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Changes in the electrocorticogram after implantation of intracranial electrodes in humans: The implant effect

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HIGHLIGHTS

- First-of-kind 2-year ECoG data from 121 patients treated with responsive cortical stimulation.
- Cortical spectral power and spike rate were not stable until 5 months after electrode implantation.
- Duration of ECoG changes similar to transient seizure reductions seen after electrode implantation.

ABSTRACT

Objective: Subacute and long-term electrocorticographic (ECoG) changes in ambulatory patients with depth and cortical strip electrodes were evaluated in order to determine the length of the implant effect.
Methods: ECoG records were assessed in patients with medically intractable epilepsy who had depth and/or strip leads implanted in order to be treated with brain-responsive stimulation. Changes in total spectral power, band-limited spectral power, and spike rate were assessed.
Results: 121 patients participating in trials of the RNS® System had a total of 93994 ECoG records analyzed. Significant changes in total spectral power occurred from the first to second months after implantation, involving 55% of all ECoG channels (68% of strip and 47% of depth lead channels). Significant, but less pronounced, changes continued over the 2nd to 5th post-implant months, after which total power became more stable. Similar patterns of changes were observed within frequency bands and spike rate.
Conclusions: ECoG spectral power and spike rates are not stable in the first 5 months after implantation, presumably due to neurophysiological and electrode-tissue interface changes.
Significance: ECoG data collected in the first 5 months after implantation of intracranial electrodes may not be fully representative of chronic cortical electrophysiology.

1. Introduction

Closed loop neuromodulation therapies for disorders of the brain and for brain computer interface devices rely on accurate electrophysiological measurements. These devices require that stimulation be delivered in response to detection of specific electrophysiological patterns and/or events. Whether using micro- or macro-electrode arrays, electrophysiological changes induced by the implantation procedure could alter electrophysiological patterns acutely. If this is the case, then initial detection and responsive stimulation settings could be selected that are not optimal for therapeutic efficacy over the longer term. An additional concern is that experiments based only on acute intracranial brain recordings may not reflect the baseline electrophysiology, thus providing data that does not accurately represent the chronic electrophysiological state.

Determining whether there are changes in the electrocorticographic (ECoG) signal over the initial months (subacute) or years (long-term) after the implantation of intracranial leads is important for diagnostic as well as therapeutic neurostimulation applications. In randomized controlled trials of closed loop cortical stimulation (RNS® System) and of open-loop scheduled stimulation of the anterior nucleus of the thalamus (Medtronic Activa®), patients with medically intractable partial onset seizures had 20–25% reduction from baseline in clinically reported seizures after placement of intracranial electrodes but before stimulation was enabled. The seizure reduction abated over time in patients randomized to sham stimulation, although there was not a complete return to the clinical seizure baseline during the 3 to 4 month

Abbreviations: DBS, deep brain stimulation; ECoG, electrocorticographic; Hz, hertz; ms, milliseconds.

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blinded periods (Fisher et al., 2010; Morrell, 2011). Other studies have also reported a reduction in seizure frequency in some patients that occurred after implantation of depth leads but prior to enabling stimulation (Hodaie et al., 2002; Valentin et al., 2013) or a reduction in seizure frequency that was maintained without stimulation (Velasco et al., 2006; Valentin et al., 2013). In addition, a trial of an investigational seizure advisory system using chronically implanted cortical strip leads (NeuroVista, Seattle, OR) provided similar observations of an acute implant effect (Cook et al., 2013). This implant effect could impact the reliability of ECoG data obtained during diagnostic procedures for localization of functional areas or the seizure focus (DiLorenzo et al., 2014b; King-Stephens et al., 2015) and could influence experiments that rely on acute ECoG recordings. Similarly, in a therapeutic application where a brain-computer interface controls a prosthetic, it is important that the control signals, i.e., ECoG signals, be stable over the long term. If they are not, long-term system performance may be suboptimal (Polikov et al., 2005).

The RNS System (NeuroPace, Inc., Mountain View, CA) provides closed loop, responsive brain stimulation for adjunctive treatment of medically intractable partial onset seizures. Depth and/or cortical strip macroelectrodes are placed at the patient's seizure focus or foci. ECoG data is obtained and stored, and the neurostimulator is programmed by the physician to provide stimulation in response to specific ECoG patterns identified by the physician. Detection algorithms and stimulation parameters are subsequently adjusted according to the patient's clinical response and the ECoG data. The RNS System provides the largest dataset to evaluate the stability of ECoG activity in ambulatory persons both acutely and over years.

ECoG data acquired by the RNS System in patients with medically intractable partial onset seizures was evaluated to determine the length of time until the ECoG signal was stable. Interictal ECoG records were analyzed to determine whether there were quantitative changes over months and years. The intent was to objectively determine whether acute or chronic electrophysiological changes occur with implantation of leads, and if so, whether the changes are different with depth or with strip leads, and whether the duration of the effect is measurable.

2. Methods

2.1. Data

ECoG data were collected from patients participating in a double-blind, randomized, sham-stimulation controlled trial of a responsive neurostimulator (RNS® System), now approved by FDA as an adjunctive treatment for adults with medically intractable partial onset seizures from 1 or 2 foci (Morrell, 2011; Heck et al., 2014). All subjects provided informed consent at the time of participation in the trial. An RNS® Neurostimulator was placed within a craniotomy and depth and/or cortical strip leads were placed at one or two seizure foci. One month after implant, subjects were randomized to receive responsive or sham stimulation for four months, after which all subjects entered an open-label period and were able to receive responsive stimulation through 2 years. Antiepileptic medications were held constant over the first 5 months after implantation. The design, methods, patient selection criteria, and results of this study were previously published (Heck et al., 2014; Morrell, 2011).

2.2. System overview

The RNS System provides brain-responsive stimulation via a cranially implanted programmable neurostimulator connected to 1 or 2 recording and stimulating depth and/or cortical strip leads that are surgically placed in the brain according to the seizure focus (Sun and Morrell, 2014). Each lead contains 4 electrodes with surface areas of 0.08 cm^2. The neurostimulator continually senses ECoG activity through the electrodes and is programmed by the physician to detect specific patterns in the ECoG, such as epileptiform discharges or patterns characteristic of the onset of an electrographic seizure. When the neurostimulator detects one of these patterns, it responds by providing brief pulses of electrical stimulation in order to disrupt the activity. The typical patient receives about 100–200 ms bursts of stimulation per day, for a total stimulation time of 5.9 min per day on average.

The neurostimulator stores brief segments of ECoG activity, typically 90–180 s of 4-channel data, where each channel represents the electrographic signal sensed using a bipolar electrode configuration bandpass-filtered at 4–90 Hz and sampled at 250 Hz. ECoG records are stored based on physician-specified triggers such as a detected event, a magnet swipe by the patient, or the time of day (referred to as "scheduled" ECoG records). Subjects download the neurostimulator data with a remote monitor and transmit this via the internet to a secure database for review by the healthcare provider.

2.3. Analyses

Analyses were performed on scheduled ECoG records stored over the first 2 post-implant years. Each ECoG record was typically 90–180 s of 4-channel data. To ensure that within-subject data were longitudinal, only ECoGs from subjects who had at least 100 scheduled ECoG records stored over a period of at least one year were included. Scheduled ECoG records provide a daily snapshot of ECoG activity that is independent of neurostimulator detection and stimulation settings. Records containing detections of events with duration >10 s were not included in the analysis in order to exclude ECoG samples that could represent an electrographic seizure.

The following was calculated for each channel within each ECoG record: total spectral power, normalized spectral power within the delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), low gamma (25–50 Hz), and high gamma (50–125 Hz) frequency bands, and spike rate.

Total spectral power was calculated by integrating the power spectral density over all frequencies (0–125 Hz) where the power spectrum was estimated using Welch's periodogram method. Normalized spectral power within each frequency band of interest was calculated by dividing the spectral power within each frequency band by the total spectral power.

Two different methods were used to estimate the spike rate. In the first method, spikes were identified using half-waves, similar to the algorithm described by Gotman and Gloor (1976). ECoG data were filtered from 5–50 Hz using a 4-pole Butterworth band-pass filter and segmented into half-waves based on local minima and maxima. Waveforms were identified as spikes when two consecutive half-waves met the following criteria: for the first half-wave, a minimum amplitude of 4x the baseline amplitude (which is the average half-wave amplitude of the entire ECoG) and a maximum duration of 150 ms, where the ratio of the relative amplitude to the pseudo-duration must have been at least 8/100 (based on points B and C in Fig. 3 of Gotman and Gloor, 1976); and for the second half-wave, a minimum amplitude of 4x the baseline amplitude with a maximum duration of 240 ms, where the ratio of the relative amplitude to pseudo-duration must have been at least 7/90 (based on points E and F in Fig. 3 of Gotman and Gloor, 1976).

In the second method, spikes were identified based on the method described by Donoho and Johnstone (1994) when the signal amplitude exceeded a threshold based on an estimate of the background activity level (Donoho and Johnstone, 1994). In this

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