

Project Summary:

Abstract: About 40% of people with epilepsy have generalized-onset seizures, which are associated with an electrical discharge simultaneously involving of both cerebral hemispheres in a synchronous fashion. Genetic causes underlie generalized epilepsies in most cases. Almost 80% of genetic generalized epilepsies (GGE) respond to medical therapies. In contrast to focal epilepsies, there are no approved surgical therapies to treat medically refractory cases. For this reason, we intend to utilize a natural nonhuman primate model of GGE for the development and testing of neurostimulation therapies. Our group collected extensive data on the epileptic baboon using functional and structural neuroimaging as well as invasive electrophysiology. We are poised to adapt a recently FDA approved responsive neurostimulator (RNS[®] System; NeuroPace, CA) to target cortical and subcortical structures that are part of the epileptic network or highly connected to it, both to record intracranial electrocorticography (ECoG) and for stimulation. One aim is to collect ECoG data in an unrestrained baboon to better understand the diurnal pattern of their seizures and to develop a seizure-detection algorithm. The second aim is to utilize closed-loop stimulation to disrupt the epileptic network responsible for generalized seizures. In this study, we aim to provide a proof of concept for the adaptation of responsive neurostimulation in the baboon and its applicability as a therapy for GGE. We will implant up to three epileptic baboons, either unilaterally or bilaterally, with the RNS[®] System. The baboons will be released into group cages in a specialized housing unit at the Texas Biomedical Research Institute (TBRI), where they will be separated from other baboons on a daily basis during feeding. This will enable downloading of ECoG data related to suspected ictal events. We will correlate these ictal events with behavioral changes on simultaneous video-recording to establish the sensitivity and specificity with respect to generalized tonic-clonic seizures (GTCS). Over the first month, we will collect ECoG data for analysis and the development of seizure detection algorithms. The EEG data will be downloaded from the neurostimulators, then uploaded to NeuroPace servers for analysis. The customized ictal detectors will be programmed into the neurostimulators as a basis for responsive neurostimulation for one-to-two months. Up to two locations can be targeted by each device, or up to four with two devices. Targets for stimulation may vary between baboons, but the goal will be to optimize recording and stimulation parameters. The efficacy of neurostimulation will be evaluated for the different seizure types exhibited by the baboon, including myoclonic, absence and GTCS. In addition to the seizure outcomes, behavioral effects of therapy will also be assessed.

Relevance: This study represents a new collaboration between researchers from two departments at the UTHSCSA (Neurology and Neurosurgery), two research facilities in San Antonio (UTHSCSA and TBRI), and between an academic center and private companies (UTHSCSA and NeuroPace, Inc., CA). This collaboration provides the technology, clinical and research skill set, and animal housing infrastructure required for such a complex task.

This will be the first study to sample ECoG in unrestrained epileptic baboons, providing important data on their baseline seizure frequency, the diurnal pattern of seizure activity, and their behavior and social interactions. This will be the first study to develop a seizure detection algorithm for responsive neurostimulation in a nonhuman primate, with an epilepsy syndrome resembling a common type of GGE in humans, namely juvenile myoclonic epilepsy. This study will not only evaluate the feasibility of seizure detection in this model using cortical and subcortical sites, but also the effectiveness of stimulation at different targets. In addition to evaluating the seizure outcomes, we will also obtain pilot data on potential behavioral effects of seizure reduction. Preliminary data will provide a framework for a larger study for optimization of cortical or subcortical targets and evaluation of long-term effects of neuromodulation.

As the principal investigator, Dr. Szabo (UTHSCSA) will provide direction regarding targets for electrode placement, initial analyses of ECoG and video data, collaborate with NeuroPace on the evaluation of seizure detection data and the implantation of responsive neurostimulation, and supervise analysis of seizure and behavioral outcome. Drs. Papanastassiou (UTHSCSA) and Shade (TBRI) will implant the RNS[®] Neurostimulator and leads using a stereotactic device and will oversee the perioperative care. Dr. Li (TBRI) will supervise the baboons, video recordings, downloading and transfer of ECoG data, and behavioral assessments by the postdoctoral fellow. Nick Hasulak (NeuroPace) and his research team will be responsible for the analysis of ECoG data uploaded to NeuroPace, and the development of the seizure detection algorithm and stimulation parameters.