Supplementary materials

**S1. TBI procedure**

Lateral fluid percussion injury (FPI) 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 °C 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), 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. 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; 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. First, 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.

(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:

$$F_{weighted} = \frac{\sum_{i=1}^{n} f_{sum}}{\sum_{i=1}^{n} p_{sum}}.$$ 

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:

$$f_{sum} = \sum_{x,y=1}^{m} p_{xy} \times F_y, \quad p_{sum} = \sum_{x,y=1}^{m} p_{xy}.$$ 

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 y^{th} position of the frequency vector.
Figure S1

| 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 |          |       |        |

| 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. 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 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 | Subj50 | E+ | 77 |
| Subj02 | Sham | N.A | Subj51 | E- | N.A |
| Subj03 | Sham | N.A | Subj52 | E- | N.A |
| Subj04 | 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 |

Subjects Below were excluded

Subj50, E+ 64
Subj60, E- 45
Subj70, E+ 37
Subj80, E- 41
Subj90, E+ 68
Table S2. Descriptive statistics of HFO rates in ipsilateral and contralateral sites of the lesion.

| HFO type        | Sham (n=8) ipsilateral | E- (n=18) | E+ (n=22) | Group difference |
|-----------------|------------------------|-----------|-----------|------------------|
| 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)        |                               |
| 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) |
|--------------|------------|-----------|-----------|
|              | mean (SD)  | mean (SD) | mean (SD) |
|              | range (min, max) | range (min, max) | range (min, max) |
| **Prefrontal cortex** | | | |
| Ripple       | 1.06 (1.21) | 0.87 (0.96) | 0.81 (1.28) |
| Fast Ripple  | 0.078 (0.11) | 0.31 (0.39) | 0.56 (0.76) |
| **Striatum** | | | |
| Ripple       | 0.51 (0.64) | 0.92 (1.13) | 1.65 (1.95) |
| Fast Ripple  | 0.06 (0.10) | 0.19 (0.29) | 0.72 (0.93) |
| **Perilesional areas** | | | |
| Ripple       | 1.43 (1.84) | 1.98 (2.22) | 3.77 (2.74) |
| Fast Ripple  | 0.15 (0.24) | 0.28 (0.39) | 1.66 (1.47) |
| **Hippocampus** | | | |
| Ripple rate  | 1.03 (1.18) | 2.34 (2.82) | 3.86 (2.94) |
| Fast Ripple  | 0.16 (0.24) | 0.35 (0.44) | 1.52 (1.41) |
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(1.1211) | 1.5638(1.9191) | 2.497(2.5848) |
|        | range (min, max) | (0.4197) | (0.10.2745) | (0.14.2261) |
| week2  | mean (SD)  | 1.0102(0.9501) | 1.7423(2.3464) | 2.8925(3.0728) |
|        | range (min, max) | (0.34387) | (0.14.0397) | (0.12.4073) |
| week3  | mean (SD)  | 0.96021(1.091) | 0.95295(1.3434) | 2.3268(2.8269) |
|        | range (min, max) | (0.51235) | (0.55433) | (0.12.5359) |
| week4  | mean (SD)  | 0.7244(0.625) | 1.1506(1.7117) | 2.9203(2.8053) |
|        | range (min, max) | (0.51529) | (0.69697) | (0.92955) |
| week5  | mean (SD)  | 0.68226(1.0907) | 2.016(2.2764) | 2.5952(2.617) |
|        | range (min, max) | (0.48039) | (0.10.0276) | (0.13.3634) |
| week6  | mean (SD)  | 0.17703(0.23856) | 0.29856(0.39372) | 2.1359(1.2813) |
|        | range (min, max) | (0.1463) | (0.1936) | (0.4.921) |
| week7  | mean (SD)  | 0.11035(0.2324) | 0.33146(0.37253) | 1.2283(1.3) |
|        | range (min, max) | (0.12179) | (0.17732) | (0.6.1066) |
| week8  | mean (SD)  | 0.0841(0.1524) | 0.2644(0.4153) | 1.0765(1.3516) |
|        | range (min, max) | (0.09005) | (0.17323) | (0.6.9513) |
| week9  | mean (SD)  | 0.1088(0.1587) | 0.2447(0.3051) | 1.1032(1.0323) |
|        | range (min, max) | (0.07179) | (0.1623) | (0.5.4445) |
| week10 | mean (SD)  | 0.08064(0.1579) | 0.1476(0.3051) | 1.138(1.3141) |
|        | range (min, max) | (0.08115) | (0.1656) | (0.63543) |
| within-group difference | F(2,301)=1.0779 | P=0.37 | F(2,485)=1.8151 | P=0.082 |
| Fast Ripple (num/min) | F(2,445)=0.594 | P=0.76 |
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