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Seizing the Future: Predicting Epilepsy After TBI

ECoG Spiking Activity and Signal Dimension Are Early Predictive Measures of Epileptogenesis in a Translational Mouse Model of Traumatic Brain Injury

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The latency between traumatic brain injury (TBI) and the onset of epilepsy (PTE) represents an opportunity for counteracting epileptogenesis. Antiepileptogenesis trials are hampered by the lack of sensitive biomarkers that allow to enrich patient's population at-risk for PTE. We aimed to assess whether specific ECoG signals predict PTE in a clinically relevant mouse model with ~60% epilepsy incidence. TBI was provoked in adult CD1 male mice by controlled cortical impact on the left parieto-temporal cortex, then mice were implanted with two perilesional cortical screw electrodes and two similar electrodes in the hemisphere contralateral to the lesion site. Acute seizures and spikes/sharp waves were ECoG-recorded during 1 week post-TBI. These early ECoG events were analyzed according to PTE incidence as assessed by measuring spontaneous recurrent seizures (SRS) at 5 months post-TBI. We found that incidence, number and duration of acute seizures during 3 days post-TBI were similar in PTE mice and mice not developing epilepsy (No SRS mice). Control mice with cortical electrodes (naïve, $n = 5$) or with electrodes and craniotomy (sham, $n = 5$) exhibited acute seizures but did not develop epilepsy. The daily number of spikes/sharp waves at the perilesional electrodes was increased similarly in PTE ($n = 15$) and No SRS ($n = 8$) mice vs controls ($p < 0.05$, $n = 10$) from day 2 post-injury. Differently, the daily number of spikes/sharp waves at both contralateral electrodes showed a progressive increase in PTE mice vs No SRS and control mice. In particular, spikes number was higher in PTE vs No SRS mice ($p < 0.05$) at 6 and 7 days post-TBI, and this measure predicted epilepsy development with high accuracy (AUC = 0.77, $p = 0.03$; CI 0.5830-0.9670). The cut-off value was validated in an independent cohort of TBI mice ($n = 12$). The daily spike number at the contralateral electrodes showed a circadian distribution in PTE mice which was not observed in No SRS mice. Analysis of non-linear dynamics at each electrode site showed changes in dimensionality during 4 days post-TBI. This measure yielded the best discrimination between PTE and No SRS mice ($p < 0.01$) at the cortical electrodes contralateral to injury. Data show that epileptiform activity contralateral to the lesion site has the highest predictive value for PTE in this model reinforcing the hypothesis that the hemisphere contralateral to the lesion core may drive epileptogenic networks after TBI.

Commentary

Traumatic brain injury (TBI) affects 69 million people worldwide yearly.[1] One of the severe long-term health risks of TBI is post-traumatic epilepsy (PTE), defined as the development of epileptic seizures months to years after TBI, which is different from the acute seizures that commonly occur shortly after a TBI.[2] People with PTE have shorter life expectancies than people without.[3] The latent period between TBI and PTE (months to years) presents a promising opportunity for therapeutic intervention[4] if we can identify patients at risk of PTE early enough. In a recent study, Rosella Di Sapia and colleagues[5] identified cortical electrical signals that predict PTE after a severe TBI in mice and may one day translate to markers of PTE risk in humans.

The authors used a mouse model whereby a controlled impact to the cortex induces a severe TBI. After implanting two electrocorticogram (ECoG) electrodes (one anterior, one posterior) on each brain hemisphere immediately after TBI, they monitored the mice with 24/7 video and ECoG recordings for 1 week, and then again for 3 weeks, 1.5 months, and 5 months after injury. At the 5-month time point, 65% of the TBI mice displayed evidence of PTE, defined by at least one spontaneous seizure lasting more than 10 seconds. Post-traumatic epilepsy seizures were characterized by generalized motor convulsions and electrographic paroxysms in both hemispheres. The authors then analyzed video and ECoG recordings taken within the first week after TBI to look for patterns correlated with PTE severity, including the number of epileptiform

spikes, signal dimension, and acute seizures in each ECoG channel.

Surprisingly, acute seizures after TBI were not predictive of PTE: their incidence, number, and duration were similar in mice that did and did not develop PTE. This finding is contrary to the current belief that acute seizures may be predictive of PTE. However, the acute seizures reported in the current study seem to arise in part from surgery, as they also occurred in naïve mice that received the electrode implants but not the TBI. These control mice did not develop PTE, confirming that TBI, not just surgery, induces PTE in this model. Nevertheless, a different surgical procedure (eg, with no electrode implants) will be needed to test rigorously the relationship between early seizures and eventual PTE.

The most remarkable finding was that cortical activity *contralateral* to the contusion site had better predictive value in this mouse model than ipsilateral cortical activity. Specifically, the number of epileptiform spikes recorded at the *contralateral posterior electrode* 7 days post-TBI positively correlated with both the number and cumulative duration of PTE seizures. Similarly, ECoG signals dimensionality, a measure of nonlinear dynamics estimated by analysis of recurrence, in the contralateral hemisphere was highly predictive of PTE. The ECoG signal dimension of the *contralateral anterior electrode* provided the best discrimination between mice with or without PTE with high sensitivity (92%), specificity (87%), and accuracy (90%). Since signal dimension excludes certain aspects of the ECoG, such as high frequency oscillations,[6] the list of contralateral predictors of PTE may yet grow to include additional markers. This limitation of ECoG signal dimension measure may also hide potential markers in the ipsilateral region.

The drivers of injury-induced epilepsy, like PTE, are usually thought to be related to circuit hyperexcitability near the injury site. So, why were the ipsilateral ECoG signals less instructive? One possibility is that the ipsilateral region is severely damaged in this mouse model of severe TBI. A common caveat of rodent models of TBI is that they need a more severe lesion than humans to develop PTE because rodents are markedly resilient to injury than are humans. The TBI induced in this study is relatively severe, however histological analysis is absent, precluding precise quantification of lost brain tissue on the injured side. If most of the hemisphere was dead or the lesion size variable between mice, it could explain in part why the ipsilateral ECoG signatures are not reliable predictive markers. In other words, while the study strongly suggests that the contralateral region harbors valid markers of future PTE, it does not eliminate the possibility that the ipsilateral region does as well.

Whether the findings reported in this mouse model will translate to humans remains to be seen. It will require careful monitoring of patients' cortical signals, ideally 24/7, during the acute post-TBI phase. It is, however, unclear whether the predictive features found in mice can be picked up on a scalp EEG, as opposed to a brain ECoG, which is an intracranial EEG, and during the deep sedation typically provided to patients with severe TBI in the intensive care unit. But if so, this finding could be transformative as it would help stratify the patient population for clinical trials for anti-epileptogenesis therapies, which would otherwise be too costly and inconclusive because of the heterogeneous PTE outcomes. Whether the early predictors uncovered in the present study have any value in females remains unknown since the study only included male mice. If the predictors are sex-dependent, sex will need to be included in patient stratification strategies.

What might these predictive signatures of PTE tell us about the origins of epileptogenesis? A tantalizing clue comes from the observation that in TBI patients: dysfunctional thalamocortical connectivity is associated with decreased complexity of EEG.[7,8] The prominent and persistent decrease in ECoG signal dimensionality in mice developing PTE may reflect functional alterations of thalamic projections to the cerebral cortex. The thalamus output to the cortex is indeed critical for seizure activity in human and experimental epilepsy after acute cortical injury.[9]

Interestingly, the mice that eventually developed PTE showed fluctuations in daily circadian ECoG spikes in the first week post-TBI, with more spikes during the active (dark) phase than during the inactive (day-time) phase. The finding that circadian spike distribution is another PTE predictor also highlights the need for 24/7 monitoring and the importance of considering thalamocortical networks in this process, given that thalamocortical neuromodulation is critical in circadian rhythms.

In conclusion, the findings support the significance of casting a wide network[10] when looking for predictors of PTE: predictors such as changes in spike frequencies or ECoG signal dimension suggest that epileptogenesis entails the early recruitment of large-scale circuits, presumably including interhemispheric circuits and thalamocortical circuits, far from the initial lesion. Ultimately, we may be able to prevent PTE by targeting these large-scale circuits early, taking advantage of the large therapeutic window afforded by PTE latency. In the meantime, PTE biomarkers found in this TBI animal model will be useful in the lab to stratify mice to discover and test of anti-epileptogenic therapies. It is also important to note that some of the aspects of the early changes in ECoG dynamics may be adaptive and important for recovery of the injured brain, warranting preclinical studies to decipher both the adaptive and maladaptive aspects of the early network changes after TBI, which will be crucial to develop antiepileptogenesis therapies.

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Declaration of Conflicting Interests

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