Supplementary materials

S1. TBI procedure

Lateral fluid percussion injury (FPI) [1] was performed to induce TBI in rats. Prior to the injury, rats were anesthetized with 2% isoflurane in 100% oxygen at a rate of 1.5-2.0 ml/min and then mounted to a stereotactic surgery frame. Body temperature was maintained at 36.6-38.0 ℃ with a thermostatically controlled heating pad. After skull exposure, a 5 mm-diameter craniotomy was performed (AP = −3.0, L = 6.0). A plastic injury cap was affixed to the skull over the craniotomy by applying silicone adhesive, cyanoacrylate glue, and dental cement. After the inhaled isoflurane was tapered off and the first toe pinch reflex was observed, FPI was performed using a pressure pulse duration of 30 msec, and a pressure of 3.2–3.5 atm delivered through the plastic cap. Following FPI, the rat was monitored for duration of apnea and the time of first responsiveness to toe pinch. The rats Isoflurane anesthesia was then re-administered to remove the injury cap. Rats in the sham control group received a craniotomy in similar conditions but without FPI.

S2. MRI scan and TBI evaluation

At the completion of experiments, animals were deeply anesthetized and perfused with saline and paraformaldehyde (200 mL of 4%). The brain was removed and placed into Fomblin oil. The fixed brain was scanned using a 14mm diameter 1H radiofrequency coil. As suggested by Kamsu et. al. (2013)[2], the 3D T2 RARE sequence with parameters of TR/TE = 1700/63 ms, 512×200×200 and voxel size of 80 μm3, 2-average, and RARE factor = 6 was applied. The FOV was 4.0×1.6×1.6 cm and the total data acquisition time was 6 hrs. The MRI data were used to estimate the brain lesion volumes and verify the electrode tracks of the recording sites.

S3. Automatic detection of HFOs

Our automatic HFO detection pipeline can be summarized as follows:

(1) HFO event localization. Our HFO detection pipeline has been described in prior studies[3-5] In brief, the HFO onset/offset detections were briefly summarized below: 3 SD as lower boundary and 5 SD as higher

boundaries threshold, respectively; 20ms and 100ms were set as the shortest and longest duration of HFO events [6]; 30ms was set as the minimal gap between two HFO events.

(2) HFO event cleaning. After the first step, further approaches including artifact removal, contour classification and valley group deleting were applied to rule out false positives in the detected HFO events. Frist, common artifacts, such as sharp transitions, were removed. Then, contour classification and valley group deleting were performed based on the approach developed in our previous studies [7].

(3) There might exist multiple closed-loop contours in one event and all contours should be included in identifying type of event to give the most accurate classification. Consequently, the overall weighted frequency was implemented in distinguishing ripple and fast ripple events. The event was identified as ripple if its' overall weighted frequency was below 240 Hz. Otherwise, the event was be considered to be a fast ripple. The formula of the overall weighted frequency is as follows:

$$F_{weighted} = \sum_{i=1}^{n} f\_sum / \sum_{i=1}^{n} p\_sum.$$

Specifically, n stands for the number of closed-loop contours in a certain event. The terms f_sum and p_sum are the total frequency and the total power of one closed-loop contours respectively. The basis of computing these two variables is the 2D time-frequency matrix gained from the previous step. The calculation is comprised of two parts. The first part is to retrieve the power level of each entry of the time frequency map, p_{xy}. The second part is to generate f_sum and p_sum based on p_{xy}. The equations are as follow:

$$f\_sum = \sum \sum_{x,y=1}^{m} p_{xy} * F_y, \ p\_sum = \sum \sum_{x,y=1}^{m} p_{xy}.$$

The term m represents the total number of complete grid cell that is within the corresponding contour and x, y are the index of the time and frequency vectors respectively. The variable F_y is the frequency at the yth position of the frequency vector.

Figure S1

Ripple rate — Analysis of Variance

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Group	59.2	2	29.609	3.53	0.0297
Area	728.3	7	104.038	12.4	0
Period	94.1	7	13.44	1.6	0.1309
Group*Area	212.5	14	15.179	1.81	0.0329
Group*Period	48.1	14	3.435	0.41	0.9724
Area*Period	330.8	49	6.752	0.8	0.8297
Group*Area*Period	749.5	98	7.648	0.91	0.7157
Error	8792.5	1048	8.39		
Total	11401.1	1239			

Fast ripple rate — Analysis of Variance

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Group	76.03	2	38.0125	15.01	0
Area	43.41	7	6.2018	2.45	0.0171
Period	20.91	7	2.9865	1.18	0.3116
Group*Area	90.97	14	6.4976	2.57	0.0012
Group*Period	46.83	14	3.3453	1.32	0.1874
Area*Period	111.41	49	2.2738	0.9	0.673
Group*Area*Period	267.21	98	2.7267	1.08	0.2939
Error	2653.44	1048	2.5319		
Total	3285.7	1239			

Figure S1. 3-way ANOVA table for ripple rate and fast ripple rate in response to the factor of group, area, and period.

Figure S2

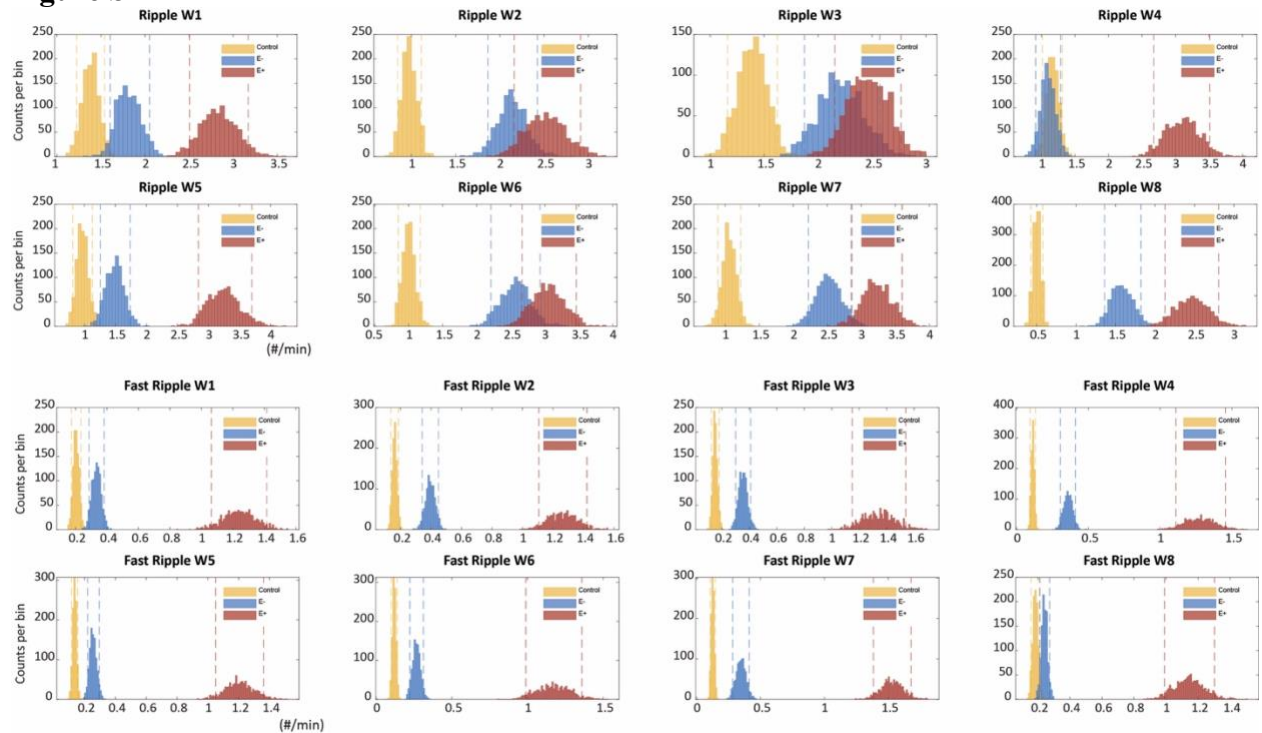**Figure S2. The bootstrapping results for the HFO rate weekly data.** The nboot = 1000 was applied for the bootstrapping analysis for ripple rate and fast ripple rate in the week1 – week8 data from the control, E- and E+ group. The 95% confidence of interval was used to evaluate the within-group stability.
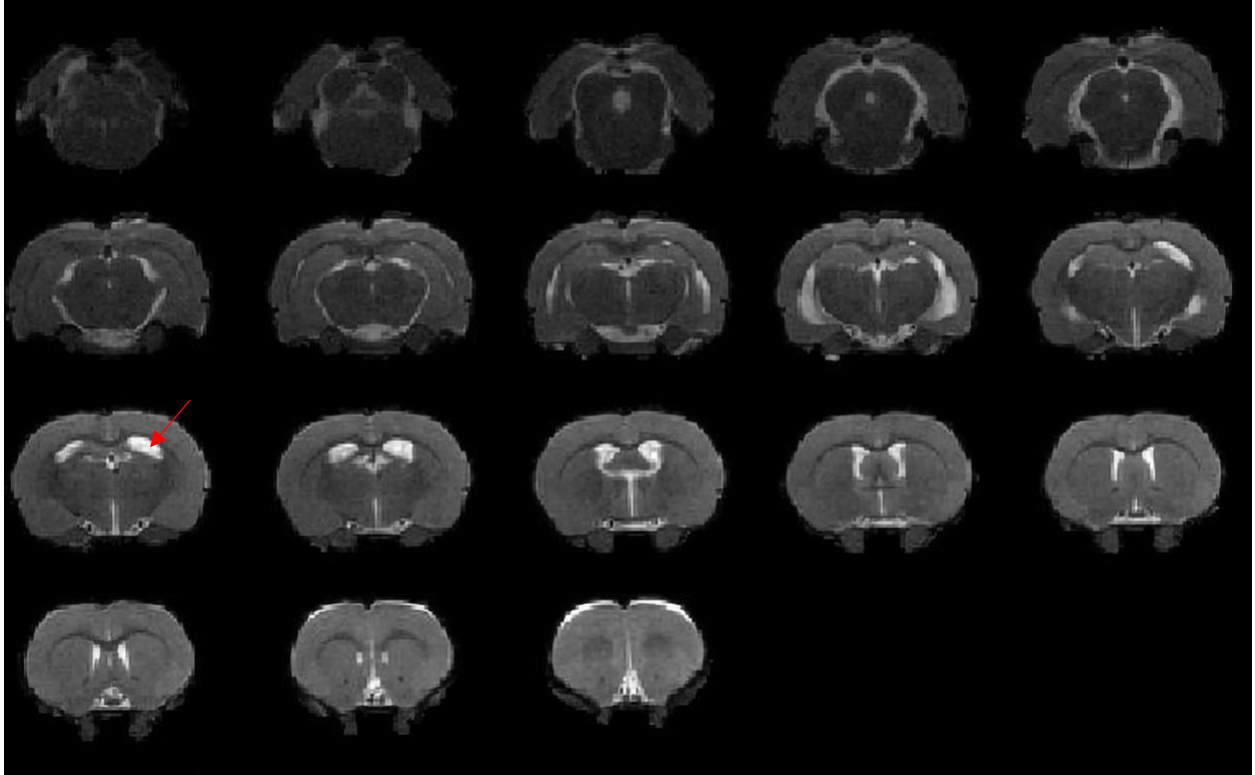
Figure S3. Illustration of the brain lesions (red arrow) assessed by the structural MRI scans. Detailed parameters: T2-weighted, Rapid Acquisition with Relaxation Enhancement (RARE) image volume (TR/TE= 500/60ms, RARE factor 8).

Table S1. Subject information.

SID	Group	first seizure(day)	SID	Group	first seizure (day)
Subj01	Sham	N.A		**Subjects Below were excluded**	
Subj02	Sham	N.A	Subj49	E+	77
Subj03	Sham	N.A	Subj50	E+	64
Subj04	Sham	N.A	Subj51	E-	N.A
Subj05	Sham	N.A	Subj52	E-	N.A
Subj06	Sham	N.A	Subj53	E+	83
Subj07	Sham	N.A	Subj54	E-	N.A
Subj08	Sham	N.A	Subj55	E-	N.A
Subj09	E+	78	Subj56	E+	84
Subj10	E+	75	Subj57	E-	N.A
Subj11	E-	N.A	Subj58	E-	N.A
Subj12	E+	79	Subj59	E+	69
Subj13	E+	56	Subj60	E-	N.A
Subj14	E-	N.A	Subj61	E+	42
Subj15	E-	N.A	Subj62	E+	47
Subj16	E-	N.A	Subj63	E-	N.A
Subj17	E+	68	Subj64	E-	N.A
Subj18	E-	N.A	Subj65	E+	45
Subj19	E+	66	Subj66	E+	37
Subj20	E+	64	Subj67	E-	N.A
Subj21	E+	50	Subj68	E+	41
Subj22	E-	N.A	Subj69	E+	68
Subj23	E+	48			
Subj24	E-	N.A			
Subj25	E+	59			
Subj26	E+	47			
Subj27	E+	78			
Subj28	E+	88			
Subj29	E-	N.A			
Subj30	E+	37			
Subj31	E-	N.A			
Subj32	E+	64			
Subj33	E+	40			
Subj34	E-	N.A			
Subj35	E-	N.A			
Subj36	E-	N.A			
Subj37	E+	78			
Subj38	E+	88			
Subj39	E+	39			
Subj40	E-	N.A			
Subj41	E-	N.A			
Subj42	E-	N.A			
Subj43	E-	N.A			
Subj44	E+	86			
Subj45	E+	36			
Subj46	E+	72			
Subj47	E-	N.A			
Subj48	E-	N.A			

Table S2. Descriptive statistics of HFO rates in ipsilateral and contralateral sites of the lesion.

HFO type		Sham (n=8)	E- (n=18)	E+ (n=22)	Group difference
		ipsilateral			
ripple	mean (SD)	0.94 (1.36)	1.75 (2.01)	2.54 (2.61)	$F_{(2, 45)} = 1.65$, $p=0.20$
	range (min, max)	(0, 9.05)	(0, 10.27)	(0, 13.36)	
fast ripple	mean (SD)	0.13 (0.20)	0.33 (0.41)	1.23 (1.35)	$F_{(2, 45)} = 6.11$, $p<0.05$
	range (min, max)	(0, 1.42)	(0, 2.34)	(0, 6.10)	
		contralateral			
ripple rate	mean (SD)	0.82 (1.09)	1.31 (2.05)	2.50 (2.73)	$F_{(2, 45)} = 2.17$, $p=0.13$
	range (min, max)	(0, 4.80)	(0, 14.03)	(0, 14.22)	
fast ripple rate	mean (SD)	0.099 (0.17)	0.23 (0.34)	1 (1.18)	$F_{(2, 45)} = 5.67$, $p<0.05$
	range (min, max)	(0, 1.21)	(0, 2.02)	(0, 6.95)	

Table S3. Descriptive statistics of HFO rates (num/min) in brain regions

HFO type		Sham (n=8)	E- (n=18)	E+ (n=22)
		Prefrontal cortex		
Ripple	mean (SD)	1.06 (1.21)	0.87 (0.96)	0.81 (1.28)
	range (min, max)	(0, 2.60)	(0, 5.16)	(0, 7.67)
Fast Ripple	mean (SD)	0.078 (0.11)	0.31 (0.39)	0.56 (0.76)
	range (min, max)	(0, 0.57)	(0, 2.06)	(0,4.37)
		Striatum		
Ripple	mean (SD)	0.51 (0.64)	0.92 (1.13)	1.65 (1.95)
	range (min, max)	(0, 2.52)	(0, 6.39)	(0, 6.39)
Fast Ripple	mean (SD)	0.06 (0.10)	0.19 (0.29)	0.72 (0.93)
	range (min, max)	(0, 0.47)	(0, 2.02)	(0, 5.46)
		Perilesional areas		
Ripple	mean (SD)	1.43 (1.84)	1.98 (2.22)	3.77 (2.74)
	range (min, max)	(0, 9.05)	(0, 10.27)	(0, 13.36)
Fast Ripple	mean (SD)	0.15 (0.24)	0.28 (0.39)	1.66 (1.47)
	range (min, max)	(0, 1.42)	(0, 2.34)	(0, 6.02)
		Hippocampus		
Ripple rate	mean (SD)	1.03 (1.18)	2.34 (2.82)	3.86 (2.94)
	range (min, max)	(0, 4.74)	(0, 14.03)	(0, 14.22)
Fast Ripple	mean (SD)	0.16 (0.24)	0.35 (0.44)	1.52 (1.41)
	range (min, max)	(0, 1.2)	(0, 1.77)	(0, 6.95)

Table S4. Descriptive statistics of HFO events weekly distribution.

Period		Sham (n=8)	E- (n=18)	E+ (n=22)
		Ripple (num/min)		
week1	mean (SD)	1.0632 (1.2115)	1.5638(1.9191)	2.497(2.5848)
	range (min, max)	(0,4.197)	(0,10.2745)	(0,14.2261)
week2	mean (SD)	1.0102(0.9501)	1.7423(2.3464)	2.8925(3.0728)
	range (min, max)	(0,3.4387)	(0,14.0397)	(0,12.4073
week3	mean (SD)	1.0985(1.692)	1.6576(2.4993)	2.0734(2.5629)
	range (min, max)	(0,9.0566)	(0,13.4258)	(0,11.7615)
week4	mean (SD)	0.96021(1.1091)	0.95295(1.3434)	2.3268(2.8269)
	range (min, max)	(0,5.1235)	(0,5.5433)	(0,12.5359)
week5	mean (SD)	0.7244(1.0625)	1.1506(1.7117)	2.9203(2.8053)
	range (min, max)	(0,5.1529)	(0,6.9697)	(0,9.2955)
week6	mean (SD)	0.68226(1.0907)	2.016(2.2764)	2.5952(2.617)
	range (min, max)	(0,4.8039)	(0,10.0276)	(0,13.3634)
week7	mean (SD)	0.7739(1.3686)	1.8138(2.2756)	2.6596(2.5401)
	range (min, max)	(0,4.7967)	(0,10.2725)	(0,9.2186)
week8	mean (SD)	0.41375(0.64553)	1.3301(1.8156)	2.4822(2.6234)
	range (min, max)	(0,2.4337)	(0,7.4788)	(0,6.8755)
within-group difference		$F_{(2,301)}=1.0779$	$F_{(2,485)}=1.8151$	$F_{(2,445)}=0.594$
		P=0.37	P=0.082	P=0.76
		Fast Ripple (num/min)		
week1	mean (SD)	0.17703(0.23856)	0.29856(0.39372)	1.1359(1.2813)
	range (min, max)	(0,1.4286)	(0,2.027)	(0,6.0263)
week2	mean (SD)	0.1463(0.1936)	0.33146(0.37253)	1.2283(1.3)
	range (min, max)	(0,0.6787)	(0,2.0617)	(0,4.9921)
week3	mean (SD)	0.11035(0.2324)	0.3464(0.4474)	1.1005(1.5191)
	range (min, max)	(0,1.2179)	(0,1.7732)	(0,6.1066)
week4	mean (SD)	0.0841(0.1524)	0.2644(0.4153)	1.0765(1.3516)
	range (min, max)	(0,0.9005)	(0,1.7323)	(0,6.9513)
week5	mean (SD)	0.1088(0.1587)	0.2447(0.3051)	1(1.0323)
	range (min, max)	(0,0.7179)	(0,1.623)	(0,5.4445)
week6	mean (SD)	0.0908(0.15797)	0.2376(0.3448)	1.138(1.3141)
	range (min, max)	(0,0.8115)	(0,1.656)	(0,6.5463)
week7	mean (SD)	0.11421(0.16437)	0.30533(0.4983)	1.1631(1.1315)
	range (min, max)	(0,0.47154)	(0,2.3415)	(0,4.0356)
week8	mean (SD)	0.10517(0.2248)	0.23167(0.251)	1.1336(1.0788)
	range (min, max)	(0,0.8599)	(0,1.0726)	(0,2.77)
within-group difference		$F_{(2,301)}=1.0679$ P=0.38	$F_{(2,485)}=0.6378$ P=0.72	$F_{(2,445)}=0.1258$ P=0.99

References

1.   Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nature Reviews Neuroscience*. 2013;14(2):128-142. doi:10.1038/nrn3407
2.   Kamsu JM, Constans JM, Lamberton F, et al. Structural layers of ex vivo rat hippocampus at 7T MRI. *PLoS One*. 2013;8(9):e76135. doi:10.1371/journal.pone.0076135
3.   Gelinas JN, Khodagholy D, Thesen T, Devinsky O, Buzsáki G. Interictal epileptiform discharges induce hippocampal–cortical coupling in temporal lobe epilepsy. *Nature Medicine*. 2016;22(6):641-648. doi:10.1038/nm.4084
4.   Staba RJ, Wilson CL, Bragin A, Fried I, Engel Jr J. Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *Journal of neurophysiology*. 2002;88(4):1743-1752.
5.   Gardner AB, Worrell GA, Marsh E, Dlugos D, Litt B. Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings. *Clinical Neurophysiology*. 2007;118(5):1134-1143. doi:10.1016/j.clinph.2006.12.019
6.   Bragin A, Engel Jr J, Wilson CL, Fried I, Buzsáki G. High‑frequency oscillations in human brain. *Hippocampus*. 1999;9(2):137-142.
7.   Weiss SA, Alvarado-Rojas C, Bragin A, et al. Ictal onset patterns of local field potentials, high frequency oscillations, and unit activity in human mesial temporal lobe epilepsy. *Epilepsia*. 2016;57(1):111-121. doi:10.1111/epi.13251