Extended online Materials and Methods and references.

Animal procedure. Unilateral single freeze lesions were made in P0–1 mice pups on a CD-1 (or c57bl/6) background to induce neocortical microgyria in the right S1 area (SFLS1R), as the PI and colleagues previously described in rat[1]. Briefly, mouse pups <48 hrs old were immersed in ice for ~4 minutes until movements and responses to tail pinch were absent. The skull was exposed through a scalp incision and a freezing probe with a 1 mm diameter circular tip, cooled to < -100 °C, was placed on the skull over somatosensory cortex 2.3 mm from the midline and 0.2 mm rostral to the bregma for 1 sec. The scalp was then sutured, the pup warmed and returned to the dam. This procedure routinely resulted in the development within barrel cortex of a microsulcus, consisting of an invagination of the cortical surface, and an associated 4 layered microgyrus measuring ~300 µm across (e.g. Supplemental Fig.S1)[1]. Within a typical litter, 3 pups were administered a freeze lesion and the remaining 3 pups underwent sham surgery (i.e. identical surgical procedures minus the freeze lesion). The entire litter was kept in a vivarium maintained at 22–23 °C on a 12:12 h light-dark cycle. The mice were weaned and housed together based on the same sex. Food and water were available ad libitum. ***Histology.*** Adult-treated mice were anesthetized with isoflurane and were euthanized. Brains were dissected in saline and cut into 300µm serial sections using a vibratome (TPI, St. Louis, MO). Brain slices were then fixed for overnight minutes in 4% paraformaldehyde. These sections were then washed in 0.01 M phosphate-buffered saline (PBS). The sections were then mounted on a glass slide embedded with DAPI based mounting medium and sealed with cover slip. Brain sections were imaged with an upright microscope under 1 to 10X objectives. ***Intracranial EEG recordings***. For implantation of EEG electrodes, 0.4-1 year old mice were anesthetized under isoflurane anesthesia (2%, delivered in medical-grade oxygen) and secured in a stereotaxic frame. Polyimide-insulated stainless steel wires (125 µm, California Fine Wire Co) and connecting pins (0.02 inch gold pins, Mill Max Manufacturing Corp, Oyster Bay, NY) were implanted into the S1 or M1 region of the cortex, VPM group of the thalamus, or CA1 region of hippocampus either ipsilateral or contralateral to the freeze lesion. A ground electrode was placed into the olfactory bulb area (e.g. Supplemental Fig.S1A1). A screw free, glue-based electrode assembly system that allows for long-term recordings was used for all EEG recording sessions[2;3]. Mice were returned to the vivarium after EEG electrode implantation. EEG recordings were performed in a 24 hour cycle with simultaneous video behavior monitoring and automated infrared (IR)-activity tracking at a frequency of twice per month to minimize disturbances. During recording, animals were able to move freely in a recording chamber supplied with water gel. A bundle of soft and light-weight fine-wires connecting the screw-free EEG electrodes to the recording amplifiers was anchored on the center of a circular recording arena that allowed for free movement of the animal. A piezo-electric floor sensor was placed in the recording chamber to monitor animal movement. EEG and floor-sensor signals were amplified via a differential AC amplifier (Model 1700, A-M system), digitized using Power 1401, and analyzed using a Spike2 software program (Cambridge Electronic Design). Offline

analysis was conducted using custom programs developed on Matlab® or with Spike2. Overnight EEG recordings yielded large amounts of data, which were used to assess the integrity of ongoing neural activity. The following EEG features were compared between sham and SFLS1R mice: ***Power spectrum and band.*** Spectral power was calculated the FFT were performed by Spike-2® program using a 2.56 seconds Hanning window across continuous range (0-50Hz) or conventional frequency bands (δ:1-4 Hz, θ:4-8 Hz, α:8-12 Hz, σ12-16Hz and β:16-24 Hz) for each electrode. Power-band values are typically normalized to δ band power, and δ-band power is normalized with total band power. In some cases, EEG power values of ictal activity were normalized to background activity, typically represented by quiet waking (QW) period (e.g. Figs. 3B4 and 5B4). ***Coherence.*** Coherence analysis was used to reveal the extent at which brain signals from separate brain regions were synchronized over time and across frequency. Data are presented as coherence across time-frequency plots or as the cross-correlation between signals. ***Wavelet analysis.*** Wavelet analysis was performed using a custom-written program utilizing the Wavelet toolbox of the Matlab® program. ***Sleep architecture.*** Body muscle tone, respirations, and animal movements were recorded using a piezo-electric floor sensor, which replaced the invasive EMG signals traditionally used in sleep detections[4;5]. Sleep-state analysis was performed using the NeuroScore software (V3.0, DSI, St. Paul, MN) followed by blind manual verification and corrections. Briefly, sleep-stage detection was based on a Fast-Fourier Transform of the EEG signal from 1 to 20 Hz, yielding power in δ, θ, α, σ and β bands plus integrated floor sensory activity across 2-second epochs. REM sleep was identified by periods of low-amplitude sleep events characterized with an increased θ power and concomitant low δ and σ power in association with a lack of movement, typically defined by θ/ δ>1.2. Changes in δ power were used to distinguish NREM sleep from quiet waking (QW) epochs (without movement) or active awake epochs (with movement). We also assessed sleep architecture and its relationship to seizure activity in SFLS1R mice using the same software. ***Epileptiform activity.*** An investigator visually inspected all EEG data and recorded segments containing epileptiform activities. The visual inspection was combined with an automated seizure detection program using NeuroScore®. In Neuroscore program, epileptiform activities (ictal spikes, IS), are defined as barrage of high-voltage EEG spikes whose amplitude typically exceed two times of the mean amplitude of slow-wave sleep. The parameters for IS detection typically are: minimum spike duration (30ms) and maximum spike duration (100ms), maximum spike interval 300ms, and minimum train duration 300ms and minimum spikes (4). Upon completion of the automated detection, visual inspection is performed by an experienced person to make corrections. The following seizure parameters were examined across the 24 hour recording period: total number of seizure spike-train events, total seizure duration, longest seizure duration, average number of spikes per seizure event, and averaged power spectrum (normalized to NREM power). The timing of epileptiform activity along with its duration was plotted against specific sleep stages (REM, NREM, Wake, and Active wake), which enabled us to test whether epileptiform discharges correlated with specific stages of the sleep-wake cycle. ***Behavior***. All behavior testing was performed by an investigator blinded to the test group. Behavior monitoring was

performed using a high-throughput automated home-cage behavior system[6], which provided an open field test, assessment of locomotion activities, social interactions, and repetitive behavior. The system automatically tracked animal activity (horizontal movement, rear-ups) level changes using a SmartCage™ automated platform and data collected using CageCenter™ software across both light and dark cycles using 24 IR-sensors and a piezo-electric floor sensor[7]. IR-video recordings were timed with EEG recordings to examine behavior correlates of EEG seizures. All tests were performed by an investigator blinded to the experimental group*. Open field (OF) test.* The test subjects were placed in the center of an OF within the test chamber and continuously monitored for the 10 – min test session. *Social Interaction (SI) test.* The SI testing arena consisted of a home cage with two clear transparent enclosures (8 X 6 X 12 cm) affixed at each end. The floor of the enclosures was a metal grid elevated 6 cm above the home cage floor to facilitate social interactions. The test subject was placed into the center of the arena at the beginning of the test and allowed to freely explore the empty enclosures for a 10 – min habituation session. Immediately following the habituation session a stranger mouse was placed into one of the empty enclosures and the test subject was allowed to freely explore both enclosures for the 10 – min sociability session. CageScore™ was used to evaluate time spent with stranger mouse versus the empty enclosure, activity counts, total distance traveled, and number of rear up counts. *Novel object recognition (NOR) test.* The NOR test was conducted over two days. The first day consisted of a 30 – min habituation session where the test subject was allowed to freely explore the arena. After 24 h, the test subject was placed back into the arena for a 10 – min habituation session. The subject was then removed from the arena and placed into a holding cage for approximately 2 minutes while two identical objects where placed into the arena. The subject was then placed back into the same arena for a 10 – min familiarization session. The subject was then removed a second time and placed into the holding cage while the objects where cleaned. After approximately one hour the test subject was placed back into the arena with one familiar object and one novel object and was allowed to freely explore both objects for the 5 minute test session. During the testing phase, time sniffing each object was recorded. Objects where red plastic dice and a clear plastic sphere. Gap-crossing tests were performed based on methods described by Barneoud et al[8]. Briefly, animals were housed in a testing room illuminated with dim red light for 24 hours prior to the testing. During the testing phase, a 2 foot-high platform (10 by 40 cm width) with adjustable gap was used to measure the maximum gap distance a mouse would cross within a 5 minute testing period. The tests were repeated two times across two separate days and the results were averaged. ***Optogenetic interrogation.*** To interrogate the circuit mechanisms underlying seizure, we implanted a multi-mode fiber optic patch cable (Ø150µm, Thorlabs) via a 1.25mm OD multimode ceramic zirconia ferrule (Precision Fiber Products, Inc, Milpitas, CA 95035) was glued together with the S1R EEG electrode to form an optrode configuration and implanted near the FL region in S1 (e.g. Supplemental Fig.S1A) of VGAT-ChR2 mice (Stock Number. 014548, Jackson laboratories) approximately 0.3mm below the skull, which is near layer 2/3 of the S1 region (histologically verified). The multi-mode fiber optic patch cable was coupled to a

blue laser (473nm, 100 mW, DPSS blue laser, www.lasercentury.com) via a SMA mating end. Laser pulses were delivered via a custom made pulse generator at three frequencies (1, 5 and 10Hz). It was estimated that an area of approximately 0.3mm depth and 0.3mm width was illuminated upon activation of the fiber based on tests using similar fiber in brain slice *in vitro*[9]. **Ethosuximide administration**. Mice were anesthetized under isoflurane anesthesia (2%, delivered in medical-grade oxygen). EEG recording wires were mounted first before ES (0.3mg/0.5 ml distilled water) was administered via i.p. injection. The mouse was then transferred to the recording arena for 24 h EEG recordings. Sham-injected mice (saline only) were used as controls. ***Statistics.*** All values are expressed as mean ± SEM. Two-tailed Student's t test was performed for two group comparisons. A paired t-test was performed between groups before and after ES treatment. Analysis of variance (ANOVA) was used for comparison between three or more distinct groups. A Kolmogorov-Smirnov test was also used to examine if the distribution was nonparametric Significance was placed at $P < 0.05$.

Reference List

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Supplemental Table S1. Animal information.

Animal No.	DOB	Sex	Strain	FL	EEG sites	Implant date	Seizure	Optogenetics	ET treatment	Death (Days)
201440	10/2/2013	F	CD1	S1R	S1R/M1R/VPMR	6/3/2014	CSWS			387
201441	10/2/2013	F	CD1	S1R	S1R/VPMR	6/3/2014	CSWS			
201444	10/2/2013	F	CD1	S1R	S1R/S1L	6/26/2014	CSWS			
201445	10/2/2013	F	CD1	S1R	S1R/S1L	6/26/2014				
201448	5/7/2014	M	CD1	S1R	S1R/S1L	7/2/2014				
201451	5/7/2014	M	CD1	S1R	S1R/S1L	7/10/2014				
201456	5/14/2014	F	CD1	S1R	S1R/S1L	7/17/2014				124
201457	5/14/2014	F	CD1	S1R/S1L	S1R/S1L	7/17/2014				
201465	5/29/2014	M	CD1	S1R	S1R/S1L	7/24/2014				
201475	5/2/2014	F	CD1	S1R	S1R/M1R	9/12/2014	CSWS			
201476	5/7/2014	M	CD1	S1R	S1R/M1R	9/12/2014				
201477	4/16/2014	M	CD1	sham	S1R/M1R	9/12/2014				
201479	7/28/2014	M	CD1	sham	S1R/S1L	9/26/2014				
201480	5/29/2014	F	CD1	S1R	S1R/VPMR	9/26/2014	CSWS			
201481	5/29/2014	F	CD1	S1R	S1R/VPMR	9/26/2014	CSWS			452
201482	5/29/2014	F	CD1	S1R	S1R/VPMR	9/26/2014	CSWS			
201490	7/28/2014	M	c57bl/6	S1R	S1R/M1R	11/6/2014	CSWS	S1 stimulation		
201493	8/18/2014	M	CD1	S1R	S1R/M1R/M1L	11/18/2014				
201494	6/30/2014	F	CD1	sham	S1R/M1R/M1L	11/19/2014				
201495	6/30/2014	F	CD1	S1R	S1R/M1R/M1L	11/19/2014				

2015127	9/23/2014	M	c57bl/6	S1R	S1R/S1L/M1R	2/24/2015	CSWS		11/5/2015	
2015134	7/25/2014	F	c57bl/6	S1R	S1R/S1L/M1	3/10/2015	CSWS	S1 stimulation		410
2015156	9/30/2014	M	CD1	sham	S1R/S1L/VPM	5/22/2015				457
2015157	9/30/2014	M	CD1	S1R	S1R/S1L/VPM	5/22/2015	CSWS		10/12/2015	
2015158	9/30/2014	M	CD1	S1R	S1R/S1L/VPM	5/22/2015	CSWS			
2015164	5/31/2014	M	CD1	S1R	S1R/M1R/CA1R	6/16/2015	CSWS		10/14/2015	660
2015165	6/16/2014	M	CD1	S1R	S1R/M1R/CA1R	6/16/2015				655
2015166	6/16/2014	F	CD1	S1R	S1R/M1R/CA1R	6/16/2015	CSWS			
2015167	4/18/2014	M	CD1	sham	S1R/M1R/CA1R	6/17/2015				
2015168	7/15/2014	F	CD1	sham	S1R/M1R/CA1R	6/17/2015				482
2015169	7/15/2014	F	CD1	sham	S1R/M1R/CA1R	6/17/2015				666
2015170	7/21/2014	M	CD1	sham	S1R/M1R/CA1R	6/17/2015				592
2015171	9/21/2014	F	c57bl/6	S1R	S1R/S1L/M1R	7/10/2015	CSWS	S1 stimulation		
2015208	6/11/2014	M	CD1	S1R	S1R/M1R/VPMR	12/16/2015				
2016209	6/11/2014	M	CD1	S1R	S1R/M1R/VPMR	12/16/2015				642
2016210	6/11/2014	M	CD1	S1R	S1R/S1L/VPMR	12/16/2015				
2016217	6/5/2014	M	CD1	S1R	S1R/M1R/VPMR	1/12/2016	CSWS			662
2016218	11/27/2014	F	CD1	S1R	S1R/M1R/VPMR	1/12/2016	CSWS		1/19/2016	
2016219	11/27/2014	F	CD1	S1R	S1R/S1L/VPMR	1/12/2016				
2016220	2/7/2014	F	CD1	sham	S1R/VPMR/M1R	1/13/2016				725
2016221	6/8/2014	M	CD1	S1R	S1R/VPMR/CA1L	1/20/2016	CSWS			701
2016222	5/31/2014	F	CD1	S1R	S1R/S1L/VPMR	1/20/2016	CSWS			

2016224	7/21/2014	M	CD1	sham	S1R/S1L/VPMR	1/21/2016				635
2016225	9/23/2014	M	CD1	sham	S1R/VPMR/CA1L	1/21/2016				
2016226	7/5/2015	M	CD1	S1R	S1R/M1R/VPMR	1/29/2016	CSWS		2/3/2016	227
2016227	7/5/2015	M	CD1	S1R	S1R/M1R/CA1L	1/29/2016				
2016228	5/17/2015	F	c57bl/6	S1R	S1R/S1L/VPMR	2/3/2016	CSWS	S1 stimulation		
2016234	9/6/2014	M	CD1	S1R	S1R/M1R/VPMR	2/15/2016				
2016235	9/6/2014	M	CD1	S1R	S1R/S1L/VPMR	2/15/2016				533
2016236	9/6/2014	F	CD1	S1R	S1R/VPMR/CA1L	2/15/2016	CSWS		2/22/2016	
2016240	11/27/2014	F	c57bl/6	S1R	S1R/S1L/VPMR	2/18/2016	CSWS	S1 stimulation		
2016246	1/10/2016	F	CD1	sham	S1R/M1R/VPMR	4/17/2016				
2016249	7/11/2015	F	c57bl/6	S1R	S1R/S1L/CA1R	4/30/2016	CSWS			
2016250	7/11/2015	M	c57bl/6	S1R	S1R/S1L/CA1R	5/1/2016	CSWS			
2016251	5/10/2015	F	c57bl/6	S1R	S1R/S1L/CA1R	5/1/2016	CSWS			
2016252	5/10/2015	M	c57bl/6	S1R	S1R/S1L/CA1R	5/2/2016				
2016253	5/17/2015	F	CD1	S1R	S1R/S1L/CA1R	5/2/2016	CSWS			358