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Review

Seizures induced by direct electrical cortical stimulation – Mechanisms and clinical considerations

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HIGHLIGHTS

- CS-induced seizures are used to define the epileptogenic zone in some centres.
- Other centres consider them as a by-product of CS with limited added value.
- Contribution to improve postsurgical outcome and recording time is uncertain.

ABSTRACT

Direct electrical cortical stimulation (CS) is widely used to map eloquent cortex. It can be applied extra-operatively in patients undergoing intracranial EEG recordings using chronically implanted electrodes (subdural, depth or a combination), or it can be used intraoperatively. Seizures can be induced by CS but there is controversy regarding the utility of CS induced seizures in defining the epileptogenic zone and hence practice varies considerably between centres. Some centres use seizures induced by direct CS routinely to aid in defining the epileptogenic zone. In contrast, others do not rely on such information and explicitly avoid stimulating seizures during cortical mapping. Intra- and extraoperative techniques have been used to stimulate seizures with varying results, which may in part reflect these methodological differences. We here aim to review current views, definitions and studies on seizures induced by direct electrical CS. In addition we discuss mechanisms and methodological considerations of this procedure.

Contents

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1. Historical perspective

Direct electrical cortical stimulation (CS) is widely used both in intraoperative and extraoperative settings to define eloquent cortex (Stephani and Luders, 2011). In addition to its role in defining eloquent cortex, CS can elicit seizures. Such stimulation induced seizures were first reported during the early pioneering days of neurosurgery when intraoperative electrical stimulation of the cortex elicited patient's habitual auras (Cushing, 1909; Foerster and Penfield, 1930; Penfield and Jasper, 1954). Since then, induction of seizures by CS reproducing the patient's habitual seizure semiology has been utilized and promoted by Bancaud and Tailarach. Direct CS was used to define the epileptogenic zone in patients undergoing invasive presurgical investigations with depth electrodes for pharmacoresistant epilepsy (Bancaud et al., 1974). The epileptogenic zone was defined as the region that produced the whole ictal, electro-clinical pattern. Indeed, much of the published data relates to stimulation studies using depth electrodes/stereo EEG (SEEG). There are, to our knowledge, only two studies that investigated stimulations eliciting auras/seizures using subdural electrodes (Schulz et al., 1997; De Salles et al., 1994). Despite very early anecdotal reports on this subject, very few studies have systematically investigated the clinical utility of direct intraoperative or extraoperative CS eliciting seizures to delineate the seizure onset or epileptogenic zone. In part, this may reflect difficulties in defining stimulation induced seizures and the fact that stimulation techniques may vary between epilepsy centres. It may also mirror historical differences and traditions. In France, stimulation induced seizures have been routinely used as an important part of the invasive work-up for epilepsy surgery and form part of the definition of the epileptogenic zone since the work of Bancaud and Talairach. In contrast, many other centres influenced by the North American approach to epilepsy surgery have not traditionally relied on the use of stimulation induced seizures in the pre-surgical work up (see also Supplementary Table S1). The approach there has been strongly influenced by the work of Wilder Penfield, and, although there is mention of the induction of seizure symptoms and auras during cortical stimulation, the emphasis rests on intraoperative electrical stimulation being used to "safeguard" function (Penfield, 1930, 1958).

We here aim to outline current definitions and studies on seizures induced by direct CS and their utility in clinical practice. We will summarize current understanding of the mechanisms and methodological considerations of CS aimed at eliciting habitual seizures. We compare the varied approaches in regards of the use of CS induced seizures, and we examine the evidence underlying the differing practices. We are aware that many other centres perform epilepsy surgery and may use modified approaches compared to the concepts predominating in France and North America or even combine aspects of the two.

This review focuses on stimulation induced seizures, referring to electrically-induced electro-clinical events and resembling the seizures that occur spontaneously. It does not cover direct CS mapping used to delineate eloquent cortex or single pulse electrical stimulation which has emerged as a tool to delineate connectivity of cortical regions and potentially adds to assessing cortical excitability (Valentín et al., 2005; Flanagan et al., 2009; van 't Klooster et al., 2011; David et al., 2013).

2. Definition of seizures induced by direct CS

In CS induced seizures the EEG seizure discharges are triggered as an immediate result of the electrical stimulus (see Figs. 1 and 2). Thus CS induced seizures in humans are an immediate phenomenon and different from kindling. Kindling is a phenomenon whereby repeated electrical stimulations not sufficient to elicit seizures lead to the development of chronic epilepsy in rodents. Although kindling has been widely used as an epilepsy model up to now there is no unequivocal evidence of kindling as a mechanism of epileptogenesis in humans (Berg and Shinnar, 1997). In stimulation induced seizures, both clinical signs, if present, and EEG discharges outlast the electrical stimulus and the intracranial EEG pattern evolves in frequency and distribution, as is seen in spontaneous seizures. When recruiting eloquent cortex, stimulation induced seizures will be associated with clinical symptoms.

There are two different possible (or plausible) scenarios regarding timing of symptoms in relation to the stimulation and the EEG seizure. (1) The symptom is generated during the stimulation, before significant propagation of the electrical discharge has occurred. This means that there is close co-localisation of a cortical region that can generate this symptom and can be considered as the symptomatogenic area of the CS. Furthermore, this area also has a low threshold to produce electrical seizures. (2) The symptom only occurs during the spread of the EEG seizures. This means that a connected area, local network or wider network of cortical areas activated by the electrically triggered ictal discharge (afterdischarge) could generate the symptom.

Afterdischarges have been often mentioned in the same context as stimulation induced seizures (Blume et al., 2004). Afterdischarges are defined as epileptiform rhythmic discharges (such as repetitive spikes or polyspikes, or sinusoidal rhythmic spikey discharges), elicited by and outlasting CS. Such afterdischarges are typically confined to the electrodes that were stimulated, but may spread to functionally connected areas (Blume et al., 2004; Lesser et al., 2008). These are seen in isolation and do not evolve in frequency and distribution. However, when afterdischarges spread to different adjacent and remote electrodes, the EEG discharge then fulfils criteria for stimulation-induced EEG seizures.

3. Different views on the use of CS induced seizures in defining the epileptogenic zone inform practice in presurgical epilepsy work-up

Firstly with regard to the traditionally predominant approach in North America: stimulation induced seizures have largely been mentioned as a by-product of the CS procedure aimed at defining eloquent cortex. In this regard, afterdischarges elicited by direct CS are seen as heralds of CS induced seizures (Blume et al., 2004; Lee et al., 2010). There have been several attempts to define afterdischarges. Early definitions stress that afterdischarges are an (1) EEG seizure pattern following repetitive electrical stimulation of a discrete area of the brain via cortical or intracerebral electrodes and (2) burst of rhythmic activity following a transient such as an evoked potential or a spike (Chatrian et al., 1974). Blume and colleagues have studied afterdischarges in more depth and concluded that these were not associated with the seizure onset (Blume et al., 2004). The semiology of such stimulation induced seizures may be non-habitual; in our experience, stimulation