



## Review

## Epileptogenic focus localization in treatment-resistant post-traumatic epilepsy



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## ABSTRACT

Pharmacologically intractable post-traumatic epilepsy (PTE) is a major clinical challenge for patients with penetrating traumatic brain injury, where the risk for this condition remains very high even decades after injury. Although over 20 anti-epileptic drugs (AED) are in common use today, approximately one-third of epilepsy patients have drug-refractory seizures and even more have AED-related adverse effects which compromise life quality. Simultaneously, there have been repeated recommendations by radiologists and neuroimaging experts to incorporate localization based on electroencephalography (EEG) into the process of clinical decision making regarding PTE patients. Nevertheless, thus far, little progress has been accomplished towards the use of EEG as a reliable tool for locating epileptogenic foci prior to surgical resection. In this review, we discuss the epidemiology of pharmacologically resistant PTE, address the need for effective anti-epileptogenic treatments, and highlight recent progress in the development of noninvasive methods for the accurate localization of PTE foci for the purpose of neurosurgical intervention. These trends indicate the current emergence of promising methodologies for the noninvasive study of post-traumatic epileptogenesis and for the improved neurosurgical planning of epileptic foci resection.

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## 1. Introduction

The prevention and clinical management of post-traumatic epilepsy (PTE) are important priorities for health care professionals worldwide. Following traumatic brain injury (TBI), the brain initiates immediate neuronal and glial responses which typically lead to significant cell losses in lesional and peri-lesional areas, and which in turn lead to long-term changes in neural network organization, particularly in the hippocampus and neocortex [1]. Within minutes to hours after injury, shearing of white matter tracts, contusions, hematomas and edema lead to neurotransmitter release, free-radical generation, calcium-mediated damage, angiogenesis, mitochondrial dysfunction and inflammatory responses, all of which have been associated with epileptogenesis [2–4]. The resulting imbalance between excitatory and inhibitory neurotransmitters is thought to imply an increased risk for spontaneous seizures due to the formation of excessive recurrent excitatory synapses [5]. These processes develop throughout a latent period of time and culminate with the emergence of spontaneous, recurrent seizures.

Although several studies have proposed that PTE onset is preceded by an increase in seizure susceptibility, the electrophysio-

logical correlates of post-traumatic epileptogenesis remain poorly understood, as do the effects of anti-epileptic drugs (AED) and of other treatments upon brain regions that are at risk for developing epileptic foci [6,7]. In addition, most information about epileptogenic mechanisms has been derived from animal models, and there is a paucity of studies which have attempted to understand this phenomenon in humans [8]. Without the aid of electrophysiological measurements acquired from TBI patients, it is difficult to dissociate injury-related cellular alterations which promote seizure occurrence from compensatory and neuronal repair mechanisms, which has been a major goal of PTE research in animal models [9]. Furthermore, aside from (1) the presence of appreciable neuronal loss, and (2) the subsequent depletion of synaptic inhibition within granule cells subsequent to TBI, little is currently known about how either short or long-range neuronal electrical activity is affected by mechanical trauma [1]. Consequently, renewed efforts are needed (1) to understand the electrophysiological correlates of epileptogenesis, (2) to formulate optimal anti-epileptogenic strategies, and (3) to improve clinical outcome in patients with pharmaco-resistant manifestations of PTE. In this review, we discuss the epidemiology of treatment-resistant PTE, address the need for effective anti-epileptogenic treatments, and highlight recent progress in the development of noninvasive methods for the accurate localization of PTE foci for the purpose of neurosurgical

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intervention. These trends indicate the current emergence of promising methodologies for the noninvasive study of post-traumatic epileptogenesis and for the neurosurgical planning of epileptic foci resection.

## 2. Epidemiology

Though epidemiological estimates regarding the prevalence of PTE vary, it has been suggested that as many as 20% of acquired epilepsy cases are due to TBI, with a 30 year cumulative incidence of up to 16% in the case of severe injuries [10–12]. Some authors have reported that the likelihood of developing epilepsy after TBI is as high as 30–50% [13], and that PTE is among the most common forms of acquired epilepsies [14]. Over half of all patients with penetrating head injuries acquire PTE, which develops within 2 years in approximately 80% of all cases, though substantial risks for PTE onset extend for longer than 10 years post-TBI [15]. The latter condition is also the most frequent cause of remote symptomatic epilepsy in 15 to 34 year olds, and accounts for around 30% of epilepsy cases in this age group [16–18]. In the pediatric population, TBI is one of the most significant epilepsy risk factors, with a seven-fold increase in epilepsy risk in children [19]. Overall, TBI patients are almost 30 times more likely to develop epilepsy than the general population [14], and the probability for PTE to be pharmacologically resistant is high in both focal as well as generalized cases of the disease [20].

Pharmacologically intractable PTE is a major clinical problem for patients with penetrating head injuries, where the risk for this condition remains very high even decades after injury [21]. Although over 20 AED are in common use today, approximately one-third of epilepsy patients have drug-refractory seizures and even more have AED-related adverse effects which compromise life quality [22,23]. Beghi [24] found that, in randomized clinical trials involving treatment using phenytoin, phenobarbital or carbamazepine, the difference between active treatment and placebo has been virtually lacking for the prevention of PTE. Based on a review of the available scientific and clinical literature, the conclusion of this study was that the failure to influence PTE risk is similar to that identified by meta-analyses of randomized clinical trials on seizure prevention for other conditions. Additionally, adverse treatment events related to AED may require drug withdrawal or substitution in as many as 30% of patients, such that the prevention of epilepsy onset (i.e. anti-epileptogenesis) has come to be acknowledged as a major priority in the field of epilepsy research [25,26].

Although TBI is one of the most common causes of acquired symptomatic epilepsy, there is as yet no effective treatment against post-traumatic epileptogenesis and no reliable biomarker which can allow clinicians to predict patient susceptibility to PTE [14,27]. It is known, however, that TBI patients with a single late seizure have a 65–90% chance of progressing to PTE, which is less likely to be medically tractable than other causes of chronic seizures [28]. It has been observed that, after the first late post-traumatic seizure, over 80% of patients develop a second seizure within 2 years [15]. Additionally, magnetoencephalographic (MEG) recordings from some mild TBI patients have been shown to exhibit epileptiform spikes within 12 to 140 months after injury [29]. Thus, because months to years can often elapse between TBI and PTE emergence, the delay between the traumatic event and PTE onset provides an excellent opportunity for the implementation of anti-epileptogenic therapies [14,27,30].

## 3. PTE focus localization

Partly because of the poor ability of previous methods to localize epileptogenic foci, surgical interventions for their removal in

PTE patients have often involved the excision of relatively large portions of brain tissue [10–12]. Accordingly, one significant drawback of epileptogenic foci removal is that spatial uncertainties related to their localization can translate into the unnecessary excision of peri-focal tissues which are not involved in ictogenesis. Based on a thorough review and analysis, Marks et al. [31] concluded that seizure localization in TBI patients with uncontrolled epilepsy was difficult at the very least, partly due to anatomical changes induced by injury and partly due to the often multifocal nature of post-traumatic seizures. The authors acknowledged that intractable PTE patients may benefit from epilepsy surgery, though accurate seizure localization was essential before undertaking neurosurgical intervention. Insightfully, Marks et al. note that “[ascertaining] whether certain cortical regions have a selective epileptogenic vulnerability following head injury [...] would help determine whether certain post-traumatic seizure disorders are amenable to surgical intervention”. In their own study, for instance, two patients with drug-resistant PTE underwent partial frontal lobectomies, and a third had a partial callosotomy. All three patients had poor outcome following surgery, which was attributed to the difficulty of localizing epileptogenic foci outside the temporal lobe. The authors speculated that, if mesial temporal lobe epilepsy were a common outcome of TBI, successful surgical intervention would be easier than in cases involving the resection of extra-temporal foci, which are more difficult to localize. A more recent study by Hakimian et al. [32] similarly found that, although epileptogenic foci in medically intractable PTE are extra-temporal in approximately 50% of cases [33], their surgical resection is still associated with poor outcome in patients where epileptogenic area localization cannot be performed with high accuracy in the absence of invasive electrophysiological recordings. Due to such poor localization, considerably less research has been undertaken to elucidate the neuropathology of extra-temporal foci in humans, despite their commonality. Thus, the ability to perform accurate localization of extra-temporal foci using noninvasive electroencephalography (EEG) may considerably expand the range of opportunities for research into this poorly understood type of epilepsy.

## 4. Challenges of surgical interventions in PTE

Despite repeated recommendations by radiologists and neuroimaging experts to incorporate localization based on EEG into the process of clinical decision making regarding PTE patients [28,34], little progress has been accomplished towards the use of EEG as a reliable tool for locating epileptogenic foci for the purpose of surgical resection. One complexity which has often been associated with this task is that head trauma commonly leads to widespread epileptogenicity [35], such that the identification of multiple foci based on EEG recordings is very challenging in the absence of accurate localization. Numerous researchers have lamented that seizure focus localization is greatly complicated by injury extent and heterogeneity, as well as by the presence of complex lesion profiles, including prior craniotomies [14,32,36]. Nevertheless, the usefulness of EEG for defining a patient's probability to develop epilepsy has hardly been exploited, partly because more than 20% of PTE patients have a negative EEG during the first 3 months post-TBI [37]. In spite of this, however, it has been acknowledged that, even when epileptiform activity is absent, recordings from patients with PTE frequently exhibit anomalous readings such as decreases in slow wave (0.5–3 Hz) base activity in the region of a localized ictogenic focus [38]. The identification of such foci, however, is problematic because they do not always occur in lesioned areas [21] and because sites remote from the primary injury cannot be dismissed as unlikely to generate seizures [39].

The task of mapping epileptogenic foci in PTE patients can be substantially more challenging than in non-TBI patients due to diffuse encephalomalacia and to white matter connectivity disruptions that are caused by mechanical stresses in the head during the traumatic event. Because of such phenomena which can affect the brain far from the site of predominant injury, epileptogenic foci can evolve at locations which have traditionally been difficult to predict or identify [39]. Although resection of encephalomalacia has been hailed as a highly effective treatment of intractable epilepsy [40,41], the difficulty of accurately localizing epileptogenic foci in PTE patients has continued to be a substantial deterrent from using this therapeutic strategy on a frequent basis in this patient population. Hakimian et al. [32], for example, noted that extratemporal resections of PTE foci may often involve invasive monitoring, which can be problematic and is discouraged. Factors such as the spatial extent of TBI, possible anoxia at the time of injury, the presence of bilateral lesions, prior craniotomies and breach rhythms can all lead to potential complications which make surgical intervention more challenging. On the other hand, in those patients where surgery is feasible, such interventions can lead to excellent seizure control, with a low risk of complications. Although, unsurprisingly, the use of invasive electrocorticography recordings has been reported to aid in the localization of epileptic foci in PTE, this procedure has also been found to be responsible for substantial surgical complications due to a higher risk of parenchymal damage and hemorrhage during the placement of subdural electrodes. For example, it has been found that some of the most common complications encountered in the neurosurgical practice of PTE focus resection are related to invasive monitoring because the presence of adhesions and scar tissue make the placement of subdural electrodes more dangerous, given the higher risk for parenchymal damage and hemorrhage [32].

## 5. Recent advances and emerging methods

A prominent disadvantage of seizure focus localization as previously performed in most clinical settings is that the technique has been based upon sensor-space EEG analysis, that is, upon the inspection and largely qualitative analysis of EEG waveforms recorded at the scalp without attempting to localize the neuronal sources of these electric potentials. By contrast, the inverse localization of electrophysiological sources via EEG is a much more powerful technique which aims to identify the brain locations of electrically active neuronal currents based on noninvasive recordings of scalp potentials. In the context of the present review, inverse localization refers to the process of identifying the cortical sources of electrical activity which are responsible for generating the electric potentials measured at the scalp by EEG sensors [42,43]. Illustrations which convey the gist of this technique are available in a number of textbooks [44,45], journal articles [46–48] and peer-reviewed online sources [49,50], which the reader is encouraged to consult. Briefly, inverse localization is performed as follows. Firstly, the locations of cortical sources which can elicit scalp EEG potentials are either posited or determined rigorously using one of the various methods available [51]. Secondly, the scalp potentials due to these cortical sources are calculated based on the standard equations of electrostatics [52] (this step is known as solving the “forward” problem of bioelectricity). Thirdly, given a set of experimentally-acquired scalp EEG signals and the forward solution from the previous step, the cortical locations which are most likely to elicit these signals are estimated using one of various statistical methods available for this purpose [53]. Many – if not most – of these methods aim to minimize the quantitative differences between the forward and inverse solutions through the use of an adequate optimization algorithm, as described elsewhere

[54]. The improved benefit of localizing cortical activation sources using inverse localization *versus* standard analysis of scalp EEG topography has been documented extensively [55–59]. One reason for this is the fact that typical scalp EEG patterns can extend over large portions of the scalp, which usually limits the ability to localize activation sources below the lobar level. By contrast, in the case of anatomically-constrained inverse localization, cortical areas which are electrically-active can be identified as specific portions of gyri and sulci, as documented elsewhere based on validation studies [60–62] and on comparisons of the two approaches [63–65].

In the context of identifying PTE foci, inverse localization has thus far been extremely underappreciated and, until very recently, the technique has been implemented using relatively simple models of head anatomy in the context of idealized geometries (e.g. concentric spheres) and under the assumption of just a few brain activation sources [66,67]. Unfortunately, idealized models can reflect the anatomy and conductivity profile of the head only to a very limited extent, and the use of just a few current dipoles during inverse localization is ill-advised in scenarios which involve multifocal PTE seizures.

Because focal epilepsy is more likely to be pharmaco-resistant than generalized epilepsy in adults [68], accurate inverse localization of epileptogenic foci may greatly benefit the task of identifying brain areas which can be subjected to surgical resection in medically intractable PTE. Although such localization has been impractical in the past, two recent studies have demonstrated that effective and accurate inverse localization of epileptogenic activity is feasible in the context of accurate inverse localization and that the use of noninvasive EEG to identify PTE foci holds considerable clinical promise. In these studies [55,56], EEG source localization was demonstrated in six patients with acute TBI using anatomically constrained models of the head which account for TBI-related pathology. Multimodal MRI volumes were employed to create highly detailed head models via the finite element method using as many as 25 tissue types, including six types accounting for pathology. The necessity of using a comprehensive number of tissue types was confirmed for TBI, where deviations from normal anatomy add to the challenge of performing inverse localization. Interestingly, when TBI-related pathology was intentionally omitted from each localization model, substantial mis-estimations of cortical electric source locations of up to 3.5 cm were found. This highlights the importance of including TBI-related changes in head tissue conductivities when performing EEG inverse modeling and localization, and additionally demonstrates that anatomically constrained inverse localization using this approach can benefit TBI patients by providing useful insights on their pathophysiology, epileptogenic processes and ictogenic manifestations.

Aside from EEG, MEG is another noninvasive technique which has been recently used for inverse localization of electrical brain activity in TBI patients, albeit not yet for the purpose of epileptiform activity localization, to our knowledge [69,70]. Whereas EEG-based inverse localization may require detailed head models with different compartment types accounting for the conductivity of each tissue, MEG inverse localization can be performed using considerably simpler head models as a direct consequence of the magnetic properties of biophysical tissues, as detailed elsewhere [43]. Unfortunately, however, MEG is only available at a handful of dedicated facilities throughout the world due to the exceedingly high instrumentation and maintenance costs of this neuroimaging modality. In addition, because the magnetic fields of the brain are extremely weak compared to those of biomagnetically active sources in everyday life, MEG recordings must be acquired in purpose-built magnetically shielded rooms. This can impose substantial logistic, medical and technological constraints, all of which can

be strong deterrents against the use of MEG in a variety of clinical contexts, particularly when patients with acute TBI are involved.

## 6. Conclusion

Because many TBI patients develop epilepsy months and even years after their traumatic event, the PTE population is a prime target for the formulation of anti-epileptogenesis therapies, whose development has been undermined by a lack of reliable biomarkers, including electrophysiological biomarkers [14]. The identification of such biomarkers remains one of the most fundamental aims of epilepsy research today, and the relatively slow development of epilepsy in TBI survivors make this patient group ideal for anti-epileptogenesis therapy studies. Thus, the ability to localize epileptiform activity accurately based on noninvasive scalp EEG recordings offers a unique opportunity to minimize the necessity of using invasive electrocorticography recordings, particularly in patients with multifocal PTE where substantial challenges to the placement of subdural electrode grids exist. When used in conjunction with highly detailed anatomy and conductivity models of the TBI head, this approach may hold considerable promise for (1) improving patient outcome following neurosurgical intervention aimed at PTE focus resection, and for (2) developing and quantifying the effects of existing, as well as novel, anti-epileptogenic treatments and interventions. For these reasons, more attention should be devoted to the development of noninvasive approaches for the localization of epileptiform loci, greater utilization of such methods by clinicians should be encouraged, and further investments by funding agencies should be urged in order to allow such techniques to be used for the ultimate purposes of facilitating clinical care and improving patient outcome.

## Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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