IMAGING INDIVIDUAL HIPPOCAMPAL SEIZURES AND THE LONG-TERM IMPACT OF REPEATED SEIZURES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/945,012, filed December 6, 2019, which is incorporated herein in its entirety for all purpose.

BACKGROUND

[0002] When seizure activity invades critical circuits involved in consciousness or cardiorespiratory regulation, the risk of accidents or death increases, respectively. How such seizures evolve and propagate remain poorly understood, but there is evidence of both cortical and subcortical circuit involvement. Standard methods of recording seizures, such as electrophysiology and optical imaging, have limited spatial coverage and cannot capture the evolution of the brain-wide activity associated with certain events. For example, focal to bilateral tonic-clonic (FBTC) seizures, formerly known as secondarily generalized seizures, are difficult to treat and significantly impact patients' quality of life and safety. fMRI offers brain-wide information and has been used to visualize both focal and generalized-onset seizures in humans and in animals, but its use for visualizing FBTC seizures has been difficult due to associated motor activity that result in motion artefacts.

[0003] The relationship behind seizures, kindling, and sub-threshold activity has long been difficult to understand. This is critical for epilepsy diagnosis and treatment. The methodology provided herein can be used to diagnose and make treatment decisions for epilepsy. This is a new method that can define concrete relationships among seizures, kindling, and sub-threshold activity for the first time.

SUMMARY

[0004] Methods and models are provided for the analysis of events associated with seizures in the brain, e.g. events that model epileptic seizures; including assessing the impacts of functional and electrical neural circuit changes. The methods and models may include, for example, one or more of analysis of single seizures, triggering by sub-threshold stimulus, analysis of focal to bilateral tonic-clonic (FBTC) seizures, analysis of excitatory ventral hippocampal (VH) networks, analysis of migrating seizure cores, and the like.

[0004a] According to an aspect of the present invention, there is provided a model for the analysis of events associated with brain seizures, the model comprising: a kindled animal brain that, upon stimulation, provides for neural events reflecting functional and neural circuit changes; and allows analysis of the neural events resulting from a single seizure.

[0005] In some embodiments, methods and models are provided for identification and localization of migrating seizure cores in an individual. In some embodiments, methods and models are provided for the design of therapeutic agents to treat epileptic seizures, including without limitation FBTC seizures. In some embodiments the identification of migrating seizure cores is used in the identification of seizure onset zones. Methods of analysis may include, without limitation, determining electrophysiology, e.g. local field potentials (LFP), and functional

WHAT IS CLAIMED IS:

1. A model for the analysis of events associated with brain seizures, the model comprising:

a kindled animal brain that, upon stimulation, provides for neural events reflecting functional and neural circuit changes; and allows analysis of the neural events resulting from a single seizure.

2. The model of claim 1 wherein the analysis of the neural events comprises one or both of electrophysiology and magnetic resonance imaging (MRI).

3. The model of claim 1 or claim 2, wherein the analysis of the neural events is performed with simultaneous measurement of electrophysiology and functional magnetic resonance imaging (fMRI).

4. The model of any of claims 1-3, wherein the stimulation is electrical and targeted to a region of interest.

5. The model of claim ~~5~~4, wherein the region of interest is the hippocampus.

6. The method of any of claims 1-5, wherein the neural events reflecting functional and neural circuit changes comprise one or more of focal to bilateral tonic-clonic (FBTC) seizures, changes in excitatory ventral hippocampal (VH) networks, changes triggered by sub-threshold stimulus, and induction of a migrating seizure core.

7. The method of claim 6, wherein the stimulation that provides for neural events reflecting functional and neural circuit changes is electrical stimulation.

8. The method of claim 7, wherein the electrical stimulation is delivered by optogenetics.

9. The method of claim 8, wherein the animal brain comprises neurons genetically engineered to comprise a light activatable polypeptide.

10. The model of claim 9, wherein the light-activatable polypeptide is a channelrhodopsin.

11. The model of claim 10, wherein the channelrhodopsin is operably linked to a promoter expressed in excitatory hippocampal neurons.

12. The model of claim 11, wherein the promoter is calmodulin-dependent kinase II alpha (CaMKIIα) promoter.

13. The method of any of claims 8-12, wherein the stimulation that provides for neural events is below the threshold to trigger seizures.

14. The model of claim 13, wherein the stimulation is from about 5 Hz to about 15 Hz.

15. The method of claim 13, wherein the stimulus is applied to evaluate underlying functional circuit changes.

16. The method of any of claims 8-12, wherein the stimulus is sufficient to trigger a seizure.

17. The model of claim 16, wherein the stimulation is from about 35 Hz to about 45 Hz.

18. The model of claim 16, wherein the stimulus is applied to evaluate seizure circuit dynamics.

19. The model of any of claims 1-18, wherein a migrating seizure core is identified.

20. The model of claim 19, wherein the migrating seizure core is used in localization of a seizure inset zone.

21. The model of claim 20, wherein the SOZ is imaged by single-photon emission computed tomography (SPECT).

22. The model of any of claims 1-21, wherein kindling is achieved using electrostimulation, optogenetics or chemical treatment.

23. The model of claim 22, wherein optogenetic kindling is performed by:

a. delivering a polynucleotide that encodes a light-activatable protein to a target neuron to a first region of the brain,

b. illuminating the first region of the brain repeatedly with a frequency and a pulse width sufficient to induce kindling; and

c. repeating step b. over the course of multiple days.

24. The model of any of claims 1-23, wherein the animal is sedated and treated with a short-acting neuromuscular blocker to abolish motion during imaging of seizures.

25. The model of claim 24, wherein the animal is sedated with dexmedetomidine and blocked with vecuronium.

26. A method for developing a therapeutic intervention for epilepsy, the method comprising:

treating the model of any of claims 1-25 with a therapeutic intervention, and determining the effect on neural events reflecting functional and neural circuit changes.

27. The method of claim 26, wherein the therapeutic intervention is surgical.

28. The method of claim 26, wherein the therapeutic intervention is electrical.

29. The method of claim 28, wherein the therapeutic intervention comprises deep brain stimulation.

30. The method of claim 28, wherein the therapeutic intervention is pharmacologic.

31. The method of any of claims 26-30, wherein the neural event comprises a seizure.

32. The method of any of claims 26-30, wherein the neural event comprises a migrating seizure core.

33. The method of any of claims 26-30, wherein the neural event comprises an epileptic comorbidity.

34. The method of any of claims 26-30, wherein the neural event comprises a focal to bilateral tonic-clonic (FBTC) seizure.

35. The method of any of claims 26-30, wherein the neural event comprises alterations in a excitatory ventral hippocampal (VH) network.