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 example of the present disclosure, 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.

[0004b] In an aspect, the present disclosure refers to a method of generating a model for the analysis of events associated with brain seizures, the method comprising:

receiving simultaneously collected electrophysiology data and magnetic resonance imaging (MRI) data that was collected from a kindled animal brain, wherein the electrophysiology data, the MRI data, or both includes data of at least one neural event reflecting functional and neural circuit changes, wherein the at least one neural event was responsive to a stimulation of the brain;

analyzing the electrophysiology data and the MRI data to determine corresponding changes in the electrophysiology data and MRI data indicative of the neural events,

wherein analyzing the electrophysiology data comprises calculating a band power during a stimulation divided by a band power prior to the stimulation, and

wherein analyzing the MRI data comprises:

segmenting the MRI data of the animal brain into a plurality of individual regions;

quantifying activation volumes of the plurality of individual regions; and

selecting a subset of the plurality of individual regions having the largest activation volumes; and

generating a map of a network associated with the at least one neural event based on the MRI data, the electrophysiology data, or a combination thereof.

[0004c] In an aspect, the present disclosure refers to a method of developing a therapeutic intervention for epilepsy, the method comprising:

determining the effect on neural events reflecting functional and neural circuit changes obtained by applying a therapeutic intervention to the model generated by the method of the above aspect, wherein the therapeutic intervention was surgical, electrical, comprises deep brain stimulation, or is pharmacologic.

[0005] In some examples, 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