Brain Stimulation 6 (2013) 718–726

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Long-Term Measurement of Impedance in Chronically Implanted Depth and Subdural Electrodes During Responsive Neurostimulation in Humans

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ARTICLE INFO

Article history:
Received 5 October 2012
Received in revised form
7 February 2013
Accepted 20 February 2013
Available online 26 March 2013

Keywords:
Epilepsy
Responsive neurostimulation
Impedance
Current-controlled stimulation
Electrode–tissue interface

ABSTRACT

Long-term stability of the electrode–tissue interface may be required to maintain optimal neural recording with subdural and deep brain implants and to permit appropriate delivery of neuromodulation therapy. Although short-term changes in impedance at the electrode–tissue interface are known to occur, long-term changes in impedance have not previously been examined in detail in humans. To provide further information about short- and long-term impedance changes in chronically implanted electrodes, a dataset from 191 persons with medically intractable epilepsy participating in a trial of an investigational responsive neurostimulation device (the RNS® System, NeuroPace, Inc.) was reviewed. Monopolar impedance measurements were available for 391 depth and subdural leads containing a total of 1564 electrodes; measurements were available for median 802 days post-implant (range 28–1634). Although there were statistically significant short-term impedance changes, long-term impedance was stable after one year. Impedances for depth electrodes transiently increased during the third week after lead implantation and impedances for subdural electrodes increased over 12 weeks post-implant, then were stable over the subsequent long-term follow-up. Both depth and subdural electrode impedances demonstrated long-term stability, suggesting that the quality of long-term electrographic recordings (the data used to control responsive brain stimulation) can be maintained over time.

Introduction

Devices for monitoring and stimulating the brain

Devices for electrically interfacing with the brain have generated considerable interest for treating a wide variety of neurological disorders. These devices range from penetrating arrays of microelectrodes for recording and extracting movement intent [1] to macroelectrodes for localizing seizure foci [2]. Implantable devices have also been utilized for electrical stimulation of neural tissues, from microscale stimulation for auditory perception in rodents [3] to macroscale deep brain stimulation for treatment of Parkinson's

Financial disclosures: Dr. Sillay reports no relevant biomedical financial interests or conflicts of interest. Dr. Rutecki owns stock in Cyberonics. Ms. Cicora, Dr. Morrell, and Dr. Wingeier are employees of NeuroPace and own stock and stock options in the company; Drs. Morrell and Wingeier also have patents and patent applications relevant to neurostimulation. Dr. Worrell disclosed consulting and scientific advisory board membership for NeuroVista, and consulting and funded research for Medtronic. Dr. Drazkowski reports no relevant biomedical financial interests or conflicts of interest. Dr. Shih reports having received research funding from Eisai Inc. and Visualase Inc. Dr. Sharan reports grant support and consulting fees from St. Jude, consulting for Medtronic, grant support from Boston Scientific, consulting for NLT Spine, stock ownership in ICVrx and Integrated Care Pharmacy, and royalty payments from Zimmer. Dr. Williams reports patents in the areas of electrocorticography and implantable brain electrodes. Finally, Drs. Sillay, Rutecki, Worrell, Shih, Drazkowski, and Sharan participated as investigators in the NeuroPace RNS® System pivotal trial. Source(s) of financial support: UW institutional startup funds.

Disclaimers: None.

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http://dx.doi.org/10.1016/j.brs.2013.02.001

disease in humans [4]. Closed-loop devices that can record signals from brain tissue and deliver or adapt stimulation based on these signals are of particular recent interest. Efforts here include responsive neurostimulation for epilepsy [5], bidirectional brain–machine interface [6], and closed-loop stimulation for Parkinson's disease [7].

The performance of closed-loop systems requires that clinically relevant signals be discernible in the electrographic data. The actual prominence of these clinically relevant signals depends on factors such as the functional synchrony and amount of tissue generating the activity, the distance between the electrodes and the generated electrical activity, the amount and character of spontaneous activity in the region, the electrical and geometric properties of the surrounding tissue, and the electrical properties, such as impedance, of the electrode–tissue interface. Performance of closed-loop neurostimulation also depends upon the design of depth or subdural electrodes [8,9] and the robustness of implantable algorithms to detect pathological electrographic activity in the presence of broad-spectrum background noise and drift in signal properties [10]. Fundamental to these issues is the requirement of a stable electrode–tissue electrical interface. Therefore, regardless of whether electrodes are used for recording or stimulation, the electrical properties of the electrode–tissue interface are critical to device performance.

Electrode–tissue instabilities with implanted microelectrodes are documented. The impedance of chronically implanted microelectrodes often changes in the weeks to months following implantation, presumably as a result of tissue remodeling at the electrode interface [11,12]. The time course of impedance change is similar to the time course of the general reactive gliosis response to electrode insertion and the chronic response to the ongoing presence of the device [12–15]. Reactive tissue and consolidated scar tissue have higher resistive properties than normal tissue [12,16]. These tissue and impedance changes could have significant impact on the functioning of microelectrodes by causing decreases in signal amplitude over time [1]. These changes can compromise the quality of electrographic recordings and the ability to resolve extracellular single-unit potentials [12].

Impedance and dynamics of the device–brain interface

Historically, researchers have used impedance measurements to assess a number of factors related to performance of implanted electrodes. Electrical impedance measurement methods are convenient in that they can be performed using the same interface connectivity that is used for electrical stimulation or recording. The low levels of current used in typical impedance measurements are well below the threshold for stimulating neural activation and also correspond to charge densities within the range considered safe to avoid electrode or tissue damage [17]. Traditionally, impedance has been used to test for electrode integrity; sudden large increases in impedance can indicate a connector or lead conductor failure and decreases can be caused by cracks in electrode insulation or moisture absorption by dielectric layers [18].

Changes in electrode impedance can alter the performance of implantable devices. For electrical stimulating devices, increases in electrode impedance can affect current delivery, device battery life, and stimulation thresholds [11,19–21]. Furthermore, the volume of tissue activation is dependent on the electrode–tissue interface impedance when using voltage-controlled stimulation [16,22].

Early neuroprosthetic devices could determine electrode discontinuity or device malfunction but could not make accurate measurements of electrode–tissue impedance [23,24]. Although developments in neurostimulator technology have made collection of impedance data technically possible, reports of impedance measured over the long term are sparse in the literature [25]. Information regarding electrode stability over time is required in order to predict the performance of devices that provide long-term electrographic monitoring and stimulation.

While there is extensive literature regarding chronic measurement of impedance at the electrode–tissue interface in other animals, there have been few studies of impedance change in humans. There are some reports of impedances in subcortical electrodes (deep brain stimulation devices) for treatment of Parkinson's disease, but little is known about the long-term impedance characteristics of depth electrodes in devices providing treatment for epilepsy with non-responsive stimulation in the thalamus [26], subthalamic nucleus [27,28], or hippocampus [29–31]. Furthermore, little is known about impedances of chronically implanted epidural or subdural cortical electrodes used in cortical stimulation devices for the treatment of pain [32], tinnitus [33], and movement disorders such as Parkinson's disease [34] and dystonia [35].

Mounting experimental and clinical evidence shows that impedances in depth electrodes that deliver neurostimulation change over the first two to three weeks after implant [36]. Currently available implantable devices can acquire low resolution impedance measurements during a patient's routine clinical visit. This has led to a number of studies that have reported variability in impedance trends over time and across patients in DBS electrodes [23,37]. Impedance of DBS electrodes has been shown to decrease reversibly with delivery of stimulation [23].

Known peri-implant tissue changes may correlate with changes in the modeled device–tissue interface [38], and with observed *in vivo* electrical reactance measurements [12] that suggest shifts in intracellular volume over time. Short-term implants of subdural and depth electrodes in patients undergoing evaluation for resective epilepsy surgery have been associated with infiltrates of T cells and eosinophils, most commonly in the perivascular and subarachnoid spaces, and the presence of microhemorrhages, astrocytes, and microglia. These changes, observed in the days and weeks after explantation, have been reported to be more extensive with subdural than with depth electrodes [39].

Early attempts to characterize depth electrode tissue response have also been reported in the movement disorders literature. Depth electrode–tissue response has been examined by light microscopy [40] and by electron microscopy in patients undergoing chronic neurostimulation for movement disorders [41], with findings of mild gliosis around the lead track without obvious evidence of stimulation-induced damage. Specifically, a foreign body multinucleate giant cell-type reaction was observed, containing highly electron-dense inclusions, which were inferred to represent phagocytosed material. The reaction was determined to be present irrespective of the duration of implantation, and was suggested to be a "response to the polyurethane component of the electrodes' surface coat" [41].

With this background, two preliminary studies have recently addressed impedance change and stability over time. A report of prospectively acquired impedance data found long-term stability of impedance; however, there were not sufficient data to draw conclusions regarding impedance during the dynamic peri-implant period [37]. Impedance over time has also been addressed in a small series of cortical and depth electrodes in the epilepsy population [42], suggesting that impedances are relatively stable over time and indicating that impedance of depth electrodes is typically lower and less subject to variability than impedance of subdural strip electrodes.

The current study provides acute and long-term longitudinal impedance measurements of both depth and subdural electrodes in a large cohort of patients with epilepsy who were participating in an investigational trial of a responsive neurostimulator.