PREDICTING SUCCESSFUL GENERATION AND INHIBITION OF SEIZURE-LIKE AFTERDISCHARGES AND MAPPING THEIR SEIZURE NETWORKS USING FMRI

CROSS REFERENCE

[0001] This application claims priority to U.S. Provisional Application No. 62/980,964, filed February 24, 2020, which is incorporated herein in its entirety for all purpose.

INTRODUCTION

[0002] Targeted therapies such as deep brain stimulation (DBS) or more recently optogenetics promise to revolutionize the treatment of refractory epilepsy by interfering with specific neuronal circuits involved in the generation and propagation of seizures. However, while considered a goal of many experimental epilepsy therapies, it is unknown whether local inhibition at the seizure origin is sufficient to curtail seizure activity or whether rapid seizure propagation across a wider network necessitates a multi-site approach. Furthermore, because of our poor understanding of seizure networks in animal models, there has been limited development toward such approaches. A greater understanding of seizure propagation pathways is a necessary step toward enabling targeted therapies for treating refractory patients.

[0003] Optogenetics employs genetic targeting, which can be used to disentangle the roles of different cell types and networks in seizure maintenance. Most investigations into using optogenetics for seizure control have focused on spontaneous seizure models, which on the one hand afford an opportunity to study ictogenesis and how different brain states relate to intervention efficacy. On the other hand, without temporal control of seizure onset, it is challenging to define the exact origin of the seizures or employ advanced imaging methods such as optogenetic functional MRI (of MRI) or calcium imaging.

[0004] Development of methods to inhibit seizures and to map seizure networks are of great clinical interest. The present disclosure addresses this issue.

SUMMARY

[0005] Methods are provided herein for mapping and reducing seizures. In one example, the present disclosure provides a method of analyzing a seizure network, the method comprising: generating an activation map with fMRI data, wherein the fMRI data includes data acquired during administration of an effective amount of light that specifically activates a depolarizing light-reactive protein thereby leading to optogenetic stimulation, wherein the depolarizing light-reactive protein is expressed by a target neuron responsive to delivery of a first polynucleotide.

In one aspect, the present disclosure provides a method of analyzing a seizure network, the method comprising: generating an activation map with fMRI data, wherein the fMRI data includes data acquired during administration of an effective amount of light that specifically activates a depolarizing light-reactive protein thereby leading to optogenetic stimulation, wherein the depolarizing light-reactive protein is expressed by a target neuron; wherein the activation map comprises voxel-wise activation time maps that are generated for comparing the spread of seizure activity between afterdischarges, and the activation map shows where afterdischarge can be suppressed locally for therapeutic intervention.

In another example, the present disclosure provides use of a first polynucleotide that encodes a depolarizing light-reactive protein, in the manufacture of a composition for analyzing a seizure network in a subject, wherein the composition is to be delivered to a target neuron in the subject to express the light-reactive protein in the target neuron, and an effective amount of light that specifically activates the light-reactive protein is to be administered to the subject thereby leading to optogenetic stimulation and generation of an activation map with fMRI. In some examples seizures are inhibited locally, for example with local optogenetic inhibition. In some examples the seizures result from optogenetically induced afterdischarges (AD). Methods are also provided for generating a seizure network map, which can find use in identification of targets

for intervention. ADs that can be suppressed locally show similar but less widespread seizure networks compared with those that could not be inhibited. It is shown that success in generating or curtailing seizures is related to their onset time, with inhibition proving less effective on earlier-

What is claimed is:

1. A method of analyzing a seizure network, the method comprising:

generating an activation map with fMRI data, wherein the fMRI data includes data acquired during administration of an effective amount of light that specifically activates a depolarizing light-reactive protein thereby leading to optogenetic stimulation, wherein the depolarizing light-reactive protein is expressed by a target neuron; wherein the activation map comprises voxel-wise activation time maps that are generated for comparing the spread of seizure activity between afterdischarges, and the activation map shows where afterdischarge can be suppressed locally for therapeutic intervention.

2. The method of claim 1, wherein the fMRI data further includes data acquired during administration of an effective amount of light that specifically activates a second hyper-polarizing light-reactive protein, wherein the second light-reactive protein is to be administered after the first-light reactive protein thereby inhibiting an afterdischarge generated by the first light-reactive protein, wherein the second light-reactive protein is expressed by the target neuron.

3. The method of claim 1 or 2 wherein, the fMRI data is cerebral blood volume (CBV)-weighted fMRI.

4. The method of any of claims 1-3, wherein the first polynucleotide is operably linked to a calmodulin-dependent kinase II (CAMKII) or a human synapsin (hSyn) promoter.

5. The method of any of claims 2-4, wherein the second polynucleotide is operably linked to a calmodulin-dependent kinase II (CAMKII) or a human synapsin (hSyn) promoter.

6. The method of any of claims 2-5, wherein the promoter operably linked to the first polynucleotide is different from the second polynucleotide.

7. The method of any of claims 2-6, wherein the fMRI data includes data acquired when optogenetic inhibition is applied during optogenetic stimulation.

8. The method of any of claims 1-7, wherein the fMRI data is combined with local field potential (LFP) recording to generate the activation map.

9. The method of any of claims 1-8, wherein early spiking is demonstrated to be predictive of successful inhibition of seizures.

10. The method of any of claims 1-9, wherein the first polynucleotide encodes a ChR2 protein.

11. The method of any of claims 2-10, wherein the second polynucleotide encodes an eNpHR3.0 protein.

12. The method of any of claims 1-11, wherein the light-reactive proteins are configured to be expressed in the ventral hippocampus.

13. The method of any of claims 1-12, wherein the light-reactive proteins are configured to be expressed in the dorsal hippocampus.

14. The method of any of claims 2-13, wherein the light used for optogenetic inhibition is from 2000mW/mm^2 to 3000mW/mm^2.