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Research Article
EEG Signal Quality of a Subcutaneous Recording System Compared to Standard Surface Electrodes

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Purpose. We provide a comprehensive verification of a new subcutaneous EEG recording device which promises robust and unobtrusive measurements over ultra-long time periods. The approach is evaluated against a state-of-the-art surface EEG electrode technology. Materials and Methods. An electrode powered by an inductive link was subcutaneously implanted on five subjects. Surface electrodes were placed at sites corresponding to the subcutaneous electrodes, and the EEG signals were evaluated with both quantitative (power spectral density and coherence analysis) and qualitative (blinded subjective scoring by neurophysiologists) analysis. Results. The power spectral density and coherence analysis were very similar during measurements of resting EEG. The scoring by neurophysiologists showed a higher EEG quality for the implanted system for different subject states (eyes open and eyes closed). This was most likely due to higher amplitude of the subcutaneous signals. During periods with artifacts, such as chewing, blinking, and eye movement, the two systems performed equally well. Conclusions. Subcutaneous measurements of EEG with the test device showed high quality as measured by both quantitative and more subjective qualitative methods. The signal might be superior to surface EEG in some aspects and provides a method of ultra-long term EEG recording in situations where this is required and where a small number of EEG electrodes are sufficient.

1. Introduction

Electroencephalography (EEG) is a standard procedure to obtain information about the metabolic and electric status of the brain. The EEG is widely used in both the diagnostics and the monitoring of the state of human cognitive system, ranging from epilepsy and impaired consciousness to sleep disorders. The clinical application of EEG is now well described; however, the quality of long-term ambulatory monitoring of EEG is still compromised by inconvenient equipment and unstable electrodes, thus requiring continuous supervision. The positions of the electrodes on the scalp are given according to international conventions, such as the 10/20 system [1]. Standard scalp EEG-recordings are suitable for many applications in neurology; however, for long-term continuous monitoring it is desirable to perform recordings without causing discomfort to the patient, and outside clinical facilities [2]. In addition, EEG recorded over a prolonged period of time may provide deeper insight and open completely new avenues of research and applications compared to conventional EEG. Examples include the diagnosis of infrequent seizures and characterization of more frequent
pathological events, together with the monitoring of drug
titration and the development of brain-computer interface
techniques [3]. Continuous EEG recording is a prerequisite
for the monitoring of, for example, vigilance level [4] or sleep
stages [5]. This also provides the basis for early detection of
the onset of epileptic seizures [6] or indices of impending
severe hypoglycaemia [7, 8].

For continuous EEG recordings to become a reality
the device should be convenient to use, not hamper daily
activities, and at the same time provide EEG of high quality
with a minimum of electric noise and device-related artifacts.
Standard clinical EEG recording systems are not suited for
this purpose, as the electrode leads and bulky batteries
are inconvenient, electrodes are easily dislodged, gel-based
electrodes tend to dry out, and artifacts are often seen in
outpatient monitoring [9].

To this end, the company HypoSafe is developing an
EEG recording system which consists of a miniaturized
subcutaneous implant placed behind the ear and an external
part which provides the implant with power, receives and
stores the EEG signal, and conducts real-time data analysis
if required. Both data and power transmission employ an
inductive link, so that the inner device does not require an
internal energy supply. This ultra-long-term wearable capabil-
ity, lack of artifacts, and a perfect electrode contact make the
system robust and convenient. In preliminary experiments
the study subjects found the device comfortable and aside
from a temporary transient soreness at the implantation site,
no adverse events have been reported. Subjects informed that
they slept well with the implantable electrode.

The current paper presents a comparative analysis of
EEG signal quality of the first generation of a miniaturized
subcutaneous implanted recorder [10] against standard
scalp electrodes used in conjunction with a state-of-the-art
recording system. The EEG was analysed both qualitatively
and quantitatively over recordings of different brain states
during physical activity.

2. Materials and Methods

The considered dataset originates from a continuous EEG
recording, and according to a protocol which aims to test
the robustness and performance of an EEG based hypoglycaemia
alarm for type 1 diabetes patients. The project was approved
by the regional ethical committee and the Danish Health
and Medicines Authority and registered at ClinicalTrials.gov
(identifier number NCT01238016). For optimal function of
the device, before implantation in diabetes patients, a series
of implantations were conducted in healthy volunteers. The
population reported in this paper consists of these healthy
individuals, who all wore the device for one month. They were
consulted weekly during the study period and any reported
adverse events were recorded.

2.1. Devices

The Subcutaneous Device. The implantable part of the device
consists of an insulated lead (length 100 mm and diameter
1 mm) with three embedded platinum-iridium electrodes
located 30 mm apart, each with an area of 35 mm². The lead
is fixed to the implant housing which is 3.0 mm thick and
ovoid shaped, with diameters of 16 and 20 mm, and covered by
biocompatible epoxy; see Figure 1. The outer device consists
of a disc for the inductive link (height, width, depth of 28 mm,
20 mm, 4 mm) connected to a box (height, width, depth of
69 mm, 29 mm, 10 mm) containing processing units, memory
card, and a Li-ion battery. EEG data are sampled at 65.1 Hz
with an analog high-pass filter with a cut-off frequency at
0.5 Hz and a roll-off of 40 dB/decade and a low-pass filter with
cut-off at 30 Hz and a roll-off of 80 dB/decade. The common
mode rejection ratio was 60 dB, least significant bit below
0.5 μV, and the input impedance higher than 20 MΩ. The
battery can provide the implant and processor with power
for 2 days before it needs to be recharged, and the storage
capacity is sufficient for storage of one month of continuous
measurement. The external device gives tactile feedback, so
that the user knows when the inner and outer devices are
optimally aligned and in link.

The Control Setup. To verify the quality of EEG data obtained
from the test device, standard scalp electrodes (reusable
silver EEG cup electrodes, 200 cm lead, 10 mm cup, Embla
Systems Inc., Amsterdam, Netherlands) were placed directly
above the electrodes of the inner device, and simultaneous
recordings were performed. The skin was initially prepared
with Nuprep skin preparation gel, while the Ten20 conductive
EEG paste (Weaver and Company, Aurora, CO, USA) was
used for the disc electrodes, which were fastened with EC2
genuine grass electrode cream (Natus Neurology, Warwick,
RI, USA). The EEG data from cup electrodes were sampled
with a g.USBamp (Guger Technologies, Austria) at 64 Hz
and preprocessed using a digital Butterworth band-pass filter
of 8th order with cut-off frequencies at 0.5 Hz and 30 Hz.
All signals were finally resampled to 207 Hz for straight-
forward comparison.

2.2. Protocol. Five healthy subjects (all male, aged 33 ±
8 years) participated in the study. None had a history of
diabetes, epilepsy, or any other chronic disease and were
not taking regular medication. The device was implanted via
local analgesia and sterile technique through a 15 mm incision
behind the ear. The electrode was placed in an open needle
and inserted from the top of the incision in the subgaleal
space in the direction towards a point between Cz and Pz,
according to the international 10/20 system. The implant
housing of the device was placed in a pocket made by blunt
dissection behind the auricular helix. When the device was in
situ the incision was closed with resorbable sutures.

Approximately ten days after the insertion, the subjects
returned to the clinical research unit, and the outer part of the
device was placed on the skin by double adhesive tape directly
above the inner device. This adhesive should be changed daily
to ensure optimal data transmission. Control electrodes were
then placed on the scalp, above subcutaneous electrodes (see
Figure 1), and the impedance was checked (should be below
5 kΩ). The subjects were then asked to perform consecutive
predefined activities of 30 second length; these included rest,
closed eyes, jaw clenching, eye blinking, eye movements,
Table 1: EEG scoring sheet for subjective analysis by neurophysiologists. Each 30 s epoch was given a score for the signal quality as well as the noise level.

| Score | Signal quality                                      | Noise level                                      |
|-------|-----------------------------------------------------|--------------------------------------------------|
| 5     | EEG signal clear, evaluation straight forward       | No or very little noise present                  |
| 4     | EEG signal clear, evaluation possible and close to optimal | Some noise present but does not hamper EEG analysis significantly |
| 3     | EEG signal recognized, evaluation possible however not optimal | Moderate amount of noise present, EEG analysis challenging but still possible |
| 2     | EEG signal recognized, evaluation difficult         | Larger amount of noise present, EEG analysis challenging and less reliable |
| 1     | EEG signal is not readily recognized                | EEG severely noisy, EEG analysis unreliable       |

arithmetic mental exercise, and jumping on the spot. The total duration of the procedure was 12 minutes.

2.3. Subjective Analysis of Time Series. The recordings were analyzed both visually and quantitatively. The visual inspection was performed in a blinded fashion by two independent neurophysiologists (TWK and MDA). For each of the above tasks, 30 s epochs of EEG were provided and the neurophysiologists were asked to score the time series by a signal scale and a noise scale as shown in Table 1. In the case of more than two points of disagreement within a single epoch, the neurophysiologists were asked to reevaluate that epoch until agreement. A higher value in the signal as well as the noise scale is preferential. For each task a Mann-Whitney U-test was used of the null hypothesis that scorings of the subcutaneous and surface EEG data are independent samples from identical continuous distributions with equal medians, against the alternative that they do not have equal medians.

2.4. Analysis of Power Spectral Densities. The most apparent brain signal response is the alpha attenuation response [11]. When a subject closes the eyes, the absolute as well as relative power in the entire signal will rise in the 8–13 Hz frequency band, especially in the posterior electrodes. The power spectrum densities were calculated using Welch’s method: the data was split into 5-second segments with 50% overlap. A Hamming window was applied to each data segment and the power spectral density estimate was found by averaging the resulting periodograms.

To determine the degree of separation of alpha powers within the 5 s windows between the “eyes closed” and “eyes open” tasks, the t-statistic was calculated via Welch’s t test, given by

\[
t = \frac{\mu_c - \mu_o}{\sqrt{\sigma_c^2/N + \sigma_o^2/N}},
\]

where \( \mu_c \) and \( \mu_o \) denote, respectively, the mean alpha power for the “eyes open” and “eyes closed” states, \( \sigma_c^2 \) and \( \sigma_o^2 \) denote the corresponding variances, and \( N \) denotes the number of samples (here number of data segments). A positive t-statistic indicates that the alpha power is greater for the “eyes closed” recording; the larger the statistic the greater the differentiation from the “eyes open” recording. The corresponding p values were calculated.

2.5. Correspondence between Surface and Subcutaneous Signals. To investigate the similarity between the surface and
subcutaneous signals, the normalized correlation coefficient and magnitude squared coherence spectrum were calculated for the states of closed and open eyes. The normalized correlation coefficient, $R_{xy}$, was calculated by

$$R_{xy}(m) = \frac{\sum_{n=max(0,m)}^{\min(N_x+m-1,N_y-1)} x_{n+m} \cdot y_n}{\sqrt{\sum_{n=0}^{N_x-1} x_n^2 \cdot \sum_{n=0}^{N_y-1} y_n^2}},$$  \hfill (2)$$

where $x$ denotes the subcutaneous EEG, $y$ is the surface EEG, $N_x$ is the number of samples in each calculation, and $m$ is the lag in the range $-N_x + 1$ to $N_x - 1$. If $R_{xy} = 0$, there is no correlation between signals, while $R_{xy} = 1$ shows that the signals are in perfect correlation.

The magnitude squared coherence spectrum, $C_{xy}$, is a function of the power spectral densities, $P_{xx}(f)$ and $P_{yy}(f)$, and the cross power spectral density, $P_{xy}(f)$. It is computed using Welch’s averaged periodogram method:

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f) \cdot P_{yy}(f)}.$$  \hfill (3)$$

Similar to the normalized correlation coefficient, the values of the magnitude squared coherence are also in the range of 0 to 1, but with one value for each frequency bin.

3. Results

3.1. Device Tolerability. One study subject complained about discomfort at the site of implantation and requested explanation. This was performed one week before planned termination of the study and underwent without any further complications. No further adverse device- or procedure-related safety issues were raised in the study.

3.2. Qualitative Analysis. The neurophysiologists scored the EEG quality to be higher for the test device than the standard surface-electrode approach when the subjects were at rest, with both open and closed eyes, as well as when performing a mental task; see Figure 2. This was primarily due to more distinctive EEG responses such as the alpha rhythm associated with the “eyes closed” state. The level of noise was adjudged to be similar for the surface and subcutaneous systems.

3.3. Alpha Response. Table 2 shows that the subcutaneous electrodes enable, on average, a better differentiation for three of the five subjects (subjects 1, 3, and 4). Both the surface and the subcutaneous approaches enabled a statistically significant differentiation for 10 of all the 15 trials, although not always the same trials were found statistically significant for the implanted and scalp EEG.
Table 2: The independent, two-sample, two-tailed $t$-test for the "eyes closed" and "eyes open" alpha-band powers for the surface (surf.) and subcutaneous (subc.) electrode system. For each subject and trial, the electrode which gives the largest $t$-statistic (greatest separation between states) is given in bold. Negative (deemed incorrect because it implies that a larger alpha power was recorded during the eyes open state) and nonsignificant ($p$ values $>.05$, denoted n.s.) $t$-statistics are marked in italics.

| Subject | 1 | 2 | 3 | 4 | 5 |
|---------|---|---|---|---|---|
| System  | Surf. | Subc. | Surf. | Subc. | Surf. | Subc. | Surf. | Subc. | Surf. | Subc. |
|         | $t_{(36)}$ | $p$ value | $t_{(36)}$ | $p$ value | $t_{(36)}$ | $p$ value | $t_{(36)}$ | $p$ value | $t_{(36)}$ | $p$ value |
| Trial 1 | 7.02; $p < .01$ | 9.83; $p < .01$ | 2.73; $p < .01$ | $-0.09$, n.s. | $-2.2; p < .05$ | 2.66; $p < .05$ | 0.80, n.s. | $-0.15$, n.s. | 3.40; $p < .01$ | 1.41; n.s. |
| Trial 2 | 3.40; $p < .01$ | 4.91; $p < .01$ | 3.80; $p < .01$ | 3.55; $p < .01$ | 1.88; n.s. | 3.96; $p < .01$ | 2.33; $p < .05$ | 2.41; $p < .05$ | 2.59; $p < .05$ | 0.71; n.s. |
| Trial 3 | 4.03; $p < .01$ | 4.62; $p < .01$ | 2.48; $p < .01$ | 2.15; $p < .01$ | 1.07; n.s. | 3.89; $p < .01$ | 2.13; $p < .05$ | 2.83; $p < .01$ | 1.41; n.s. | 0.91; n.s. |
3.4. Signal Similarity. Figure 3 shows that the power spectrum densities are very similar for the surface and subcutaneous approaches; the only difference is that the subcutaneous recordings exhibited slightly less power for frequencies below 2 Hz. These results are supported by the correlation and coherence analysis in Figure 4. The mean normalized correlation coefficient was 0.73 between the two synchronously but independently recorded signals and the first side lobes were situated at lags ±22, which is equivalent to a wave with a frequency of 9.4 Hz. The coherence spectrum shows that this behavior was primarily due to high coherence in the low frequencies, where the signal power and correlation are high.

The similarity of the subcutaneous recordings over the one-month period also seems to be high. Figure 5 shows the PSDs calculated based on a one-minute noise-free EEG segment from day one and day 26 after the start of the recording.

4. Discussion

We have evaluated the quality of EEG recordings from a single-channel miniaturized partly implanted recorder against simultaneously obtained recordings from a state-of-the-art surface-electrode EEG system. By quantitative
Figure 4: Similarity between surface and subcutaneous EEG recorded signal during “eyes closed” paradigm as calculated by (a) the normalized correlation coefficient and (b) the magnitude squared coherence spectrum. The maximum correlation at lag 0 for closed eyes is 0.73. The two side lobes are situated at lags −22 and 22, corresponding to a frequency of 9.4 Hz. Outside the shown lags, the correlation coefficient is close to zero. For the coherence spectrum, primarily the lower frequencies have higher coherence. The vertical dashed lines indicate the alpha-band.

Figure 5: Comparison between power spectral densities (PSDs) one and 26 days after the start of the recording for the subcutaneous electrodes. The PSDs are made based on a one-minute long EEG segment randomly chosen from the two days. The level of similarity is very high.

comparison, we found a close correlation between these two data-sets. Likewise, the more subjective, yet structured, qualitative comparison of the data indicated that the implanted test device provided data of comparable quality.

Ultra-long term EEG recordings may constitute a complementary approach to standard EEG recordings in order to elucidate occurrence of rare EEG events. In such cases, there will inevitably be a tradeoff between the utility of a full-scale EEG recording and the requirement of extended use. The EEG-recorder tested in the present study was developed for the purpose of EEG-based hypoglycaemia detection in type 1 diabetes patients, a task which requires continuous and long-term monitoring [7,8]. The present study was undertaken to evaluate the quality of data from the test device, defined as a high signal-to-noise ratio and little or no data loss.

This proof-of-concept study considered a relatively small subject population. We have studied five healthy volunteers who used the EEG device for a period of one month. Intra-subject variation in the EEG or aberrations from the normal EEG was accordingly less essential. Another aspect of the implanted device is that the EEG recording and validation are limited to a single channel and accordingly to a small part of the brain's surface. Notice that anatomic variations in the thickness of the cranium and the overlying soft tissue may influence the subcutaneous and the surface measures differently [12]. The anatomic area considered in this study was chosen according to the requirement of the hypoglycaemia paradigm. It is prominent in the temporal area of the brain, where the hypoglycaemia alarm device is also positioned [10,13]. If the test-device is to be used at other
parts of the brain, it will be essential to evaluate the signal from these relevant areas.

A strength of the study is that the EEG obtained by subcutaneous and surface methods is evaluated and compared by complementary approaches. The spectral analysis provides a straightforward quantitative comparison showing that the two modalities give near-identical signals. As the power spectra are almost identical for all frequencies above 2 Hz, one might suspect that the power from the scalp recordings below 2 Hz originates from a nonphysiological phenomenon such as movement of the long wires between the scalp and the amplifier on a nearby table. As those wires are not present for the test-device, this artifact will not be present on that device.

Alpha activity was observed during the eyes-closed state in most study subjects. By cross-correlation analysis, it is substantiated that the two methods measure near-identical signals. A mean normalized correlation coefficient of 0.73 between the synchronously but independently recorded time series of subcutaneous and surface EEG data is high. The occurrence of significant side-lobes in the cross-correlogram at lags ±22 samples during closed eyes further highlights the high degree of matching between the two signals. The coherence spectrum shows that this is primarily due to high coherence in the low frequencies up to 12 Hz, where the signal power is also highest.

As a complementary approach, the EEG was examined visually by two independent neurophysiologists. This was achieved in a blinded manner with respect to the recording technique, in order to avoid systematic bias. We found that the noise present in each of the approaches was equivalent, irrespective of the recording methodology. Physiological noise might be expected to arise from at least two sources: (i) due to activity of the temporal muscle (EMG) which leads to increased noise especially during periods of chewing and (ii) from the eye muscles during eye movement and blinking. As expected, it was found that these physiological sources of noise were equally represented in the EEG. Noise may also arise from instability of the electrode connection to the skin or from induced currents due to electrode movements. These sources of noise are expected to be reduced when the electrode is fully implanted, thus ensuring a rigid connection with the source of the signal. This might be the reason that the reported signal quality of the subcutaneous approach was highest during rest with eyes open, eyes closed, and during a mental task. Had the evaluation continued over days, we would have expected the surface-electrode skin-contact to degrade, resulting in an inferior performance [14].

To assess short-term robustness of the recordings we compared data recorded on day one and day 26. Figure 5 shows similar power spectral densities, suggesting that the signal quality does not change over time. Further comprehensive longitudinal evaluations of the long-term durability will be published in a later study.

5. Conclusion

We have found that the proposed subcutaneous recording system provides data quality which is comparable to state-of-the-art in standard surface recording technology. This has been verified through both quantitative and more subjective qualitative methods, thus promising a method for a discreet and unobtrusive ultra-long term EEG where a small number of electrodes are sufficient. A blinded visual examination indicates especially high EEG quality when no physical movements were performed, and initial studies of the performance of the subcutaneous electrodes over a one-month period suggest its suitability for long-term EEG recordings. Further studies will evaluate the performance of the test device during multiple months’ long trials.

Conflict of Interests

Jonas Duun-Henriksen, Martin Rose, and Rasmus Elsborg Madsen are all full time employed at Hypo-Safe A/S developing and producing devices for unobtrusive subcutaneous EEG monitoring. Claus Bogh Juhl is part time employed at Hypo-Safe A/S. None of the remaining authors have any financial interests in Hypo-Safe A/S.

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