‘evoking factor’, ‘eliciting factor’ and ‘inducing factor’, to avoid misunderstanding.

Reviewed literature. Medical publications on seizure triggers and reflex seizures were reviewed. A general search was conducted in MEDLINE and EMBASE using a combination of the terms “seizure”, “trigger”, “triggering factors”, “precipitants”, “precipitating factors”, “provoking factors”, “provoked seizure”, “facilitating factors”, “reflex epilepsy”, “reflex seizure”, “photosensitivity” and “alcohol withdrawal seizure”. References were identified with general search results. Relevant papers were preliminarily identified by title and abstract according to their importance, quality, actuality and originality. Identified articles were screened according to exclusion and inclusion criteria. More publications were added by screening of reference lists of included articles and from the author's own files. By applying the inclusion and exclusion criteria 71 articles were selected for review and discussion.

Inclusion criteria. Articles published since 2000, reporting and reviewing original research in which triggers of seizures have been successfully identified. Studies focussing on reported triggers in reflex seizures, alcohol withdrawal seizures and photosensitivity.

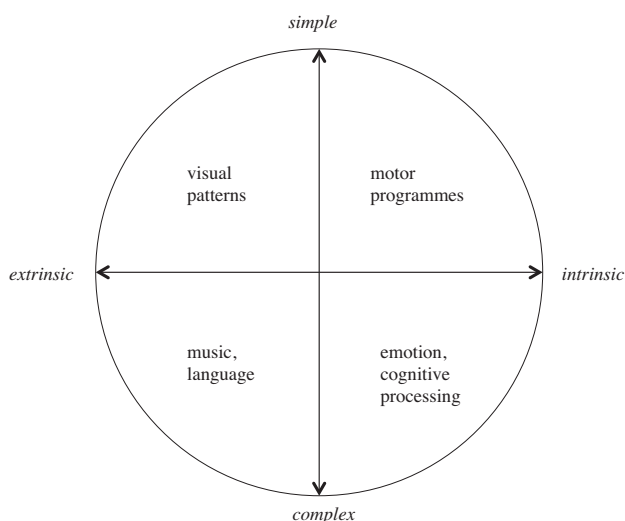


Fig. 1. Conceptual organization of exemplary triggering factors in seizures.

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