Experimental Neurology 294 (2017) 68–77

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Effects of hippocampal low-frequency stimulation in idiopathic non-human primate epilepsy assessed via a remote-sensing-enabled neurostimulator

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ARTICLE INFO

Article history:
Received 5 September 2016
Received in revised form 28 April 2017
Accepted 6 May 2017
Available online 7 May 2017

Keywords:
Epilepsy
Hippocampus
Local field potential
Non-human primate
Electrical stimulation
Low-frequency stimulation
Open-loop stimulation
Closed-loop stimulation
Deep brain stimulation
Sensing-enabled neurostimulator

ABSTRACT

Individuals with pharmacoresistant epilepsy remain a large and under-treated patient population. Continued technologic advancements in implantable neurostimulators have spurred considerable research efforts directed towards the development of novel antiepileptic stimulation therapies. However, the lack of adequate preclinical experimental platforms has precluded a detailed understanding of the differential effects of stimulation parameters on neuronal activity within seizure networks. In order to chronically monitor seizures and the effects of stimulation in a freely-behaving non-human primate with idiopathic epilepsy, we employed a novel simultaneous video-intracranial EEG recording platform using a state-of-the-art sensing-enabled, rechargeable clinical neurostimulator with real-time seizure detection and wireless data streaming capabilities. Using this platform, we were able to characterize the electrographic and semiologic features of the focal-onset, secondarily generalizing tonic-clonic seizures stably expressed in this animal. A series of acute experiments exploring low-frequency (2 Hz) hippocampal stimulation identified a pulse width (150 μs) and current amplitude (4 mA) combination which maximally suppressed local hippocampal activity. These optimized stimulation parameters were then delivered to the seizure onset-side hippocampus in a series of chronic experiments. This long-term testing revealed that the suppressive effects of low-frequency hippocampal stimulation 1) diminish when delivered continuously but are maintained when stimulation is cycled on and off, 2) are dependent on circadian rhythms, and 3) do not necessarily confer seizure protective effects.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting approximately 0.4–1% of the global population. Mesial temporal lobe epilepsy (MTLE) is the most common form of focal epilepsy and the most likely to be resistant to medical therapy, with at least one third of patients failing either mono or poly pharmacotherapy (see Duncan et al., 2006 for summary). For this population, resective surgery has long remained the only definitive treatment option, offering roughly two thirds of patients freedom from debilitating seizures (Spencer et al., 2005; Tellez-Zenteno et al., 2005; Wiebe et al., 2001; Wieser et al., 2003). Individuals who are not seizure free after surgery, and those unsuitable for resective surgery due either to lack of a single identifiable seizure focus or unacceptably high risk for neurologic deficit secondary to resection, have historically been without adequate treatment options.

To address this unmet therapeutic need and to build upon prior successes in the treatment of movement disorders, direct brain stimulation for epilepsy has been the subject of considerable research effort. In contrast to resective surgery, direct brain stimulation is a less invasive intervention that is highly customizable for meeting the evolving treatment needs of an individual patient. Numerous neuroanatomical targets for electrical stimulation have been explored for the treatment of MTLE in humans, including the vagus nerve (DeGiorgio et al., 2000), anterior nucleus of the thalamus (Fisher et al., 2010; Lee et al., 2012; Lehtimaki et al., 2015; Salanova et al., 2015), fimbria/fornix (Koubeissi et al., 2013),

Abbreviations: DBS, deep brain stimulation; EEG, electroencephalogram; ERP, event-related potential; FFT, fast Fourier transform; HFS, high-frequency stimulation; LFP, local field potential; LFS, low-frequency stimulation; LL, line-length; MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; NHP, non-human primate; RNS, Responsive Neurostimulation; SANTE, Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy.

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http://dx.doi.org/10.1016/j.expneurol.2017.05.003

and the mesial temporal lobe itself (Boëx et al., 2011; Cukiert et al., 2014; Lim et al., 2016; McLachlan et al., 2010; Min et al., 2013; Tellez-Zenteno et al., 2006; Velasco et al., 2007; Vonck et al., 2002, 2013; see Han et al., 2014 for review). Two large-scale, long-term clinical trials of direct brain stimulation therapies for epilepsy have already been conducted: 1) the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial (Fisher et al., 2010; Salanova et al., 2015) delivered stimulation in an open-loop paradigm, in which predetermined stimulation is delivered regardless of brain state, whereas 2) the Responsive Neurostimulation (RNS) Pivotal Study (Bergey et al., 2015; Heck et al., 2014) utilized closed-loop stimulation, which is modified in response to ongoing monitoring of neural activity, delivered to clinically-determined, patient-specific cortical and/or deep brain targets. While promising results of approximately 69% (SANTE) and 60% (RNS) reduction in seizure frequency after five years were reported, only a minority of participants became seizure-free.

Numerous obstacles hinder the rapid optimization of electrical stimulation therapies. Perhaps one of the greatest barriers to advancement is the vast, multi-dimensional space of stimulation parameters to be explored. Frequency, pulse width, and amplitude (Fig. 1A) are among the most commonly operationalized variables. Each of these parameters differentially effects neuronal activity and, in addition to cumulative stimulation ON time, contributes to the total electrical current requirements. Further limiting improvements in stimulation therapies is the lack of adequate platforms for stimulation testing – many rodent models of epilepsy have been developed but the translational utility of these models remains a subject of debate. On the other hand, while non-human primates (NHP) better recapitulate human neurophysiology and functional neuroanatomy, there is a relative paucity of NHP research in epilepsy, and testing in humans is often constrained by financial, logistical, and ethical considerations. As a result of these obstacles, the preponderance of stimulation studies in epilepsy have followed the precedent established by early work in movement disorders surgery demonstrating the acutely suppressive effects of high-frequency stimulation (HFS, >60 Hz) on neuronal synchrony. Low-frequency stimulation (LFS, <10 Hz) has consequently remained under-explored despite its theoretically lower current requirements and its demonstrated success in reducing seizure frequency and severity in multiple rodent models (summarized in Han et al., 2014). Further indicating the need for continued investigation, recent studies have demonstrated reductions in interictal epileptiform activity and seizure frequency as well as improvements in cognitive functioning with LFS (Koubeissi et al., 2013; Lim et al., 2016; Toprani and Durand, 2013; Toprani et al., 2013; Wang et al., 2016).

An additional challenge to the advancement of stimulation therapies is the absence of suitable biomarkers indexing stimulation efficacy, which are observable at short latencies. While stimulation programing in Parkinson's and essential tremor benefits, for instance, from the near immediate reduction in tremor amplitude following HFS, the gold standard for measuring therapeutic benefit in epilepsy remains the observed seizure frequency. Quantifying this effect necessitates long-term follow-up resulting in lengthy research trials and extended periods of clinical device programming. Indeed, clinical stimulation programming is currently conducted through an iterative process of individual parameter adjustment followed by observation of the change's effect on seizure rate. During this protracted process, patients may receive suboptimal seizure control and experience accelerated battery consumption, with some groups reporting implanted device lifespans as short as nine months (Lee et al., 2015). Closed-loop stimulation also relies on short-latency biomarkers to modulate stimulation delivery. While the RNS device has demonstrated success with power-based measures of local-field potential (LFP) activity in general, and the measure of line-length in particular, identification of signal features which better distinguish pathologic from physiologic brain states stands to improve the accuracy of stimulation delivery.

In order to investigate the effects of LFS in the mesial temporal lobe of an NHP with idiopathic epilepsy, we used a next-generation sensing-enabling brain stimulation device with wireless telemetry capability (Freestone et al., 2013; Stypulkowski et al., 2013, 2014) to create a chronic, simultaneous video-intracranial EEG monitoring platform. This implanted rechargeable clinical neurostimulator capable of simultaneous stimulation and real-time, wireless LFP recording allowed for long-term recordings in the freely behaving animal. We built upon our prior study in this animal (Lipski et al., 2015) by further characterizing both the electrographic and semiologic correlates of the NHP's clinical seizures. Next, a series of acute experiments explored the differential effects of pulse width and current amplitude on the neural response to LFS. The results from these acute experiments were then used to guide stimulation parameter selection for further exploration in a set of chronic experiments. We hypothesized that this approach would reveal potential avenues for expediting the optimization of stimulation therapies on a patient-specific basis.

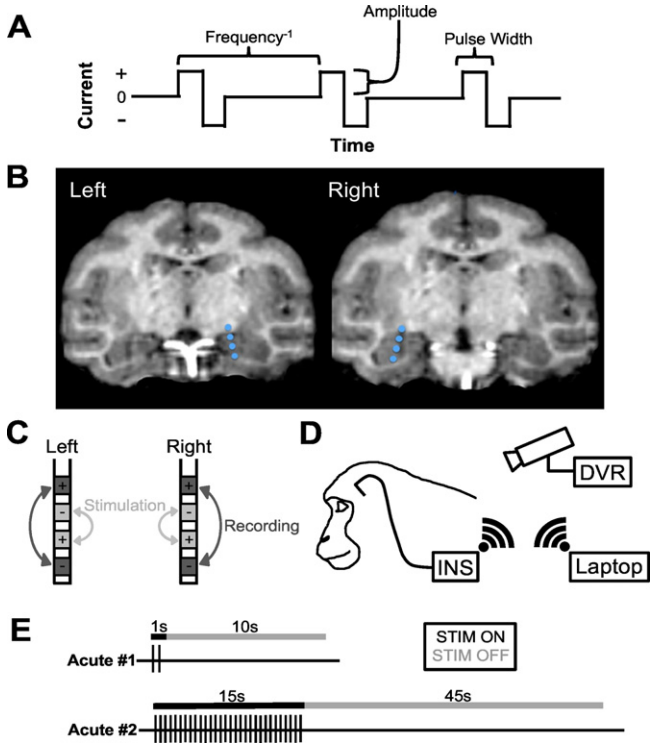

Fig. 1. Experimental design. Panel A is a schematic representation summarizing stimulation parameters of interest. Panel B shows the preoperative 3 T MRI with electrode contact locations represented by blue circles, in the two coronal planes that best matched the lead trajectories, overlaid from the intraoperative MRI (not shown). Panel C depicts the recording-stimulating bipolar montage (arrows indicating paired electrode contacts) used for both depth electrodes. "+" and "−" represent cathode and anode, respectively. The experimental setup is summarized in panel D, with intracranial electrodes connected to an implanted neurostimulator (INS) which wirelessly communicates with a laptop outside of the animal's enclosure. In parallel, a digital video recording (DVR) system continuously records the animal's behavior. Organization of single trials of stimulation trains in acute experiments 1 & 2 is shown in panel E – the x-axis is time and vertical lines indicate stimulation pulses.

2. Materials and methods

2.1. Animal

One eight-year-old male NHP (*Macaca mulatta*; 10 kg) exhibiting spontaneous, recurrent seizures for >3 years was studied. Prior to inclusion in this study, the NHP was raised in captivity as part of a behavioral study in which no other animals developed epilepsy. No pharmacologic,