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Publication Date

2019-03-01

DOI

10.1016/j.nbd.2018.06.002

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Dis. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Neurobiol Dis. 2019 March ; 123: 69–74. doi:10.1016/j.nbd.2018.06.002.

Electrophysiological biomarkers of epileptogenicity after traumatic brain injury

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Abstract

Post-traumatic epilepsy is the architype of acquired epilepsies, wherein a brain insult initiates an epileptogenic process culminating in an unprovoked seizure after weeks, months or years. Identifying biomarkers of such process is a prerequisite for developing and implementing targeted therapies aimed at preventing the development of epilepsy. Currently, there are no validated electrophysiological biomarkers of post-traumatic epileptogenesis. Experimental EEG studies using the lateral fluid percussion injury model have identified three candidate biomarkers of post-traumatic epileptogenesis: pathological high-frequency oscillations (HFOs, 80–300 Hz); repetitive HFOs and spikes (rHFOSs); and reduction in sleep spindle duration and dominant frequency at the transition from stage III to rapid eye movement sleep. EEG studies in humans have yielded conflicting data; recent evidence suggests that epileptiform abnormalities detected acutely after traumatic brain injury carry a significantly increased risk of subsequent epilepsy. Well-designed studies are required to validate these promising findings, and ultimately establish whether there are post-traumatic electrophysiological features which can guide the development of 'antiepileptogenic' therapies.

Keywords

Post-traumatic epilepsy; Traumatic brain injury; Epileptogenesis; Seizure; EEG; Electrophysiology; Biomarker; High-frequency oscillations; Repetitive HFOs and spikes; Sleep spindles

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Declarations of interest

None.

1. Introduction

Post-traumatic epilepsy is a major delayed sequela of traumatic brain injury. It accounts for 5% of all epilepsies and for up to 20% of epilepsy cases related to an ‘acquired’ brain insult (acquired epilepsies) (Frey, 2003). Risk factors for post-traumatic epilepsy can be broadly categorized into factors related to the injury per se and factors related to characteristics of the individual. The former include penetrating injuries, injury severity, biparietal or multiple brain contusions, intracranial hemorrhage, and frontal or temporal location of the lesion (Pitkanen and Immonen, 2014). There is conflicting data on the predictive value of seizures occurring within the first week of the trauma (early seizures). In a population-based study comprising > 4500 people with traumatic brain injury, early seizures were not a predictor of subsequent epilepsy, adjusting for potential confounders (Annegers et al., 1998). However, a number of studies have found an association between early seizures and development of post-traumatic epilepsy (Englander et al., 2003; Frey, 2003). Factors related to the characteristics of the individual include age > 65 years at the time of the injury, a family history of epilepsy, and a past history of depression (Christensen et al., 2009; Piccenna et al., 2017). Preliminary data also suggest that variation in selected genes, e.g. the interkeukin-1β (IL-1β), glutamic acid decarboxylase 1 (GAD1) and adenosine A1 receptor (A1AR) genes, may increase susceptibility to post-traumatic epilepsy, but these findings require validation in well-designed studies (Cotter et al., 2017).

There may be a 6-month to a 30-year interval between the causative traumatic brain injury and the onset of unprovoked seizures (Annegers et al., 1998). In 80% of cases, however, seizures commence within the first 2 years after the injury (Verellen and Cavazos, 2010). This latent or silent period reflects an epileptogenic process that starts after the trauma and culminates in an unprovoked seizure. This latency provides a ‘window of opportunity’ to implement interventions to arrest this process, ultimately preventing the development of epilepsy (Temkin, 2009). To date, several agents have been tested for their ability to prevent post-traumatic epilepsy, but none has demonstrated ‘anti-epileptogenic’ properties (Temkin, 2009). Hope rests on the identification of biomarkers for post-traumatic epileptogenesis, which may allow development of targeted preventive therapies.

In this article, we review experimental and human evidence for electrophysiological biomarkers of epileptogenicity after traumatic brain injury, and discuss their potential to predict subsequent development of epilepsy.

2. Experimental evidence for electrophysiological biomarkers of epileptogenicity after traumatic brain injury

A number of animal models have been used to investigate electrophysiological biomarkers of post-traumatic epilepsy. Fluid percussion injury (FPI) and controlled cortical impact (CCI) are the most commonly used experimental models of traumatic brain injury. The FPI model consists of a pressurized pulse of fluid that is directed onto the surface of the brain, through a carefully made craniotomy that leaves the dura of the animal intact. FPI is a percussive injury that minimizes laceration and hemorrhaging and produces diffuse brain injury, mimicking a closed head injury seen in humans (Smith, 2016; Stalhammar et al.,

1987). Besides inducing cortical damage, FPI injures the hippocampus (Bolkvadze and Pitkanen, 2012). In the lateral FPI (LFPI) model, the craniotomy is positioned several millimeters lateral to the midline. It has been suggested that LFPI produces more severe cortical damage and epileptogenesis than midline FPI (D'Ambrosio et al., 2004).

The CCI model uses a piston to directly impact the brain, again through a craniotomy with the dura intact, causing tissue damage that includes crushing, laceration, cortical contusion, compression contusion, and hemorrhage (Bolkvadze and Pitkanen, 2012; Bolkvadze et al., 2015; Nilsson et al., 1994; Smith, 2016). One advantage of CCI over FPI is greater control of the impact parameters, e.g. velocity, dwell time, shape, and size of the piston allowing for a more uniform injury model (Lighthall et al., 1989).

Other models of post-traumatic epilepsy include: weight drop, where a column of brass weights is dropped from a designated height, through a guide tube, onto a foot plate placed over the exposed dura; closed head injury, where the cranium is struck directly to mimic clinical diffuse and concussive brain injuries; blast injury, using a controlled explosion to generate a pressure wave directed to the head; acceleration injury, where accelerating and quickly decelerating the whole body or the head alone in a constrained or unconstrained manner, results in *coup-contrecoup* head injury caused by the brain's movement within the skull; and lastly, penetrating ballistic-like brain injury, where a balloon is injected into the brain and then inflated to create a cavity in the cortical tissue (Cernak, 2005).

Regardless of the model used, animals can undergo EEG monitoring immediately after the traumatic brain injury. Numerous changes can be detected on the post-injury EEG, and these can differ according to the type of injury, the time interval between the injury and the commencement of the recording, and the type of recording (e.g. skull screws or depth electrodes). The post-injury EEG, however, may harbor potential biomarkers of post-traumatic epilepsy, which will be discussed below in relation to the different models of traumatic brain injury.

2.1. High-frequency oscillations (HFOs)

The initial studies in kainic acid-treated epileptic rats described high-frequency oscillations (HFOs) as local oscillatory field potentials ranging between 80 and 600 Hz, and typically lasting tens to hundreds of milliseconds (Bragin et al., 1999b; Bragin et al., 1999c). Subsequent recordings using microelectrodes and clinical intracranial electrodes found HFOs with similar properties in patients with epilepsy (Bragin et al., 1999a; Haegelen et al., 2013; Jefferys et al., 2012; Staba, 2012; Urrestarazu et al., 2007; Worrell et al., 2004; Zijlmans et al., 2012). HFOs are commonly classified into ripples (80–250 Hz) and fast ripples (250–600 Hz) (Zijlmans et al., 2012), and are believed to play critical roles in normal and abnormal brain functions (Staba, 2012). For example, ripple-frequency HFOs are integral to memory formation, reactivation of previous experiences, and information processing functions (e.g. somatosensory evoked potentials) (Staba, 2012). However, both ripple-frequency and fast ripple-frequency HFOs are correlated with epileptic tissue, and can increase in power in brain areas where seizures begin (Jirsch et al., 2006; Perucca et al., 2014; Staba, 2012; Weiss et al., 2016). Therefore, 'physiological' and 'pathological' HFOs cannot be differentiated on the basis of spectral frequency (Engel Jr et al., 2009).

Mechanistically, physiological HFOs reflect inhibitory postsynaptic potentials from the rhythmic discharges of interneurons that regulate pyramidal cell firing (Engel Jr et al., 2009; Staba, 2012). Pathological HFOs represent instead a burst of population spikes from local clusters of abnormally synchronized principal cells, and the central period of the burst can span from ripple to fast ripple frequencies (Staba, 2012).

HFOs may also have a role in the process of epileptogenesis. This was first hypothesized by Bragin et al. (2000), who observed that fast ripples (250–500 Hz) preceded by weeks to months the occurrence of late spontaneous seizures in three kainic acid-treated rats. This hypothesis was supported by a subsequent study of kainic acid-induced status epilepticus (Bragin et al., 2004), which identified HFOs (80–500 Hz) in 19/26 (73%) rats in the dentate gyrus ipsilateral to kainic acid injection, 1–30 days after status epilepticus; all of these 19 rats later developed recurrent spontaneous seizures, whereas none of the rats without HFOs developed seizures.

In the LFPI model (EEG sampled at 10 kHz, and loss-pass filtered at 600 Hz), Bragin et al. (2016) recorded pathological HFOs (80–300 Hz) within 2 weeks from the trauma in Sprague-Dawley rats (Fig. 1A–B). These oscillations consisted of population spikes involving hypersynchronous multiunit firing, similar to those recorded in the kainic acid model of chronic epilepsy (Bragin et al., 1999c). Pathological HFOs were present in 7/12 (58%) LFPI rats vs 0/14 (0%) age-matched control rats undergoing sham craniotomy (Bragin et al., 2016). These events were only found in cortical areas within or adjacent to the injured cortex (Fig. 1B). Importantly, 4/7 (57%) LFPI animals with pathological HFOs subsequently developed late spontaneous seizures; none of the remaining LFPI rats or the controls developed late seizures (Bragin et al., 2016). Overall, this study suggests that pathological HFOs may be a potential electrophysiological biomarker of epileptogenesis following experimental traumatic brain injury.

2.2. Repetitive HFOs and spikes (rHFOSs)

Bragin et al. (2016) also identified a new pattern of paroxysmal EEG activity consisting of a series of arcuate-shaped, rhythmic spikes within a frequency band of 10–16 Hz, with pathological HFOs (80–300 Hz) superimposed on each spike. The authors termed this activity “repetitive HFOs and spikes” (rHFOSs; Fig. 1A, C and D) (Bragin et al., 2016). rHFOSs were seen only in the 7 LFPI rats which exhibited pathological HFOs, appearing within 1–3 days of the emergence of HFOs in injured or perilesional cortex. None of the 14 sham-operated, age-matched, control animals displayed rHFOSs. All four rats which developed late seizures exhibited rHFOSs (as well as pathological HFOs) during the first two post-injury weeks.

Reid et al. (2016) found rHFOSs in 17/28 (61%) LFPI rats [a subset of which were included in the study by Bragin et al., 2016] vs 1/7 (14%) controls undergoing sham craniotomy. rHFOSs were only recorded from areas adjacent to or within the craniotomy site. Among LFPI rats, rHFOSs occurred in a significantly greater proportion of animals following moderate or severe injury than after mild injury [4/6 (66%), 12/17 (70%) and 1/5 (20%), respectively; $p = 0.031$]. A total of 14 rats developed late focal seizures and, of these, 10 (71%) had rHFOSs. Of note, rHFOSs were seen more often early after LFPI than at later

times when seizures became apparent, suggesting that rHFOSs might be a temporary phenomenon preceding the occurrence of unprovoked seizures. In the four rats which developed late seizures and which did not exhibit rHFOSs, EEG recordings were commenced late after the injury (≥ 182 days after LFPI), and as such the possibility that rHFOSs occurring early post-injury might have been missed, cannot be excluded (Reid et al., 2016).

These findings make rHFOSs a promising candidate biomarker of experimental post-traumatic epilepsy. Mechanistically, rHFOSs might represent a new phenomenon, or the transformation of normal sleep spindles from a sinusoidal shape into an arcuate pattern with a spike component produced by a repetitive burst of population spikes (Bragin et al., 2016). Their appearance could reflect a disturbance of thalamocortical circuits following traumatic brain injury, specifically in the nucleus reticularis, which has an important role in the generation and regulation of normal sleep spindles (Bartho et al., 2014).

2.3. Sleep spindles

Sleep spindles – bursts of 11–16 Hz activity, lasting ≥0.5s (Fig. 1C) – are a defining EEG feature of stage II (N2) non-rapid eye movement (NREM) sleep (Purcell et al., 2017). Studies in rodents have pointed to an increase in spindle activity immediately preceding rapid eye movement (REM) sleep (Vyazovskiy et al., 2004); similar changes also occur in humans (Purcell et al., 2017). Spindle generation involves a reciprocal interaction between GABAergic neurons in the nucleus reticularis thalami, which function as pacemakers, and bursting thalamocortical relay neurons.

In a recent study including 10 rats which developed spontaneous electrographic seizures after LFPI, Andrade et al. (2017) found that 21/23 (92%) recorded seizures occurred during the transition from stage III (N3) NREM sleep to REM sleep. Compared to LFPI rats which did not develop seizures (n = 14) and sham-operated controls (n = 10), LFPI rats with seizures exhibited significantly shorter and slower spindles during the N3-REM sleep transition. Receiver operating characteristics (ROC) analysis showed that spindle duration of < 2.13 s (86% sensitivity, 80% specificity) and dominant frequency of <9.19 Hz (64% sensitivity, 60% specificity) differentiated LFPI rats with seizures from those without. These changes in sleep architecture may be measurable on scalp EEG, carrying promise as non-invasive biomarkers of post-traumatic epilepsy. It should be noted, however, that this study was limited by the small number of electrodes (n = 2: one perilesional and the other contralateral to the traumatic brain injury core; Table 1) for reliable recording and characterization of sleep features, such as spindles, in a ‘lesional’ setting. Neither of the two electrodes sampled the frontal cortex, where sleep spindles are often better appreciated in LFPI rats (Bragin et al., 2016). Furthermore, some of the animals had received treatment with atipamezole prior to the study, a compound which has been reported to impact on spindle duration (Riekkinen Jr et al., 1991); nevertheless, no obvious treatment effects were found (Andrade et al., 2017).

It is also noteworthy that the reduction in sleep spindle duration and frequency during the N3-REM transition was identified at 9 weeks post-injury, when EEG recordings were commenced (Andrade et al., 2017). No such changes were seen in the first 2–3 weeks after

LFPI by Bragin et al. (2016), who instead noted pathological HFOs and then rHFOSs shortly after the injury.

Differences in the appearance of pathological HFOs, rHFOSs and altered sleep spindles after a traumatic brain injury could correspond to different aspects of epileptogenesis that ultimately results in the generation of spontaneous epileptic seizures (Fig. 2). Immediately following the trauma, there is cerebral metabolic dysfunction and inadequate oxygenation (particularly at the site and areas adjacent to the trauma) that can produce extracellular excitotoxicity and abnormal neuronal spike firing (Faden et al., 1989; Xiong et al., 1997). These initial disturbances could contribute to bursts of population spikes, i.e. the first appearance of pathological HFOs. Excitotoxic-induced cell damage and inflammation can trigger apoptosis and necrotic cell death and, within several days to weeks post-injury, induce sprouting and synaptic reorganization among surviving neurons (Golarai et al., 2001; Kumar and Loane, 2012; Yakovlev et al., 1997). These structural changes can strengthen connectivity within local groups of neurons that produces a greater number of widely distributed pathological HFO-generating sites. The formation of pathological HFO-generating neocortical sites may interfere with spindle-generating cortico-thalamic mechanisms that produces rhythmic, 10–16 Hz EEG spikes superimposed with pathological HFOs or rHFOSs (Bragin et al., 2016). Structural reorganization of cortico-thalamic pathways combined with neuronal disturbances in these same areas could alter normal sleep spindles, observed as a reduction in duration and dominant frequency during the transition from stage III NREM to REM sleep (Andrade et al., 2017). The progression towards spontaneous seizure occurrence initiated by the traumatic brain injury may thus reflect the dynamic activity and progressive pathological reorganization of neuronal networks during epileptogenesis.

2.4. Other potential electrophysiological biomarkers of epileptogenicity after experimental traumatic brain injury

A number of studies have found electrophysiological abnormalities weeks to months following experimental traumatic brain injury: these could be involved with epileptogenesis, but have not yet been correlated with the appearance of late spontaneous seizures (Bolkvadze and Pitkanen, 2012; Golarai et al., 2001; Kharatishvili et al., 2007; Kharatishvili et al., 2006; Statler et al., 2009; Yang et al., 2010). For example, EEG spikes can be recorded in a large percentage of Sprague-Dawley rats (Statler et al., 2009) and C57BL/6S mice after CCI (Bolkvadze and Pitkanen, 2012), as well as C57BL/6S mice after LFPI (Bolkvadze and Pitkanen, 2012). In vitro studies show evidence of stimulation-evoked hyperexcitability in the dentate gyrus of Sprague-Dawley rats after weight drop on the somatosensory cortex (Golarai et al., 2001). Evoked, and in some cases spontaneous, epileptiform discharges can also be recorded in neocortical brain slices from Sprague-Dawley rats after CCI (Yang et al., 2010). Other studies have demonstrated hyperexcitability and spontaneous epileptiform abnormalities in animal brain slices obtained at various time points post-injury (Bolkvadze and Pitkanen, 2012; Coulter et al., 1996; Hunt et al., 2009; Hunt et al., 2010; Santhakumar et al., 2000; Santhakumar et al., 2001). Whether these findings correspond to electrophysiological disturbances associated with brain injury or actual post-traumatic

epileptogenesis is unclear. Also, unlike EEG spikes, which could be recorded from the scalp, how stimulation-evoked neuronal excitability could be assessed remains to be determined.

3. Human evidence for electrophysiological biomarkers of epileptogenicity after traumatic brain injury

The value of the EEG in predicting the development of epilepsy in individuals with traumatic brain injury has received considerable attention since the early days of electroencephalography. Initial investigations suggested that EEG recordings performed shortly after the head trauma could predict subsequent occurrence of unprovoked seizures (Bickford and Klass, 1966), but research in ensuing years tempered early enthusiasm (Courjon, 1969; Jennett and Van De Sande, 1975). In a multicenter study from the mid-70s, Jennett and Van De Sande (1975) analyzed EEG recordings from 722 patients with traumatic brain injury. A high proportion of these patients had injuries which carried a high risk for subsequent epilepsy (ie 50% had a depressed skull fracture, 30% had seizures within the first week of the trauma); in fact, 310/722 (43%) patients later developed epilepsy. The proportion of abnormal EEG recordings obtained at any time point after the injury did not differ significantly between patients who subsequently developed epilepsy and those who did not develop epilepsy [282/391 (72%) vs 349/510 (68%); Table 2]. In both groups, the proportion of abnormal EEG recordings decreased as the time from the injury increased, a finding which was largely attributable to EEGs showing ‘local’ abnormalities (Table 2). Analysis of EEGs performed at different time intervals from the trauma also showed that the only significant difference between the two patient groups was in the proportion of EEGs showing any type of abnormality at > 2 years post-injury, which was higher among patients who developed epilepsy compared to those who did not (73% vs 46%, $p < 0.001$; Table 2); this late rise in abnormal EEG recordings in the former group could be explained by the fact that by this stage most patients had already developed epilepsy. In a secondary analysis, of 184 patients who underwent ≥ 1 EEGs within the first 3 months of the trauma and had > 1 year of follow-up, 90 (49%) had at least one normal recording during this early period; although this circumstance was more common among patients who did not develop epilepsy, it is noteworthy that one-fifth of patients who later developed epilepsy had ≥ 1 normal EEGs within the first 3 months of the injury [79/128 (62%) and 11/56 (20%), respectively; $p < 0.001$]. Furthermore, EEG abnormalities persisting for > 3 weeks after the trauma were found to reflect more severe brain damage, which was already evident from clinical data. Overall, these findings led the authors to conclude that: “…an EEG adds little if anything to the doctor’s ability to predict whether or not epilepsy will develop, a normal record being only marginally reassuring and an abnormal record not necessarily presaging late epilepsy” (Jennett and Van De Sande, 1975).

Subsequent investigations rekindled interest in the potential ability of the EEG to predict the development of epilepsy in individuals with traumatic brain injury (Angeleri et al., 1999; Kim et al., 2018). In a study of 137 inpatients followed prospectively for 12 months after their head trauma, focal EEG abnormalities detected at 1 month after the injury carried a > 3-fold increased risk of post-traumatic epilepsy (relative risk: 3.49 [95% confidence interval,

CI: 1.10–11.05]), adjusting for low Glasgow Coma Scale scores, early seizures and single focal lesions on brain CT (Angeleri et al., 1999).

Most recently, Kim et al. (2018) performed a retrospective case-control study of risk factors of post-traumatic epilepsy, in which 25 consecutive cases who developed epilepsy within one year of a head trauma were matched by age and injury severity to 25 controls who did not develop epilepsy within one year of the trauma. EEG epileptiform abnormalities during the acute period post-injury, comprising seizures, sporadic epileptiform discharges, lateralized or generalized periodic discharges and lateralized rhythmic delta activity, were found be associated with post-traumatic epilepsy (odds ratio, OR: 3.5 [95% CI: 0.99–11.68], $p = 0.042$). When evaluating subtypes of EEG epileptiform abnormalities, only sporadic epileptiform discharges were correlated with post-traumatic epilepsy (OR: 4.57 [95% CI: 1.60–21], $p = 0.007$). These findings remained significant even after adjusting for post-injury subdural hematoma. Differences in sporadic epileptiform discharges between cases and controls were already apparent within 5 days of the head trauma. Interestingly, while not classified as an epileptiform abnormality, EEG focal slowing was also found to be associated with post-traumatic epilepsy on univariate analysis (OR: 2.67 [95% CI: 0.97–10.1], $p = 0.04$).

4. Conclusion

The identification of biomarkers of epileptogenesis following traumatic brain injury is a prerequisite for designing and developing targeted therapeutic approaches aimed at preventing epilepsy in individuals at risk (Pitkanen and Immonen, 2014; Pitkanen et al., 2016). To date, there are no validated electrophysiological biomarkers of post-traumatic epileptogenesis. However, experimental studies have identified a number of candidate EEG biomarkers, i.e. HFOs, rHFOSs and altered sleep spindles, but these findings require further study in animals as well as in humans. Similarly, replication is needed for the recent signal suggesting that epileptiform discharges on the EEG of patients who have just suffered from head trauma may predict subsequent epilepsy. Hope rests on future well-designed research endeavors, e.g. the NIH-funded Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx; website: http://epibios.loni.usc.edu/), to validate these findings and ultimately determine which electrophysiological features are reliable biomarkers of post-traumatic epileptogenesis.

Acknowledgement

Dr. Piero Perucca is supported by the Bridging Postdoctoral Fellowship (BPF) from Monash University (BPF18-0114).

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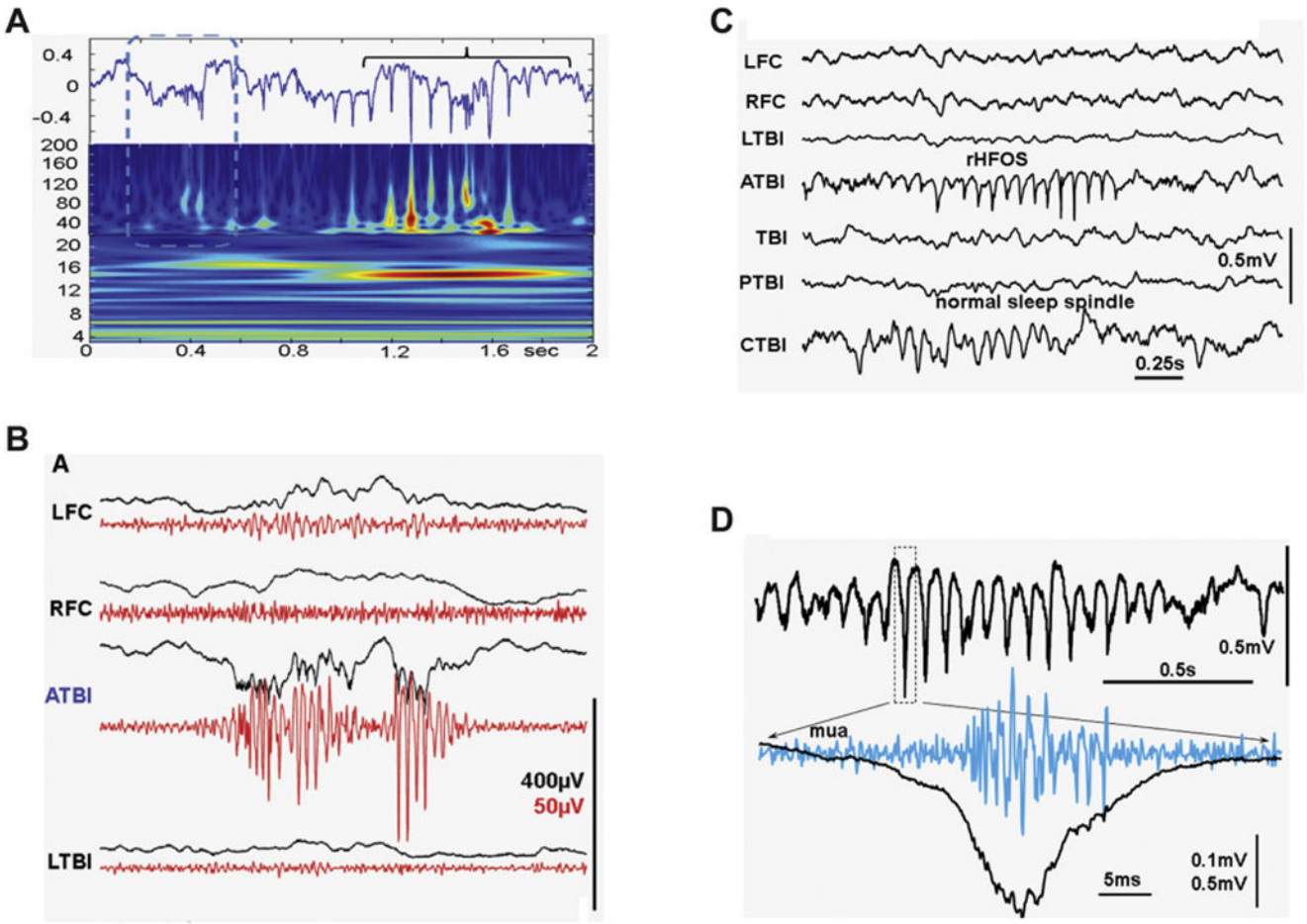

Fig. 1.

Pathological HFOs and rHFOSs after experimental traumatic brain injury (LFPI rat). (A) Raw EEG (above) with corresponding time-frequency map (below), including pathological HFOs (dashed box) and rHFOs (bracket). (B) Appearance of pathological HFOs 10 days after the traumatic brain injury in perilesional cortex (immediately anterior to the injury, ATBI), but not in other areas of neocortex (LFC, left frontal cortex; RFC, right frontal cortex; LTBI, perilesional cortex lateral to the injury). Black lines are raw EEG signals recorded within a frequency band of 0.1 Hz–10 kHz, and red lines are the corresponding signals after applying a band pass of 100–600 Hz. (C) Example of rHFOS recorded 10 days after injury in perilesional cortex anterior to the trauma (ATBI) and a normal sleep spindle that coincidentally occurred in the area contralateral to the injury (CTBI). LFC, left frontal cortex; RFC, right frontal cortex; LTBI, perilesional cortex lateral to the injury; TBI, lesional cortex; PTBI, perilesional cortex posterior to the injury. (D) rHFOS in the raw EEG recorded within a frequency band of 0.1 Hz–10 kHz (above). Note the high frequency activity contained by one of the spikes of the rHFOS (dashed box), which can be appreciated by expanding the time scale and applying a high pass filter of 500 Hz (blue line; below). Reproduced from Bragin et al. (2016), with permission from John Wiley and Sons.

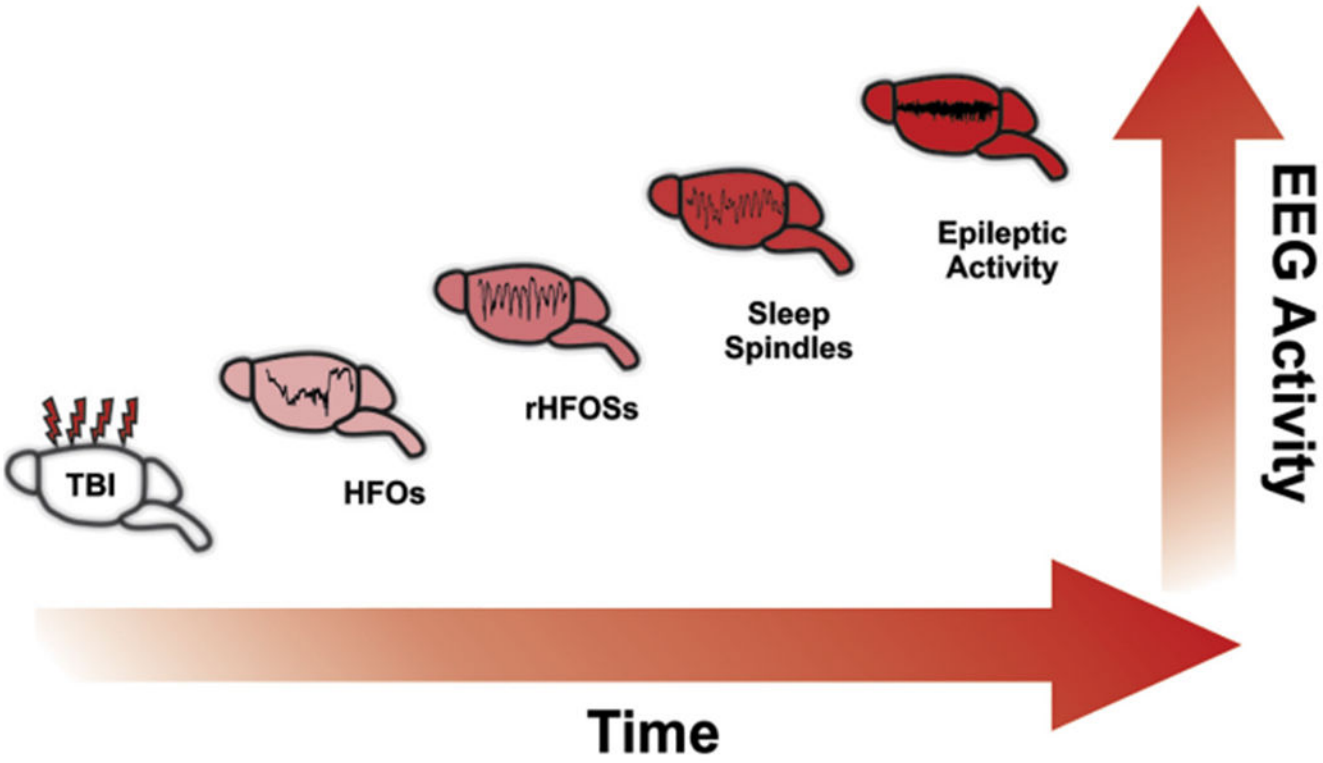

Fig. 2.

Putative EEG correlates of the process of epileptogenesis initiated by experimental traumatic brain injury, culminating in spontaneous seizure occurrence. The emergence of pathological HFOs, rHFOSs and altered sleep spindles may reflect different stages of the epileptogenic process post-injury. Pathological HFOs emerge shortly after the injury, at the site of or in the areas adjacent to the injured cortex. These are followed by rHFOSs, temporarily seen within or in close proximity to injured cortex, and by a reduction in spindle duration and frequency during the transition from stage III NREM to REM sleep. The final stage is the occurrence of unprovoked seizures. Horizontal arrow indicates increasing time since the traumatic brain injury, and vertical arrow indicates increasingly pronounced EEG activity following the injury.

Table 1:

Electrode implantations in experimental studies describing candidate EEG biomarkers of post-traumatic epileptogenesis, i.e. pathological high frequency oscillations (HFOs), repetitive HFOs and spikes (rHFOSs), and altered sleep spindles at the N3-REM sleep transition.

Candidate EEG biomarkers of post-traumatic epileptogenesis	Electrode locations in corresponding studies[a]
Pathologic HFOs (Bragin et al., 2016)	Microelectrodes[b]: TBI, ATBI, PTBI, CTBI, IFC Screw electrodes: LTBI, CFC
rHFOSs (Bragin et al., 2016; Reid et al., 2016)	Microelectrodes[b]: TBI, ATBI, PTBI, CTBI, IFC, AH, PH Screw electrodes: LTBI, CFC
Reduction in sleep spindle duration and frequency at the N3-REM sleep transition (Andrade et al., 2017)	Screw electrodes: PTBI, CTBI

AH, anterior hippocampus, ipsilateral to the injury; ATBI, parietal cortex, anterior to the injury; CTBI, parietal cortex, contralateral to the traumatic brain injury core; CFC, frontal cortex, contralateral to the injury; IFC, frontal cortex, ipsilateral to the injury; LTBI, perilesional cortex, lateral to the injury; PH, posterior hippocampus, ipsilateral to the injury; PTBI, parietal cortex, posterior to the injury; TBI, traumatic brain injury core (parietal cortex).

[a] In all studies, stainless steel screws placed over the cerebellum served as ground and reference electrodes.

[b] Electrodes consisting of pairs of 50–60 μm diameter tungsten wires with a 0.5–1 mm vertical tip separation.

Table 2:

EEG abnormalities in individuals who developed epilepsy (n = 310) vs those who did not develop epilepsy (n = 412) among 722 patients suffering from traumatic brain injury. 203/722 patients underwent > 1 EEG recordings. In this study, epilepsy was defined as epileptic seizures occurring > 1 week after the head trauma. Numerical values in cells are number of EEG recordings with abnormalities/total number of EEG recordings (%). Reproduced from Jennett and van de Sande (Jennett and Van De Sande, 1975), with permission from John Wiley and Sons.

Time after injury	Epilepsy	No epilepsy	*p* value
All abnormalities, *n.* (%)			
< 8 days	15/17 (88%)	98/121 (81%)	ns
9 days-3 months	48/59 (81%)	138/190 (73%)	ns
4–12 months	38/57 (67%)	51/87 (59%)	ns
1–2 years	35/57 (61%)	37/58 (64%)	ns
> 2 years	146/201 (73%)	25/54 (46%)	< 0.001
Any time since injury	282/391 (72%)	349/510 (68%)	ns
Local abnormalities, *n.* (%)			
< 8 days	13/17 (76%)	78/121 (65%)	ns
9 days-3 months	34/59 (58%)	103/190 (54%)	ns
4–12 months	29/57 (51%)	39/87 (45%)	ns
1–2 years	23/57 (40%)	29/58 (50%)	ns
> 2 years	94/201 (47%)	17/54 (32%)	ns
Any time since injury	193/391 (49%)	266/510 (52%)	ns
Diffuse abnormalities, *n.* (%)			
< 8 days	4/17 (24%)	29/121 (24%)	ns
9 days-3 months	24/59 (41%)	68/190 (36%)	ns
4–12 months	16/57 (18%)	19/87 (22%)	ns
1–2 years	15/57 (26%)	12/58 (12%)	ns
> 2 years	75/201 (37%)	14/54 (26%)	ns
Any time since injury	128/391 (33%)	142/510 (28%)	ns

ns = not significant.