Implanted Electrodes for Multi-Month EEG

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***Abstract*— An implanted electroencephalogram (EEG) recorder would help diagnose infrequent seizure-like events. A proof-of-concept study quantified the electrical characteristics of the electrodes planned for the proposed recorder. The electrodes were implanted in an ovine model for eight weeks. Electrode impedance was less than 800 Ohms throughout the study. A frequency-domain determination of sedation performed similarly for surface versus implanted electrodes throughout the study. The time-domain correlation between an implanted electrode and a surface electrode was almost as high as between two surface electrodes (0.86 versus 0.92). EEG-certified clinicians judged that the implanted electrode quality was adequate to excellent and that the implanted electrodes provided the same clinical information as surface electrodes except for a noticeable amplitude difference. No significant issues were found that would stop development of the EEG recorder.**

I. Introduction

An EEG (electroencephalogram) is the only definitive test to diagnose epilepsy [1]. Approximately one percent of patients treated for epilepsy has seizure-like symptoms infrequently, possibly months apart [2]. Also, a seizure cannot be induced in these patients in the clinic during an EEG session. Although these patients cannot be diagnosed as epileptic without EEG confirmation, their activities are restricted as if they are epileptic and they receive anti-epilepsy drugs that have many side effects [3]. These patients have an unmet need for an EEG recorder that operates continuously while not impeding their day-to-day life. The proposed medical device in Fig. 1 may fulfill this need.

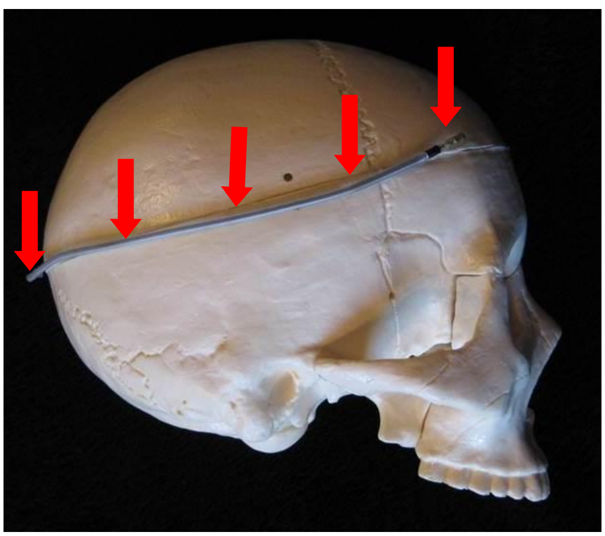

Figure 1. Model of proposed implanted EEG recorder. The entire device consists of a flexible cylinder 3 mm in diameter and 200 mm long that is inserted below the scalp and above the skull. Five 10 mm long cylindrical electrodes (not shown) would be evenly spaced along the axis of the device (red arrows). The voltage between adjacent electrodes would be acquired to create four traces of bipolar EEG.

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The electrodes in the proposed device are in a shape and location not found in any other implanted medical device. The clinical use of EEGs acquired from deep in the scalp is not in question as needle electrodes are commonly inserted there [4]. However, the foreign body reaction [5] over many weeks may degrade the electrical characteristics as has happened in other neural electrodes [6]. This proof-of-concept study quantifies the changes in electrical characteristics of the proposed electrodes when implanted in an ovine model for eight weeks.

II. Methods

A. Electrode Construction

The electrodes were part of the custom-built assembly (Sonometrics Corp., London, Ontario, Canada) in Fig. 2. Two wires in each lead were welded to different sites on the interior of the electrode. Open or shorted leads could be detected (none were) by a change in the round-trip resistance of the wires from the connector to the electrode and back.

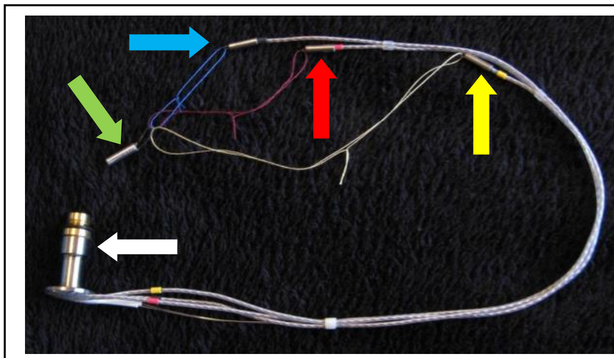

Figure 2. Electrode assembly. The implanted electrodes are 2.8 mm diameter by 10 mm long cylinders of type 304 stainless steel. The three electrodes are "front" (blue arrow), "back" (red arrow), and "reference" (yellow arrow). The lead for each electrode is a silastic-coated shielded twisted pair. Electrical connection from the electrodes to the EEG instrumentation is via the percutaneous connector (white arrow). The introducer cap (green arrow) and threads pulled the electrodes into place during surgery. The cap and threads were removed when the electrodes were positioned properly.

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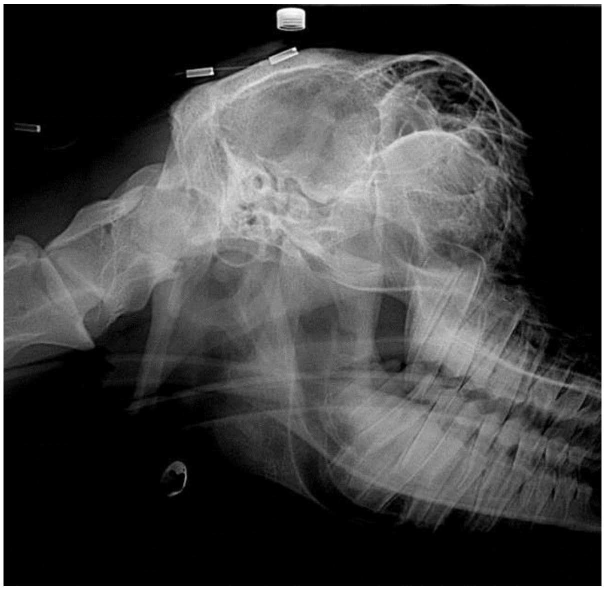
Figure 3. X-ray of the right side of sheep #2. The front electrode appears coincident with the top edge of the skull. The back electrode is to the left of the front electrode. The reference electrode is near the upper left edge of the x-ray. The electrodes were ~1 cm to the right of the midline. The metal cap at the top center of the x-ray was placed on the external surface of the head directly above the front electrode to help visualize the thickness of the scalp.

B. Electrode Implantation

The animal study protocol was approved by the Duke University Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals.

The surgery followed aseptic technique. The electrode assembly and all custom surgical tools were gas sterilized.

An adult ~70kg female suffolk sheep was sedated with ketamine hydrochloride (~40 mg/kg) and anesthetized with 1-5% isoflurane. An endotracheal tube and ventilator maintained breathing. An orogastric tube prevented rumen aspiration. An IV line (20-22 ga catheter) was placed in a leg to supply 0.9% NaCl at 5-10 ml/kg/hr. Blood gases, breathing, blood pressure, temperature, and ECG were monitored. Incisions were made through all skin layers at 1 cm to the right of the midline. The incisions were 2 cm long at the front electrode site (Fig. 3), 4 cm long at the reference electrode site, and 3 cm at the percutaneous connector site which was between the scapulae. A custom introducer and sheath was tunneled from the reference electrode site to the connector site. The introducer cap (Fig. 2) was attached to the introducer, and the introducer extracted thus pulling the electrode assembly through the sheath. The electrode assembly was pulled until the flange at the base of the percutaneous connecter passed through the incision. The sheath was pulled out of the reference electrode site, leaving the electrode assembly under the skin. The tunneling procedure was repeated between the front electrode site and the reference electrode site to finish the placement of the electrode assembly. The front electrode and the connector flange were sutured to the lowest skin layer. The layers of skin were individually closed with absorbable sutures, taking special precaution for a tight fit around the base of the percutaneous connector. Buprenorphine was the post-surgery analgesic (~0.01 mg/kg at 12-hour intervals for a day). Ceftiofur HCl was the post-surgery antibiotic (2.2 mg/kg daily for 3 days).

C. Data Collection

A data collection session was held at two-week intervals starting the second week after surgery. A session was also held one week pre-surgery with surface electrodes attached above the eventual site of the implanted electrodes.

The sheep was supported by a sling during the measurement session. The total time in the sling was under an hour with actual data collection strictly limited to a half hour to protect the welfare of the subject.

Prior to data collection, surface electrodes were attached ~1 cm to the left of the midline axially symmetric to the implanted electrodes. Gold-plated 10 mm cup electrodes (Grass Technologies, Warwick, RI) were filled ~2 mm beyond the cup lip with Ten20 conductive gel (Weaver and Co., Aurora, CO) and securely taped to shaved, abraded (NuPrep, Weaver and Co.), and alcohol-wiped skin.

At the beginning and end of each data collection, the electrode impedance was measured by forcing a small current (10 Hz, 10 to 20 nArms) into the electrode and comparing the resulting voltage to the voltage across a one kOhm resistor conducting the same current.

The middle of the session was broken into three sections: pre-sedation, sedation, and post-sedation. Sedation is not necessary to characterize the implanted electrode. However, sedation produces a known EEG response [7] regardless of the restlessness of the sheep. In addition, a sheep does not shake, chew, or blink during sedation so the EEG quality is improved. Propofol (2 mg/kg) was injected via an IV line to induce sedation. Blood oxygenation, ECG, and temperature were monitored. Breathing was not assisted.

Finally, if there was time, all the surface electrodes were squeezed together and the percutaneous connector unfastened. The noise baseline of the instrumentation could be measured once the amplifiers settled.

The electrode voltages were amplified by 100X with a bandwidth of 0.1 to 100 Hz (Iso-DAM8A, WPI Inc., Sarasota, FL) followed by a 1 kHz 16-bit 50-mV-full-scale analog-to-digital conversion with 0.15 to 100 Hz pre-filter and power-line harmonics removal digital post-filter (PowerLab 16/35, ADInstruments, Colorado Springs, CO). The raw conversion data was saved for off-line plotting and correlation analysis. The conversion data was analyzed on-line to continuously plot the EEG power in the five standard EEG frequency bands (delta, theta, alpha, beta, and gamma). The time-domain voltage data was divided into 8.192 second epochs (that is, 2^{13} samples), a Fast Fourier Transform performed to get the total spectral data within each epoch, and the root-mean-square voltage calculated in each of the frequency bands. The analysis software was LabChart7 (ADInstruments). The on-line spectral data was another safety monitor of the subject. The spectral data was saved for off-line plotting and state-change analysis.

A video recording of the sheep, synchronized to the data collection, enabled off-line determination of movement artifacts in the EEG data and of the duration of pre- and post- sedation periods.

D. Data Analysis

State Change. The change in the power in specific EEG frequency bands is sometimes used to determine a change of mental state [8]. For this study, the ability of the implanted electrodes to detect the change in the theta band power due to sedation was analyzed. The response of the implanted electrodes was compared to the response from the surface electrodes. This step controls for session-by-session variation in depth of sedation. In addition, the subject might have an inherent left-versus-right mismatch in the response, so the post-surgery response was normalized to the pre-surgery response (when the right side had a surface electrode instead of an implanted electrode). The comparison and normalization steps are taken as ratios but, because the power is expressed in dB, the ratios are calculated as subtractions.

Correlation. The raw voltage data for the implanted electrode was correlated to that of the surface electrode in each 8.912-second epoch using Excel (Microsoft Corp, Redmond, WA). Only the pre- through post-sedation portion of the measurement session was considered.

Clinician Survey. For each sheep, the deepest minute of sedation was found by the lowest power in the gamma band. The raw voltage data (that is, the traditional EEG signal) during this minute was plotted using LabChart7. The plot had waveforms from all four electrodes but did not have labels indicating implanted versus surface electrodes. Clinicians who are board-certified in EEG viewed the plots and answered questions on the quality of the EEG and differences among the four waveforms.

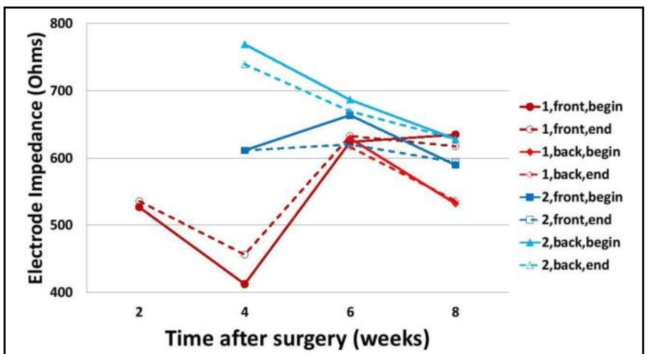

Figure 4. Impedance of implanted electrodes. The legend for the curves gives the sheep number (1 or 2), the electrode location (front or back), and measurement time (begin or end of session). The low impedance values for weeks 2 and 4 of sheep #1 may be an artifact of increasing the measurement current from 10nArms to 20nArms for all subsequent readings. No measurement was done at week 2 of sheep #2. All impedance values are below the clinical guideline of 5000 Ohms. Impedance did not trend upwards, so foreign body reaction caused no degradation in the two months under study.

III. Results

A. Electrode Impedance

The impedance results are shown in Fig. 4. Impedance was less than 800 Ohms throughout the study.

B. Spectrograms

An example of the data that was monitored during the measurement session is shown in Fig. 5. An entire half hour session is shown in the form of a spectrogram, which has time on one axis (the vertical axis in Fig. 5), frequency on the other axis, and amplitude indicated by color.

The sheep was sedated during the period that the gamma band was low (blue) and the theta band was high (red). This period was verified as sedation by the video which shows the sheep head lowering until supported by its halter and all movement ceasing other than breathing.

Deep blue at the bottom of the figure indicates that the

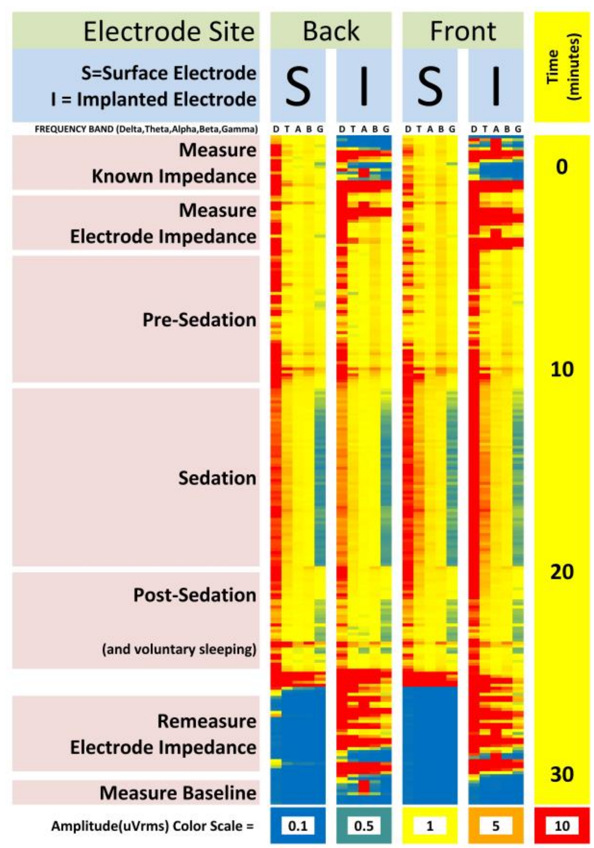

Figure 5. Spectrogram of the EEG from the four electrodes on Sheep #2 at 8 weeks post-surgery. Each of the four spectrograms is divided into five frequency bands (delta 0.2 to 4 Hz, theta 4 to 8 Hz, alpha 8 to 13 Hz, beta 13 to 30 Hz, and gamma 30 to 50 Hz). The tasks during the half-hour session are listed in the pink boxes along the left edge. The time axis is in the yellow box along the right edge. The color scale for the amplitude of the voltage within the frequency bands is given along the bottom edge. The surface electrodes were on the left side of the head and the implanted electrodes on the right. The spectrograms from all four electrodes are similar except during impedance measurements.

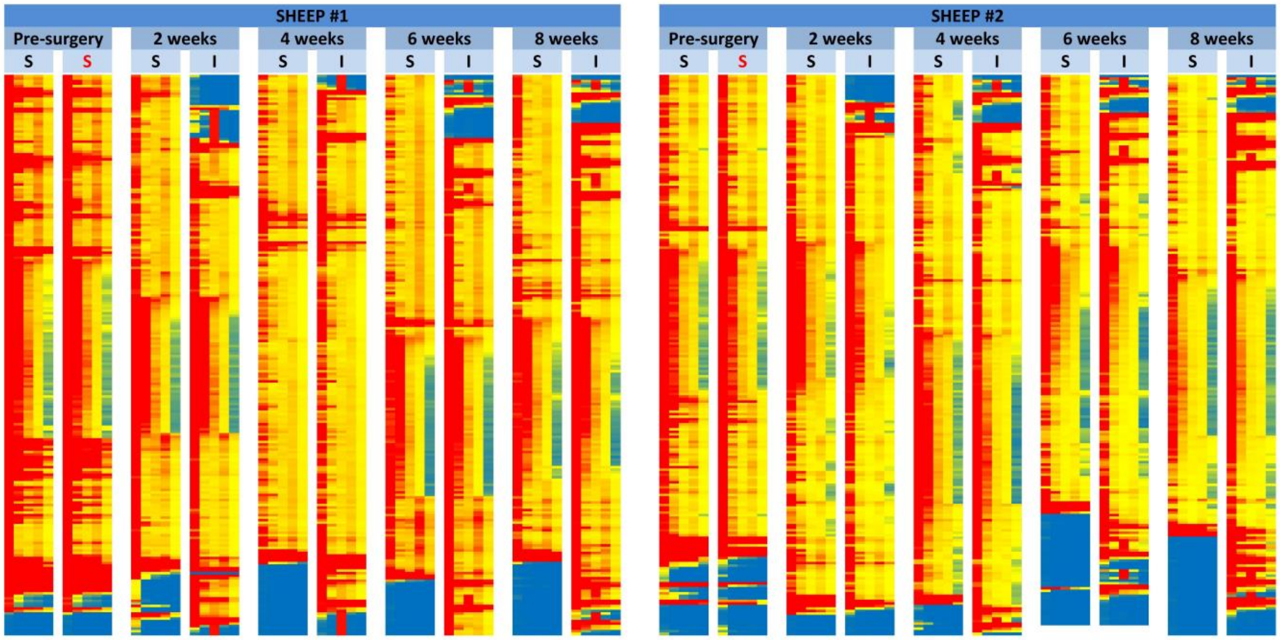

Figure 6. Spectrograms of the EEG from the front electrodes on both sheep. Time, amplitude, and frequency-band formats are the same as in Fig. 5. Measurements were taken pre-surgery and at 2, 4, 6, and 8 weeks post-surgery. The right-hand column of pre-surgery data is labeled at the top with a red "S" to indicate that the spectrogram came from a surface electrode located above the eventual site of the implanted electrode; the other columns have "S" or "I" as in Fig. 5. Spectrograms from the back electrodes are not shown but these were substantially the same as from the front electrodes (see Fig. 5 for examples of spectrograms from back electrodes). The sedative was not effective on week 4 of sheep #1 because the IV line was dislodged by sudden sheep movement at the beginning of the injection. Sheep #2 fell asleep several times during pre- and post-sedation periods as seen by sporadic low gamma voltages (green-blue on right edge of spectrograms) accompanied by low delta voltages (orange-yellow on left edge). The similarity of spectrograms from surface versus implanted electrodes did not vary with sheep or with duration of healing.

noise baseline was under 0.1 uVrms in each band.

Spectrograms for the entire study are shown in Fig. 6.

C. State Change

The results of the state-change analysis are in Fig. 7. The front electrodes have less variation than the back electrodes.

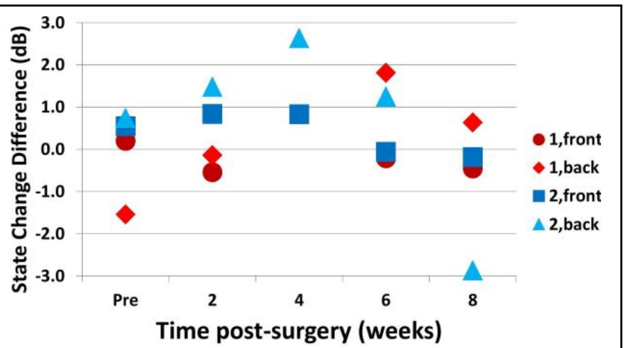

Figure 7. Comparison of detection of mental state by implanted electrodes versus by surface electrodes. The theta band voltage increased upon sedation by 9 dB (average). The theta increase from the implanted electrodes minus the theta increase from the surface electrodes is plotted. The legend for the data markers shows the sheep number (1 or 2) and the electrode location (front or back). Week 4 for sheep #1 had no data because the sheep was not sedated. The pre-surgery data used only surface electrodes and provides a basis to judge the post-surgery data. The difference between implanted and surface electrodes is small relative to the theta increase. All four electrodes could detect the state change.

D. Correlation

Correlation plots of the front electrodes for sheep #2 are shown in Fig. 8. The spectrogram is included to ease visualization that the high correlation region (red) aligns to the sedation period (blue in the gamma band). The surface-versus-surface correlation is slightly higher (i.e. more red and peak of 0.92) than the surface-versus-implanted correlation (peak of 0.86).

E. Clinician Survey

The results from two of the questions on the clinician survey are shown in Table 1. The other questions in the survey were short-answer essays that cannot be tabulated (but are available upon request).

IV. Discussion

The electrode impedance (Fig. 4) is less than a fifth of the clinical guideline of 5000 Ohms [9]. The implanted electrodes could be smaller which will increase the flexibility of the device.

The front electrodes performed better than the back electrodes in detecting the state-change (Fig. 7). The front electrodes were above the cerebrum and the back electrodes were above the cerebellum. An EEG is rarely taken from the cerebellum. In some animal studies, the cerebellum is considered inactive and the reference electrode is placed there. The cerebellum will not be used in future studies.

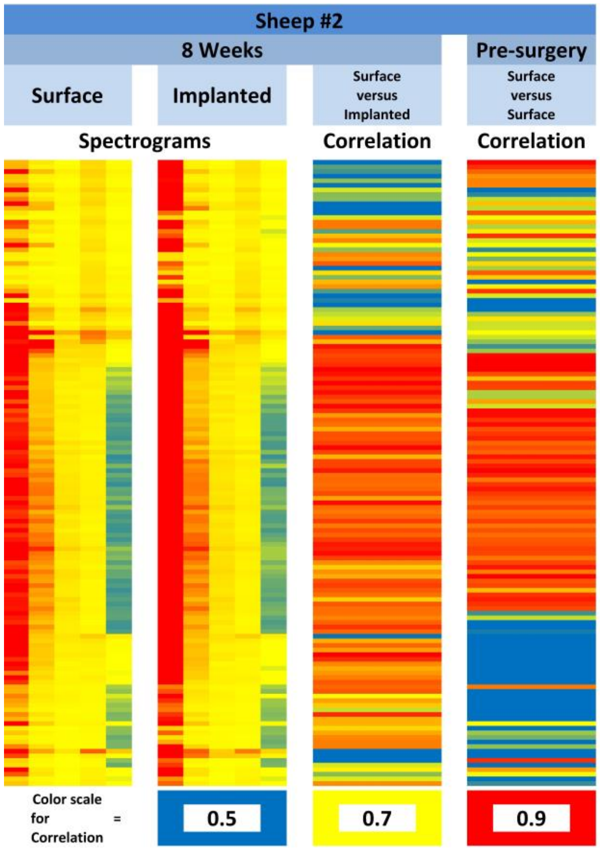

Figure 8. Time-domain correlation of surface electrode EEG to implanted electrode EEG. The front electrodes on sheep #2 were measured. The two left columns are a portion of the spectrograms from the right side of Fig 5. Time, amplitude, and frequency-band formats are the same as in Fig. 5. The sheep was sedated during the middle section of the spectrograms (see Fig. 5). The two right columns are time-domain correlations of the EEG from the two front electrodes. Correlations of 0.5 and lower are blue (see scale at bottom of figure). The correlation is high (>0.8) during sedation and fluctuating at other times regardless of the right-front electrode being surface (pre-surgery data) or implanted (8-weeks data). The pre-surgery sedation ended a few minutes earlier than the sedation at 8 weeks.

The higher correlation (Fig. 8) for surface-versus-surface compared to surface-versus-implanted may be caused by the reference electrodes. The same reference electrode was used for all four signal electrodes in the surface-versus-surface pre-surgery case. In the post-surgery cases, the two implanted electrodes had an implanted reference (Fig. 2) and the surface electrodes had a surface reference. Any voltage between the two references would lower the correlation. Future studies will place surface electrodes directly above implanted electrodes to remove this source of error.

The surface-versus-implanted correlation of 0.86 may be considered high but a clinical standard is not available to determine if it is acceptable. However, in the clinic the EEG is predominantly evaluated subjectively by humans and not quantitatively by computers. A survey of clinicians is a stronger test of an EEG instrument than a correlation value. The survey results (Table 1) were generally favorable and did not indicate a serious flaw that would preclude further use of the electrode being studied.

Question A : Rate your impression of the overall quality of the EEG signals in this referential recording (excellent, good, adequate, poor, uninterpretable) .

Response A : excellent=6 good=2 adequate=2 .

Question B : Are there any overt differences among the channels which would make you interpret them differently from one another? .

Response B : yes=3 no=7 .

Table 1. Survey of EEG-certified clinicians. Five clinicians rated the EEG from two sheep. Fig. 9 shows a ten second sample of the data viewed by the clinicians. Clinicians were blind to surface versus implanted electrodes. The EEG from the implanted back electrode had similar shape but smaller amplitude than the other electrodes. This difference prompted the three “yes” replies for Question B. One clinician also noted different frequency content in some channels.

The reduced amplitude from the back implanted electrode was a concern of the surveyed clinicians (Table 1). The correlation and state-change analyses did not indicate an issue with the back implanted electrode because these calculations are influenced by changes in the ratios of amplitudes but not the ratios per se. The pre-surgery surface electrode at the same location did not have reduced amplitude so a neural cause is unlikely. The measurement of the one kOhm resistor did not have a reduced amplitude so the cabling and instruments are not a cause. The amplitude was reduced at the first post-surgery measurement and did not change significantly for the remainder of the study, so, if the cause is a foreign body reaction, the reaction happened early and did not happen on the front electrode. The low and constant impedance was interpreted, while the study was in progress, as a lack of foreign body reaction and so histological analysis, which might have revealed a cause, was not requested. The cause of the reduced amplitude is unknown and subsequent studies will be designed to find the cause.

Study Limitations

The impedances of the surface electrodes were not measured. The sheep skin was shaved and the electrode gel correctly applied so the resistance was likely within the guidelines. Also, the low voltage in the gamma band during sedation, ~0.5 uVrms, would be difficult to achieve with high electrode impedance, so the impedance was likely low.

Sheep heal quickly so eight weeks was assumed to be adequate [10] but longer studies are now expected for neural electrodes [11].

The methodology of this study assumed high correlation of the EEG from the left and right hemispheres of sheep [12]. However, the hemispheres had a correlation of 0.92 as measured by surface electrodes which was not as close to unity as anticipated. The uncorrelated signals from the hemispheres may have been a major contributor to the surface-versus-implanted correlation of 0.86. Future studies will remove this confounding factor by placing the surface and implanted electrodes on the same hemisphere.

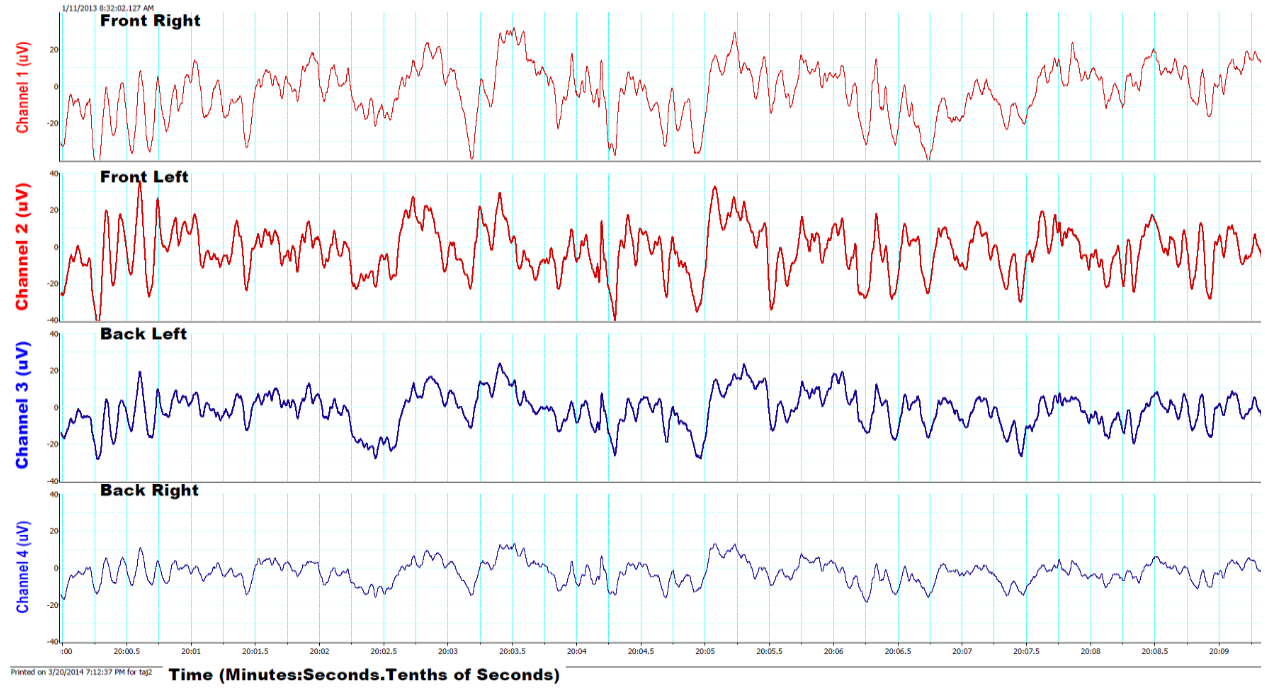

Figure 9. Representative example of raw EEG data. The top and bottom traces are from implanted electrodes. The middle traces are from surface electrodes. The middle traces appear thicker due to a plotting artifact and not from noise. This data is from sheep #1 at 8-weeks post-surgery during the deepest sedation as determined by lowest gamma amplitude. The four waveforms are alike except the amplitude from the back-right implanted electrode is smaller. No cause was found for the smaller amplitude.

Histological analysis of the tissue adjacent to the implanted electrodes was not performed because the tissue was compromised during explantation. If the electrode had developed high resistance then histological analysis would have been crucial [5]. However, the resistance remained low throughout the study (Fig. 4). Future studies will examine the tissue near the electrode.

The noise baseline measurements (Fig. 5) were done with the cables hanging loosely. The cables should have touched the sheep so that the common mode signal of the sheep was included in the baseline.

The implanted electrodes were stainless steel. Titanium is the most likely material for future studies.

V. Conclusion

A proof-of-concept study of the electrical characteristics of implanted electrodes found no significant issues that would halt the further development of an implanted EEG recorder.

Acknowledgment

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