Monitoring the Analgesic Effect of Buprenorphine With Single-Sweep Pharmaco-EEG

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ABSTRACT:

Pain is a widely present condition, with as many as 19 % of the european population suffering from chronic pain. In many cases pain is treated with opioids, but since little is known about the underlying mechanisms of opioid treatment, further studies are warranted.

This randomized, cross-over and double-blinded study included 15 healthy subjects in order to investigate the effects of buprenorphine administered through a transdermal patch. During treatment, measurements were made for blood plasma concentrations, occurrence of adverse effects and pain assessments.Evoked brain potentials (EPs) were recorded using electrical stimulation at the median nerve.

Features were extracted from the EPs using Continous Wavelet Transform to detect the latency and amplitude of the most dominant waveforms within four frequency bands (delta, theta, alpha and beta). Features were log-transformed and baseline corrected before analysis using two-way repeated measures analysis of variance (ANOVA). Afterwards, features which exhibited significant differences compared to placebo treatment, were correlated with the clinical scores.

Significant differences between buprenorphine and placebo treatment were found for all amplitude features in all frequency bands, but not for latency (ANOVA). Correlation was found between the beta band feature and bone pain scores ($P = 0.008$) as well as the plasma concentrations ($P = 0.02$).

This study showed that features found in the EEG reflect the analgesic effect of buprenorphine. This discovery might be useful in clinical drug trials to monitor the analgesic effect.

Preface

This project is made by Mikkel Gram (group 12gr1079) on the 10th semester of Biomedical Engineering and Informatics at Aalborg University, 2012.
The project is a data analysis of data collected during a previously published study. Trine Andresen developed the protocol for the study and carried out the experiments [Andresen et al., 2011].

List of Abbreviations

AP Action Potential.

CNS Central Nervous System.

CWT Continuous Wavelet Transform.

EEG Electroencephalography.

EP Evoked Brain Potential.

HTT heat tolerance threshold.

MMP Multivariate Matching Pursuit.

MP Matching Pursuit.

PDT pain detection threshold.

PTT pressure tolerance threshold.

SVM Support Vector Machine.

TMP Temporal Matching Pursuit.

WHO World Health Organization.

Contents

CHAPTER 1

Introduction

Pain is widely present, with 19 % of the European population and 25 - 30 % of the population in the USA suffering from chronic pain [Breivik et al., 2006; Smith and Torrance, 2012; Varrassi et al., 2010]. Currently pain treatment is based on the three-step ladder developed by the World Health Organization (WHO), which includes opioid treatment for moderate to severe pain [WHO, 1996]. Buprenorphine has been used in pain treatment for more than 30 years utilizing various methods of administration. Interest in the drug has increased recently after delivery through a transdermal patch became possible, ensuring stable plasma concentrations, and increased patient compliance [Andresen et al., 2010; Karlsson and Berggren, 2009].

This is partly due to the fact that the opioid-recepters affected by buprenorphine and its metabolite norbuprenorphine may be important in the treatment of bone-associated pain which is difficult to treat in clinical practice. Previous studies have found that buprenorphine provided a better analgesic effect with respect to bone-associated pain compared to another opioid, fentanyl [Andresen et al., 2010]. Therefore, buprenorphine administered through a transdermal patch is interesting for the treatment of patients with persistent pain [Andresen et al., 2010].

Pharmacological-Electroencephalography (EEG) using evoked brain potentials (EPs) has proven as a viable tool for analyzing the analgesic effects of different drugs [Graversen et al., 2011]. However it is important to make sure that differences found in the EEG are relevant for the study, and not caused by a general effect of the drug. Therefore any differences found in the EEG should correlate to the analgesic effect. Otherwise the differences might describe another effect of the drug such as sedation, instead of the analgesic effect [Graversen et al., 2011].

Many previous EEG studies have analyzed the spectral energy of the signals using time-frequency methods. One of the most basic methods is the short-time fourier transform, which analyses the signal through small windows. More recently the wavelet transform which analyses the signal by compressing and extending a mother wavelet has become more popular. The wavelet transform provides a better time-frequency resolution than the short-time fourier transform, and studies have determined it to be superior for signal analysis of EEG

[Akin, 2002; Hubbard, 1996].

Another method for time-frequency analysis is Matching Pursuit (MP), which has so far not been as widely used in EEG analysis. MP decomposes the signal into atoms chosen from a large dictionary, which describe the largest amount of energy in the signal [Durka, 2007]. Since MP is very specific about the phase, frequency and amplitude of the atoms that match the signal best, it might be an interesting tool for EEG analysis.

EEG studies using EPs generally stimulate the subjects multiple times, each time recording an EP, or sweep. This is done since the EP signal is relatively small compared to the background EEG activity [Sanei and Chambers, 2007]. Averaging of the recorded sweeps is common to improve the signal/noise ratio of the recorded signals, but the method has drawbacks as it only effectively preserves components of the EP that are time- and phase-locked. Studies have shown that nociceptive input to the brain originating from the C-fibers are generally not phase-locked, and therefore removed in the averaging process [Domnick et al., 2009; Sanei and Chambers, 2007]. Therefore single-sweep analysis of the EP is preferable in order to not remove important data from the recording before analysis.

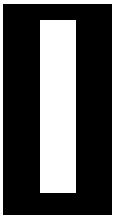
Extracted features can be correlated directly to the clinical scores, but another possibility is that the analgesic effect is only reflected by inspection of several features at once. This is possible using methods for multivariate analysis such as Support Vector Machine (SVM). These methods can estimate the total discriminative ability of a combination of several features [Ivanciuc, 2007].

We hypothesized that buprenorphine induces differences in the EEG and that these can be correlated to the analgesic effect.

Aims

The aims of this study were then **a)** to utilize the wavelet transform and matching pursuit to find features in the Pharmacological-EEG of single-sweep EPs that exibit significant differences in buprenorphine treatment compared to placebo, **b)** investigate the pros and cons of the extracted features, **c)** investigate if these features correlate to the clinical effects and **d)** investigate if the performance of the SVM can be used for correlation to the clinical scores.

PART



Background

CHAPTER 2

Pain physiology and treatment

The International Association for the Study of Pain (IASP) defines pain as [Smith and Torrance, 2012]:

> *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".*

This means that pain is a highly individual perception, which is not necessarily connected to actual tissue damage [Jensen and Sjøgren, 2009].

Nociceptive pain is conducted to the brain from the nociceptors, which are responsible for detecting tissue damage. They are present in many different tissues except for the liver, lungs and brain [Jensen and Sjøgren, 2009].
Nociceptors react to many different stimuli, such as pressure, strecthing, chemical and thermal stimuli. They conduct signals to the brain through the C- and Aδ-fibers. The Aδ-fibers are myelinated and have a conduction velocity of 5 - 25 $\frac{m}{s}$, whereas the unmyelinated C-fibers conduct signals at a velocity of 0.1 - 2 $\frac{m}{s}$. This difference in conduction velocity means that signals from the Aδ-fibers reach the pain first, which is also refferred to as *first pain*. First pain is felt as a sharp and well-defined pain, which is followed by the pain originating from the C-fibers which is more blunt and harder to locate [Jensen and Sjøgren, 2009].
Prolonged sensation of pain can induce a plastic change in the Central Nervous System (CNS), which can lead to chronic pain [Jensen and Sjøgren, 2009].

2.1 Epidemiology

Pain is widely present in the population, with 19 % of the european and 25 - 30 % of the population in the USA suffering from chronic pain [Breivik et al., 2006; Smith and Torrance, 2012; Varrassi et al., 2010].
Pain affects patients in a number of ways. General health condition of patients is adversely affected by the presence of chronic pain. In most cases chronic pain is linked to depression and vice versa. It is therefore evident that pain decreases the quality of life significantly

[Smith and Torrance, 2012].
It is hard to estimate the cost related to pain and it's treatment, due to the complex nature the condition. One study in the UK estimated the cost of back pain to a total of £ 10.7 billion with £ 1.6 billion in direct healthcare costs. Since this is just from one sub-group of patients suffering from pain, it is clear that pain imposes a large burden for society [Smith and Torrance, 2012].

2.2 Treatment

Currently pain is primarily treated based on the three-step ladder developed by the WHO, for use in treatment for cancer pain [WHO, 1996]:

1. Non-opioid analgesic should be used for moderate pain
2. If treatment is insufficient, a weak opioid can be added
3. If treatment is still insufficient, the patient should be switched to a strong opioid

Since then the three steps have been used to treat chronic pain in general. However, in many cases these guidelines have not made it into daily practice [Varrassi et al., 2010; WHO, 1996].
There is evidence to suggest that the treatment of pain today is insufficient. Out of the 19 % of europeans suffering from chronic pain, 40 % were unsatisfied with the management of their pain. Since pre-existing pain is the highest risk factor to further develop chronic pain, improved treatment of pain has great potential [Breivik et al., 2006; Smith and Torrance, 2012; Varrassi et al., 2010].

2.3 Opioids

Opioids is a group of pharmacological drugs that consists of morphine and morphine-like drugs [Jensen and Sjøgren, 2009] They are common in use for treatment of moderate to severe chronic pain, due to their strong analgesic effect. They affect the body by binding to the different opioid-receptors (μ, δ and κ) that are present both in the central nervous system and periferically [Jensen and Sjøgren, 2009].
The effects of opioids both include desired effects which is primarily the analgetic effect, but also adverse effects such as drowsiness, respiratory depression, constipation, dizziness, nausea and a strong sense of euphoria [Jensen and Sjøgren, 2009].
Each opioid has a specific affinity to the opioid receptors, and this affinity determines the biological response of the opioid. The re-

sponse also varies from person to person, making decision of the right opioid difficult [Jensen and Sjøgren, 2009].

2.3.1 Buprenorphine

Buprenorphine has been widely used in pain treatment for more than 30 years using various methods of administration. Recently, the interest in the drug has increased after transdermal patch delivery systems became available, ensuring stable plasma concentrations, and increased patient compliance [Andresen et al., 2010; Karlsson and Berggren, 2009].

This is partly due to the fact that the opioid-recepters affected by buprenorphine and its metabolite norbuprenorphine may be important in the treatment of bone-associated pain which is difficult to treat in clinical practice. Previous studies have found that buprenorphine provided a better analgesic effect with respect to bone-associated pain compared to another opioid, fentanyl [Andresen et al., 2010].

CHAPTER 3

Electroencephalography

EEG is the recording of electrical brain activity which is recorded by applying electrodes to the scalp [Sanei and Chambers, 2007].
Since the electrical field generated by a single neuron is very small, only the summation of many simultaneous discharges will be measurable from the scalp and even in this case the signal will be small [Sanei and Chambers, 2007].

3.1 EEG frequency bands

It is common to analyze EEG based on the spectral content. For this purpose five frequency bands have been created to divide the spectrum in a consistent way. The five bands are:

- Delta: 0.5 - 4 Hz
- Theta: 4 - 8 Hz
- Alpha: 8 - 12 Hz
- Beta: 12 - 32 Hz
- Gamma: 32 - 80 Hz

On figure 3.1 is shown examples of EEG signals in the different bands.

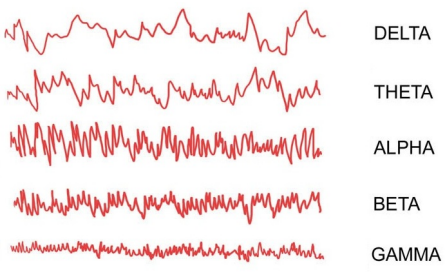


Figure 3.1: *Example of the five frequency bands: delta, theta, alpha, beta and gamma.*

The presence of activity within each frequency band changes from individual to individual but also from which state the person is in. Some frequency bands are more connected to sleep such as the delta

waves, whereas others are more active if the person is awake. In addition many brain disorders are diagnosed by inspection of the activity within the different bands [Sanei and Chambers, 2007].

3.2 Evoked Brain Potentials

EPs refer to the specific brain response to a stimuli (such as visual, auditory or somatosensory stimuli). When the stimulus is applied, a large number of Action Potentials (APs) will be induced within the brain. The sum of these APs will be measurable at the scalp electrodes, inducing a response in the EEG.
The EP signal is small compared to the background EEG activity. Therefore pre-processing of the signals is necessary to isolate the EPs [Sanei and Chambers, 2007].
Averaging is a very common method to improve signal/noise ratio, where the stimuli is reapeated a number of times, also referred to as performing several sweeps. All the recorded signals are then averaged to form a single EP, representing the average EEG response to the stimuli. This method is widely used because of it's ability to supress noise, but unfortunately it also has unwanted effects. Figure 3.2 shows how the averaged EP differs from two single sweeps used as examples.

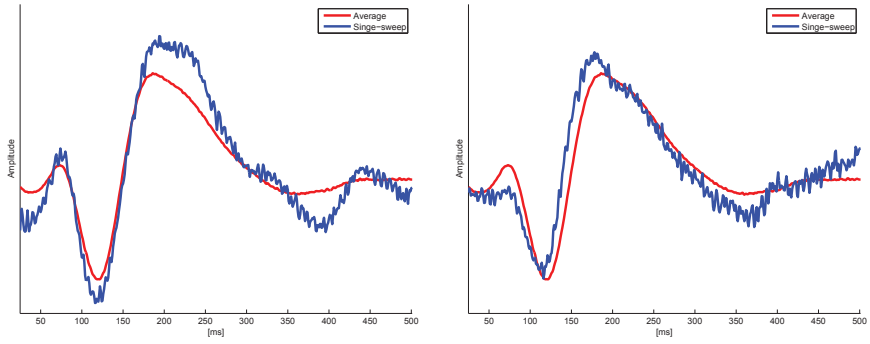


Figure 3.2: *Illustration comparing the averaged evoked potential til two single sweeps.*

While the averaging technique is very efficient at preserving the components of the EEG that are phase-locked, it will supress components that are not. This effectively means that information about these components are removed in the averaging process. Previously studies have shown that this is a drawback to the averaging procedure, since nociceptive input to the brain from the C-fibers are generally not phase-locked [Domnick et al., 2009; Sanei and Chambers, 2007]. Inspection of figure 3.2 reveals that a lot of high-frequency components are lost in the averageing process.

CHAPTER 4

Matching pursuit

MP is another method to decompose a signal. The method searches a large and redundant dictionary of signals to find the one that matches the signal best [Durka, 2007].
To perform decomposition using MP, a large dictionary of signals is required. The Gabor atoms, which are sine waves of varying frequency, modulated by gassian functions of varying widths, is an example of such a dictionary. However any dictionary of signals can be used depending on the desired application.
MP is then performed using an iterative process in the following steps [Durka, 2007]:

- Locate the atom in the dicationary that describes the largest amount of energy in the original signal
- Subtract the atom from the original signal, to obtain the first residual
- Repeat this process of comparison an deduction until the stop criteria is met

The process is depicted in figure 4.1, that shows an example of decomposition of a signal into 3 atoms.

The stop criteria can be chosen to fit the application. The most common stop criteria are to either decompose the signal into a chosen number of atoms, or to decompose the signal until the selected atoms describe more than a certain amount of the energy in the original signal [Durka, 2007].

The benefit of MP is that the decomposition is very specific about both phase, frequency and amplitude of the most dominant waveforms in the signal. On the other hand the decomposition is not complete in the way that not every frequency is investigated and represented in the decomposition.

4.1 Multivariate Matching Pursuit

Multivariate Matching Pursuit (MMP) is a generalization of MP. Here the method is applied to several signals at once, and the atom that provides the best overall match to all signals is then selected.

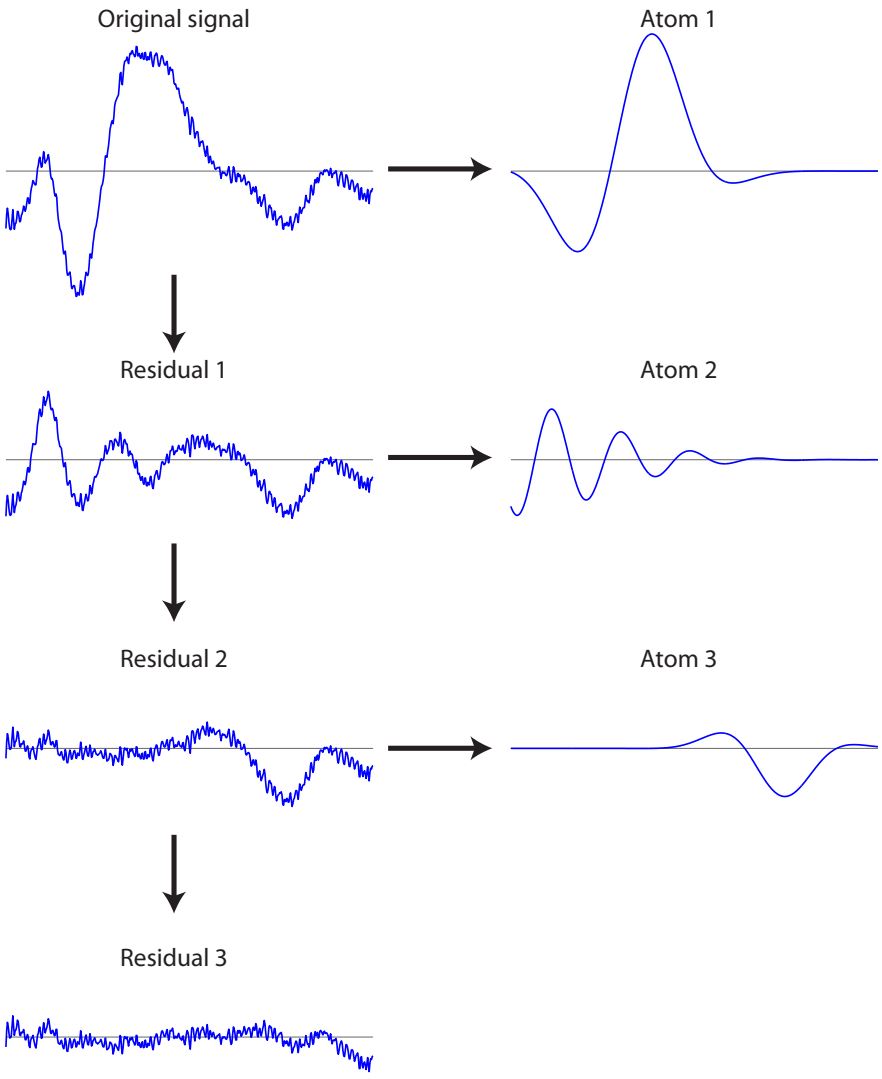


Figure 4.1: *The basic principle of matching pursuit. An example of decomposition into 3 atoms is shown here. The original signal is first decomposed into the first atom, which is the signal in the dictionary that matches the signal best. The first atom is then subtracted from the original signal, resulting in the first residual. Then the second atom is found from the first residual, and so on. This process continues until the stop criteria is met.*

The decomposition finds the atom that overall describes the largest amount of energy in the signals. The atom is then fitted to each signal by varying the amplitude. This means that each signal will be assigned the same atom with an individual amplitude, but a common phase [Durka et al., 2005].
When using MMP for classification, all signals are simultaneously decomposed into a set of atoms, which are all identical except for the amplitude. These amplitudes can be used as features for the classification.

4.2 Temporal Matching Pursuit

Temporal Matching Pursuit (TMP) is similar to the MMP in that it also decomposes multiple signals at once, but does not maintain a common phase for the atoms. This means that the atoms are fitted to the individual signal, by adjusting both the phase and amplitude of the atom. This property is important for applications where both the phase and amplitude of the signal is important. Previous studies have demonstrated phase shifts in the EP of healthy patients after pharmaceutical intervention [Schmidt et al., 2007].

CHAPTER 5

Continuous wavelet transform

The Continuous Wavelet Transform (CWT) is used for time-frequency analysis much like the fourier transform. However, it possesses several advantages with regards to resolution in both time and frequency over the fourier transform [Hubbard, 1996].

The CWT works by utilizing a mother wavelet function that is convoluted with the signal. The wavelet is compared to the signal over several iterations where the wavelet is stretched and compressed in order to achieve different frequencies. The amount the wavelet is stretched is reffered to as the scale (a). At each scale the wavelet is translated along the signal, performing convolutions continuously. The convolutions result in a set of wavelet coefficients (c), which can be describred a function defined both by the scale of the wavelet (a) and the latency (b). Equation 5.1 shows how a and b are used in the mother wavelet function (ψ) to generate a wavelet with the correct scale and latency [Hubbard, 1996].

$$c(a,b) = \int f(t)\psi(a \cdot t + b)\,dt \tag{5.1}$$

The results of the CWT depend both on the scales chosen for analysis and the type of mother wavelet. Several predefined mother wavelets are available depending on the application.

CHAPTER 6

Support Vector Machine

The SVM is a pattern recognition method based on statistical learning theory. The idea was developed for the seperation of data from different classes, and works by finding the hyperplane that seperates the classes with the largest margin [Ivanciuc, 2007].

The example data in figure 6.1A can be seperated using many different hyperplanes, but when looking at the data, not all possible solutions will be optimal for classifying new samples. In SVM classification the hyperplane with the highest margin between the classes, represent the optimal solution for seperation of the classes. An illustration of this is shown in figure 6.1.

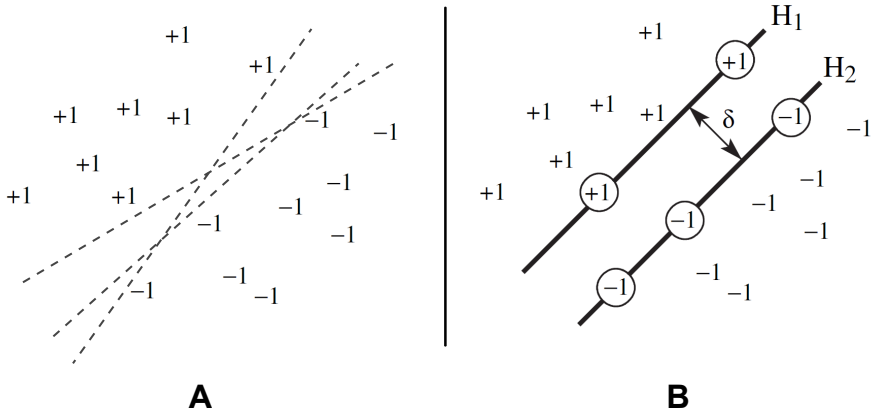


Figure 6.1: *Illustration of a classification problem. A shows that many different hyperplanes can seperate the data. B shows a SVM classifier where the maximum margin (δ) for seperation of the classes have been found. (Illustration modified from Ivanciuc [2007])*

When computing the hyperplane, a number of support vectors are used. Support vectors are the data samples on the margin. The solution to the classification problem is hereby defined based on a smaller subset of the data, more specifically the support vectors [Ivanciuc, 2007].

Sometimes the data is not linearly separable, and another kernel type can be used for seperation. This is useful for where the data is related in a non-linear way. However, care should be taken with regard to choice of kernel, since it can lead to overfitting. Since this is most

likely to happen with complex kernels, there should always be a well defined reason for choosing a more complex kernel [Ivanciuc, 2007].

The original formulation of the SVM was developed solely for cases where the data could be perfectly seperated by a hyperplane. However, since this is not the case for most cases of classification problems it was later expanded to allow for errors. This introduced slack variables which help minimize the amount of errors while still maximizing the margin [Cortes and Vapnik, 1995; Ivanciuc, 2007].

PART II

Method

CHAPTER 7

Study protocol

The protocol for the data has previously been published [Andresen et al., 2011]. The randomized cross-over double-blind study involved treatment using buprenorphine, fentanyl and placebo through a transdermal patch. However, only data from buprenorphine and placebo is included in this study to reduce the complexity of the study.

7.1 Study design

The study was carried out at the research laboratories at Mech-Sense, Aalborg Hospital, Denmark. Twentytwo healthy male subjects (age: 23.1 ± 3.8 years) without long-lasting pain complaints or lesions at the testing sites were included. In addition, routine medical examinations and blood samples were normal. Before inclusion in the study all subjects gave informed consent.

Each treatment was administered in 7 days with 3 days follow-up. Patients were hospitalized during the 7 days, in case of adverse effects. The treatment was administered through a transdermal patch, to achieve a stable release of the drug. The patches were administered by a nurse or pharmacist not otherwise involved in the project. Treatments were administered in random order, and both the subject or the investigator had no knowledge as to which treatment was being administered.

The treatment periods lasted 144 hours. During treatment 3 kinds of measurements were made at regular intervals. Blood plasma, EPs and pain measurements were performed, at the times shown in table 7.1.
Adverse effects was reported by the patient as well throughout the treatment period.

7.2 Pain assessment

Each time pain measurements were made, several modalities was used. However, for this study only heat, bone and electrical pain was included [Andresen et al., 2011]

Time [h]	**Plasma**	**EP**	**Pain**
0	√	√	√
4		√	
6	√		
9	√		
12	√		
24	√	√	√
28		√	
36	√		
48	√	√	√
60	√		
72	√	√	√
78	√		
84	√		
96	√		
120	√		
144	√	√	√
168	√		
192	√		
216	√		

Table 7.1: *Table showing when the different kind of measurements where performed in relation to the treatment.*

7.2.1 Heat stimulation

For the heat stimulation, an area of 9 cm^2, 10 cm proximal to the wrist of the right volar forearm, was heated using a "Thermo Tester" (TSA II NeuroSensory analyser, Medoc Ltd, Ramat Yishai, Israel).

The temperature was gradually increased from a baseline of 32 °C at a rate of 1 $\frac{^\circ C}{s}$ to a maximum temperature of 52 °C. The subjects were instructed to press a button when the heat tolerance threshold (HTT) was reached. Three successive stimulations were performed, and the average was calculated.

7.2.2 Bone pressure stimulation

Bone pressure stimulation was applied to a marked area on the right tibialis 15 cm below the patella. Since the site was marked, it was possible to stimulate the same area for all measurements.

Pressure stimulation was applied using a hand-held algometer (Type 2, Somedic Production AB, Sollentuna, Sweden) using a probe size of 2 mm in diameter. The pressure was gradually increased with a rate of 30 $\frac{kPa}{s}$.

The subjects were instructed to press a button when the pressure tol-

erance threshold (PTT) was reached.

7.3 Adverse effects

At each pain stimulation (baseline, 24 h, 48 h, 72 h and 144 h) patients were asked to report 4 of the most common adverse effects (nausea, drowsiness, dizziness and local irritation due to the patch). The Adverse effects were rated on the following scale:

- 1 = Nothing
- 2 = Light feeling
- 3 = Moderate feeling
- 4 = Intolerable feeling

Other adverse effects reported by the patients were rated on the same scale and recorded.

7.4 Evoked potentials

Electrical stimulation was performed using two bipolar electrodes (Neuroline 720, REF: 72001-K/12, Ambu a/s, Denmark). The electrodes were placed on the left volar forarm over the median nerve, 2 cm distal to the wrist with an inter-electrode distance of 1 cm.

The stimulation was controlled by a stimulator (Isolator Stimulator Noxi IES 230, JNI Biomedical, Klarup, Denmark).

The stimulation was performed using single stimulation (2 ms) at the pain detection threshold (PDT).

EEG recordings were sampled at 1000 Hz in AC mode at the Cz electrode (NuAmp, Neuroscan, El Paso, TX, USA). Recordings were band pass filtered online from 0.05 to 200 Hz.

Two identical recordings of 60 sweeps were performed every time EPs were recorded.

CHAPTER 8

Pre-processing

Data was filtered using a notch filter with cut-off frequencies at 49 and 51. Epochs were extracted from the data from 50 ms before until 500 ms after each stimulus. Baseline correction and linear detrending was then applied to the epochs.

8.1 Scaling

In order to make the data comparable, scaling was performed on the data. The two baseline measurements where scaled to each other. Afterwards all the other timepoints where scaled by the same amount as the corresponding baseline.
Two different approaches to the scaling was tested; Area under curve based scaling, and peak-to-peak based scaling.

Area under curve

This method works by equalizing the area under the curve of the signals. For each baseline, the averaged signal for all sweeps is found. The area under the curve is then calculated by rectifying the signal by taking its absolute value and calculating the mean.
The object of the scaling was to scale this value to 1 for both baselines. This was done by finding the scaling factor (k) for each baseline, using equation 8.1.

$$k = \frac{1}{AUC} \tag{8.1}$$

For both types of treatment all EP sweeps where multiplied by the scaling factor for the corrosponding baseline.

Peak-to-peak

This method is similar to the previous, except that it uses the peak-to-peak value of the signal instead of the area under the curve.
The average of the EP sweeps for each baseline measurement was examined from 75 ms to 315 ms after stimulation onset. The maximum and the minimum value was found within the period of time, and the

difference between them calculated as the peak-to-peak value. The scaling factor was then found using equation 8.2

$$k = \frac{1}{Peak - to - Peak} \tag{8.2}$$

After finding the two scaling factors, all EPs where multiplied by the scaling factor for the corrosponding baseline.

CHAPTER 9

Feature extraction

9.1 Matching pursuit

TMP was used for decomposition of the recorded EEG sweeps since the latency of EP components might be affected by the treatments [Schmidt et al., 2007].
Using the TMP, 15 common atoms where found for all subjects, that best described all of the recorded single sweeps. Afterwards atoms ability to seperate the two treatment was tested using the SVM. The baseline-corrected features from each atom were used to classify between treatments at 24, 48, 72 and 144 hours after treatment. The avererage of these classification performances was the used to describe the atoms discriminative power.
Atoms which exibited a large discriminative power were then selected for further analysis.

9.2 Wavelet

This project implemented the CWT in a way to analyze the different frequency bands of EEG oscillations. The objective was to find the amplitude and the latency of the most dominant waveforms within each band. This was thought to be similar to the matching pursuit algorithm, with the added benefit of additional control over the frequency bands to analyze. The four frequency bands to analyze were defined as:

- Delta: 0.5 - 4 Hz
- Theta: 4 - 8 Hz
- Alpha: 8 - 12 Hz
- Beta: 12 - 32 Hz

The morlet wavelet was chosen in order to make the two methods for feature extraction more comparable. Since MP uses a dictionary of gabor atoms, the morlet wavelet was chosen for decomposition.

Scale selection

Scales where selected based on the frequency bands. Therefore, frequencies from 0.5 to 32 Hz had to be covered by the transform with a chosen interval of 0.5 Hz.
Since wavelets are defined by scale and not frequency, a conversion to ensure that the correct scales are used for analysis is needed. For this the center frequency of the wavelet was used, which for morlet wavelets should be accurate, since the morlet wavelet is basically a sinusoid modulated by a gaussian function.
Previously a method to calculate the pseudo-frequencies from a set of given scales, using the center-frequency of a wavelet has been developed [Misiti et al., 2011]. The calculation is performed using equation 9.1.

$$F_a = \frac{F_c}{a \cdot \Delta} \tag{9.1}$$

Where F_a is the pseudo-frequency, F_c is the center-frequency of the chosen mother wavelet, a is the scale and Δ is the sampling period. This equation was rewritten to obtain the scale from a given frequency (Equation 9.2).

$$a = \frac{F_c}{F_a \cdot \Delta} \tag{9.2}$$

Using this function, scales for the morlet wavelet where chosen corresponding to frequencies ranging from 0.5 to 32 Hz, with intervals of 0.5 Hz.

Dominant waveforms

Each EP was decomposed using the CWT for the calculated scales, resulting in a set of wavelet coefficients for each scale.
The scales were then further divided into the four different frequency bands. For each band, the maximum absolute wavelet coefficient was found. This coefficient marks the most dominant waveform within that band and the value of the coefficient was recorded as the amplitude. The latency was recorded as the value b for the coefficient, since b is the latency of the wavelet.
The basic principle is shown on figure 9.1 with data generated for the purpose.

This resulted in features for both the latency and amplitude of the most dominant waveform for each frequency band within each single-sweep EP.

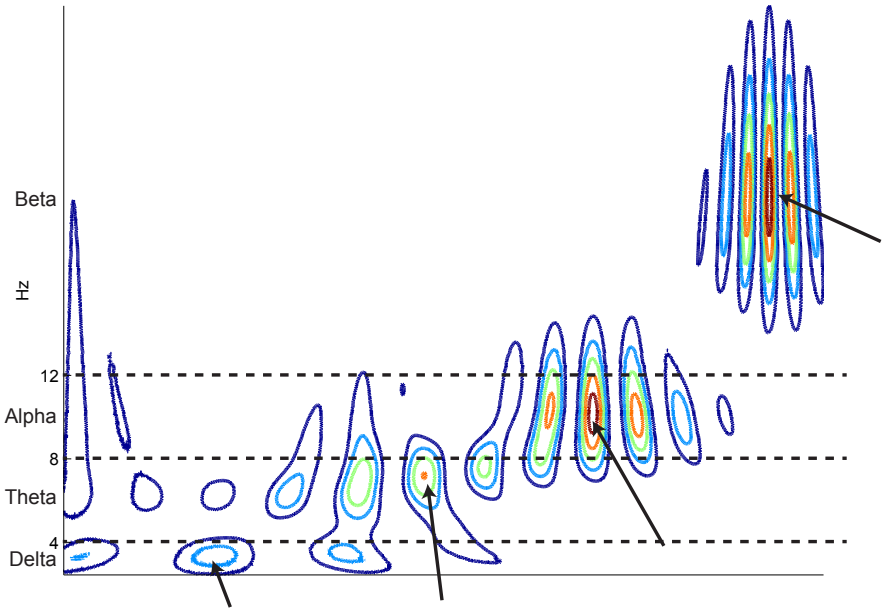


Figure 9.1: *The principle in of the implemented wavelet features using a plot of generated data. The time-frequency contour plot is divided into the frequency bands by lines. Within each band the dominant component is identified with an arrow. The amplitude and latency of these components are extracted as features.*

CHAPTER 10

Group analysis

Group analysis of the extracted features were performed by means of statistical analysis to indentify if differences in the EEG correlated to the analgesic effect.

10.1 Statistical analysis

The extracted features where log-transformed, baseline-corrected and for each recording time the mean of the feature was found. The features were then analysed using two-way repeated measures ANOVA, with time and treatment as factors.

10.2 Correlation

Features which exibited statistically significant differences between treatment with placebo and buprenorphine were checked for correlation to the clinical scores using the z-score and Pearson's linear correlation. P-value below 0.05 indicated statistical significance.

For correlation with the plasma concentrations, the values obtained 24 hours after drug administration was excluded from the correlation. This is done to account for the delay before analgesic effect is present.

Since the features of interest where pre-hoc defined by the results of the ANOVA test, adjustments for mass significance were not performed as to not discard important findings due to type II errors, which is a common problem using e.g. the Bonferroni correction [Perneger, 1998].

CHAPTER 11

Individual analysis

Features from the group analysis which showed correlation to the clinical scores, where used in an individual analysis using SVM, to determine if the results found at the group level also translated to the individual.

11.1 Classification

Classification was performed by an SVM using a linear kernel function. Classification performance was determined using leave-one-out crossvalidation.
To account for the placebo effect, the classification scheme shown on figure 11.1 was used, where the classification is performed between each recording time for buprenorphine and placebo treatment.

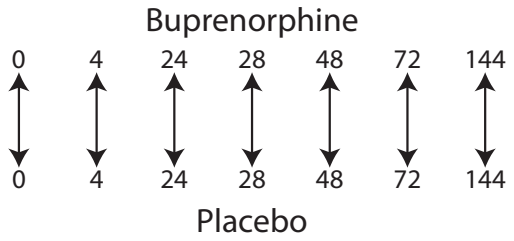


Figure 11.1: *The classification scheme used to account for the placebo effect. The arrows indicate which recordings are compared in the classification.*

This classification scheme also serves another important purpose, which is to verify the reproducability of the experiment. This is done when comparing the two baseline recordings. Here the classification performance should be close to 50 % (insignificant classification), since the two baseline recordings should be similar. Therefore it was checked that the baseline recordings were classified as being similar. Otherwise the chosen features could not be used to describe differences between the treatments.

11.2 Correlation

Afterwards correlation was performed in the same manner as described in chapter 10. Correlation was performed between the per-

formance curves obtained from the SVM and clinical scores.

PART III

Results

CHAPTER 12

Scaling

After performing both types of scaling of the data, the baselines were plotted against eachother for each method, to determine by visual inspection which method seemed to provide the most accurate estimate. The plots are shown on figure 12.1. Inspection revealed that though the methods were very similar, scaling using peak-to-peak aplitudes performed better in a few cases, such as case number 8 and 9.
In the cases there were differences in the scaling methods, it seemed to be because the main peak being wider for one of the signals. This resulted in higher difference in amplitudes, for scaling using energy.
Based on these observations, scaling was performed using peak-to-peak amplitudes.

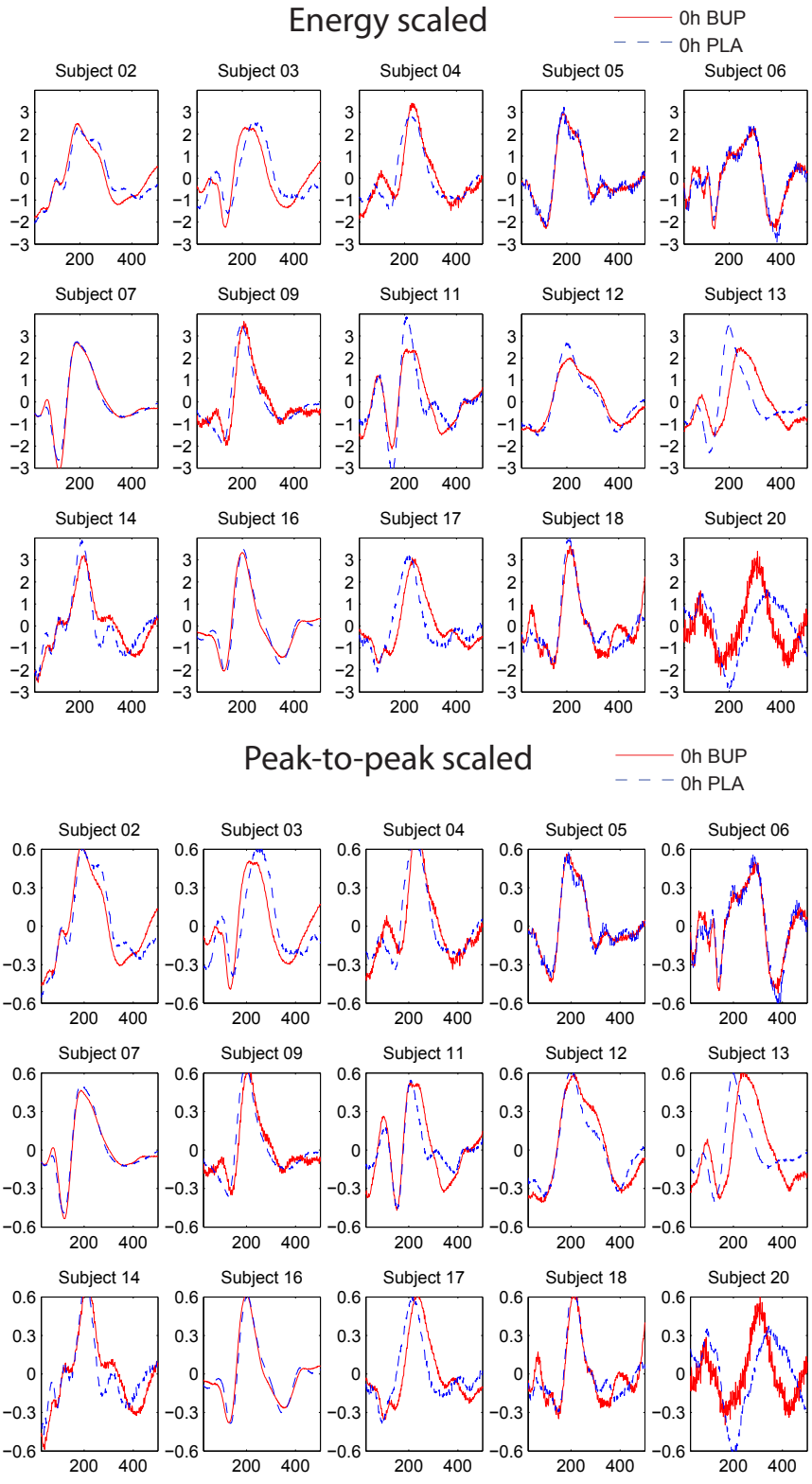


Figure 12.1: *Comparison of scaling using the energy of the signal(top) and the peak-to-peak value (bottom). The baselines are plotted against each other, to visualise how the data is scaled to each other.*

CHAPTER 13

Group analysis

The study was completed for 15 out of 22 subjects. One left the study due to a job offer distant from the site, and another was hospitalized due to reasons unrelated to the study. Furthermore 2 patients were excluded based on poor data quality of the EPs while 3 patients were excluded due to several missing measurements caused by adverse effects preventing them to participate in the experiment.

Two patients had few missing measurements. The pain scores from these patients were interpolated from the other measurements, while the extracted features from these missing measurements were removed from the analysis.

13.1 Wavelet features

Each feature was analysed using two-way repeated measures ANOVA, and the results are summarized in table 13.1, which shows the P-values obtained from each test, representing differences between treatments, recording times and if there is interaction between the two factors.

Feature	Treatment	Time	Interaction
A_{Delta}	0.34	**0.03**	0.19
A_{Theta}	-	-	**0.03**
A_{Alpha}	-	-	**<0.001**
A_{Beta}	-	-	**0.02**
L_{Delta}	0.33	0.06	0.33
L_{Theta}	0.82	0.63	0.99
L_{Alpha}	0.31	0.15	0.51
L_{Beta}	0.80	0.83	0.79

Table 13.1: *Overview of the P-values obtained through two-way repeated measures ANOVA, for the different extracted features. P-values which are statistically significant are written in bold.*

Latency features were discarded from further analysis, since no differences were revealed between treatments (ANOVA). All amplitude features showed significant differences (ANOVA). Their development over time is shown in figure 13.1.

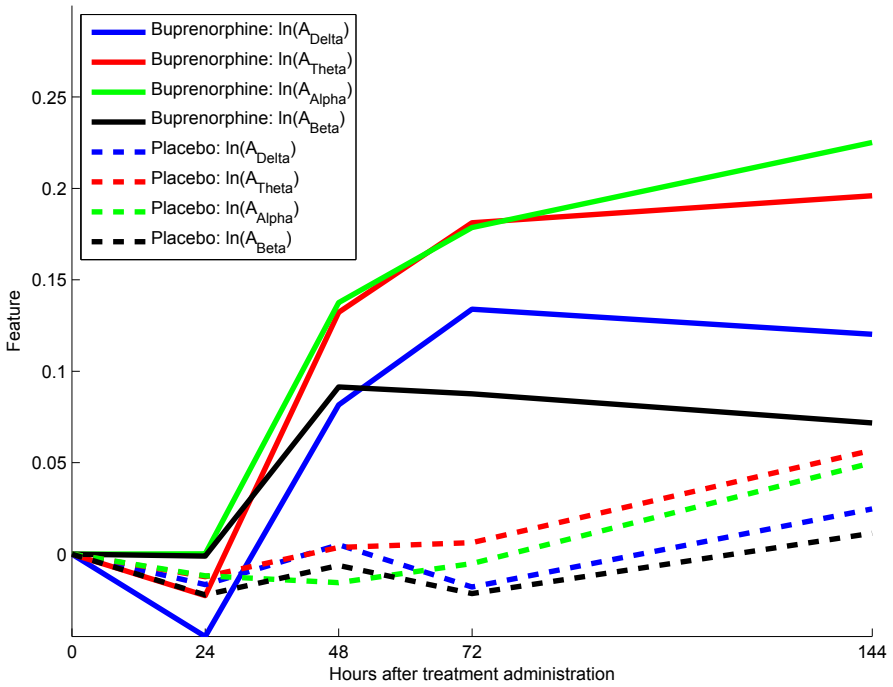


Figure 13.1: *Plot of the development of amplitude features over time for all frequency bands.*

The amplitude features were all checked for correlation with the clinical scores and the results are shown in table 13.2.

Clinical scores	A_{Delta}	A_{Theta}	A_{Alpha}	A_{Beta}
Bone pain	0.79	0.81	0.77	**0.96**
Heat pain	0.59	0.66	0.67	0.84
Electrical pain	0.19	0.33	0.41	0.42
Adverse effects	0.02	0.06	0.04	0.33
Plasma concentration	0.83*	0.81*	0.74*	**0.98***

Table 13.2: *Correlations between the wavelet amplitude features for every frequency band and clinical scores. Statistically significant ($P < 0.05$) correlations are marked in bold. *: Note that a measurement (24 hours after treatment) has been removed before correlation. This is done to account for the delay before analgesic effect is present.*

The correlations in table 13.2 show a significant relationship between the features for the beta band and the bone pain scores. Figure 13.2 shows the development over time for this feature, as well as the clinical scores.

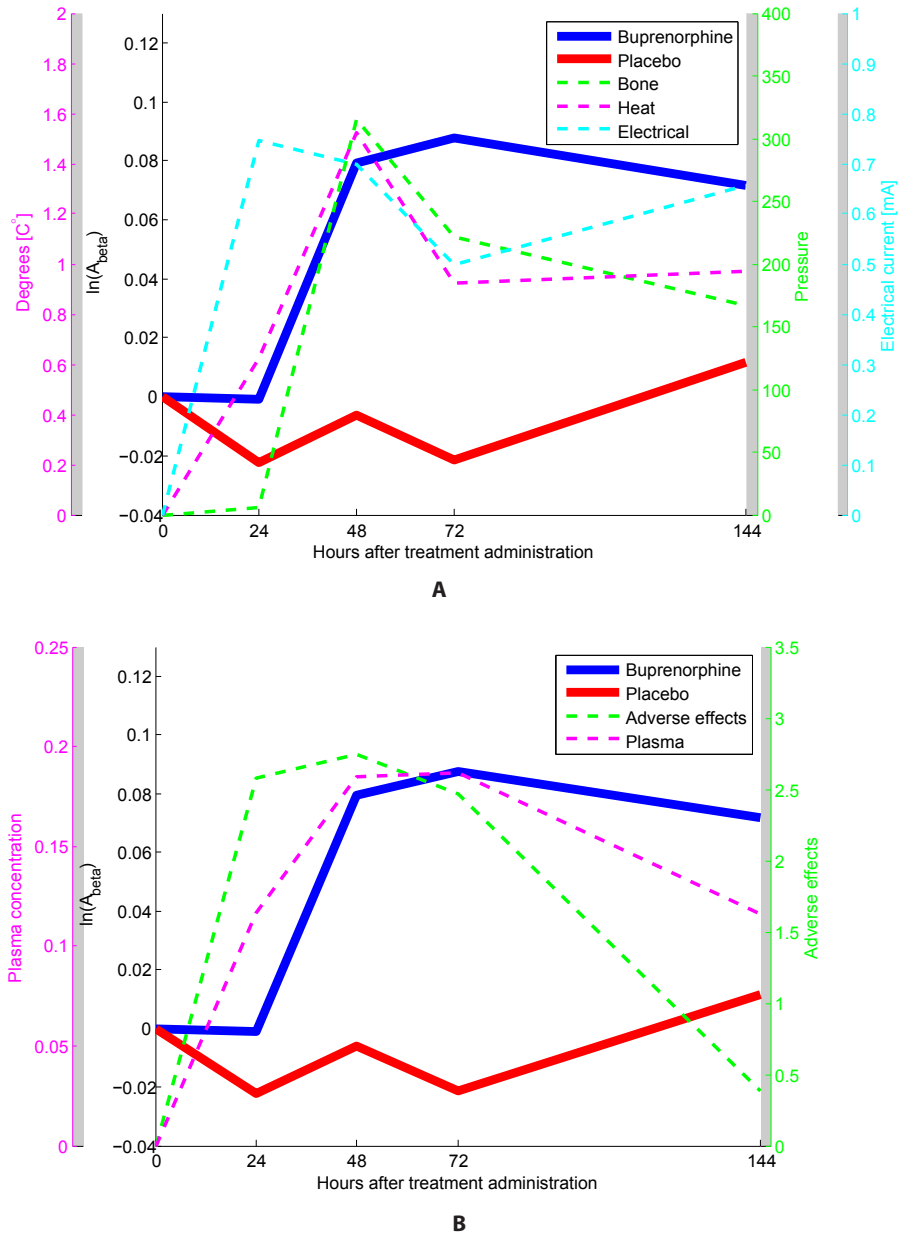


Figure 13.2: *Figure showing the development of the A_{Beta} feature and clinical scores over time on seperate scales to ease comparison. A: Graph of A_{Beta} and the subjective pain scores. B: Graph of A_{Beta} and the adverse effects and plasma concentrations.*

13.2 Matching pursuit

Twelve atoms were decomposed to select best performing ones by use of the SVM. Features for latency were discarded beforehand, due to the findings with the latency features of the wavelet transform.
Figure 13.3 shows the average performance amplitude features from the atoms at 24, 48, 72 and 144 hours after treatment initiation. Classification was performed between placebo and buprenorphine treat-

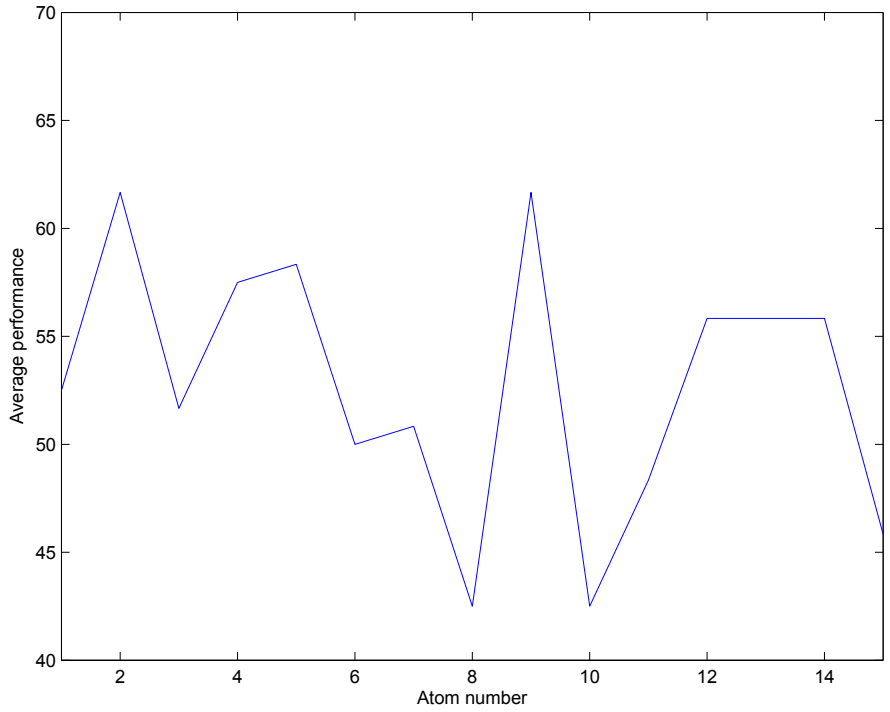


Figure 13.3: *Figure showing the discriminative power of the amplitude feature from the extracted atoms determined using the SVM. The average performance is the average of classifications for recording times 24, 48, 72 and 144 hours after treatment initiation when classifying between placebo and buprenorphine treatment.*

ment. The plot was then used to select the features that were most discriminative.

Inspection of figure 13.3 shows atoms 2 (62 %) and 9 (62 %) as the most discriminative atoms, and they were selected for ANOVA analysis.
Table 13.3 shows the results from ANOVA testing. Both atoms showed significant differences for buprenorphine treatment compared to placebo, and where therefore checked for correlation to the clinical scores.

Feature	Treatment	Time	Interaction
A_{Atom2}	-	-	**<0.001**
A_{Atom9}	-	-	**0.02**

Table 13.3: *Results of the P-values obtained through two-way repeated measures ANOVA, for the features extracted through MP. P-values which are statistically significant are written in bold.*

Table 13.4 shows the correlations for the atom features. No correlations reached statistical significance.

Clinical scores	A_{Atom2}	A_{Atom9}
Bone pain	0.71	-0.62
Heat pain	0.22	-0.51
Electrical pain	0.47	-0.37
Adverse effects	0.04	-0.53
Plasma concentration	0.70*	-0.81*

Table 13.4: *Correlations between the matching pursuit amplitude features for atoms 2 and 9 and the clinical scores. Statistically significant ($P < 0.05$) correlations are marked in bold. *: Note that a measurement (24 hours after treatment) has been removed before correlation. This is done to account for the delay before analgesic effect is present.*

13.3 Reproducibility

The only feature that exibited significant differences between treatments and correlated to the analgesic effect was A_{Beta}. This feature was checked for reproducibility in order to make sure that the data was reproducible between baselines as well as reproducible between recordings.

Baseline reproducibility

To check whether A_{Beta} was reproducible between baselines, a paired t-test was performed between the baseline values for all patients. The t-test showed that the feature was reproducible, i.e. there were no significant differences between baselines (P = 0.23).

Agreement between recordings

At every recording time, two identical EEG recordings where performed. It is important that there is agreement between the features extracted from these recordings, since it represents the ability to make the EEG measurements consistently.
The Bland-Altman plot is commonly used to compare measurement techniques and was used to investigate the agreement between the recordings [Hanneman, 2008]. Figure 13.4 shows the plot for A_{Beta}. The plot shows that the data is homoscedastic, meaning that the measurement error is consistant regardless of the value of the feature.
Furthermore, the coefficient of variance was computed, to assess the agreement between all recordings. The coefficient of variance for A_{beta} was 7.78 %, which indicates a good level of agreement between recordings [Atkinson and Nevill, 1998].

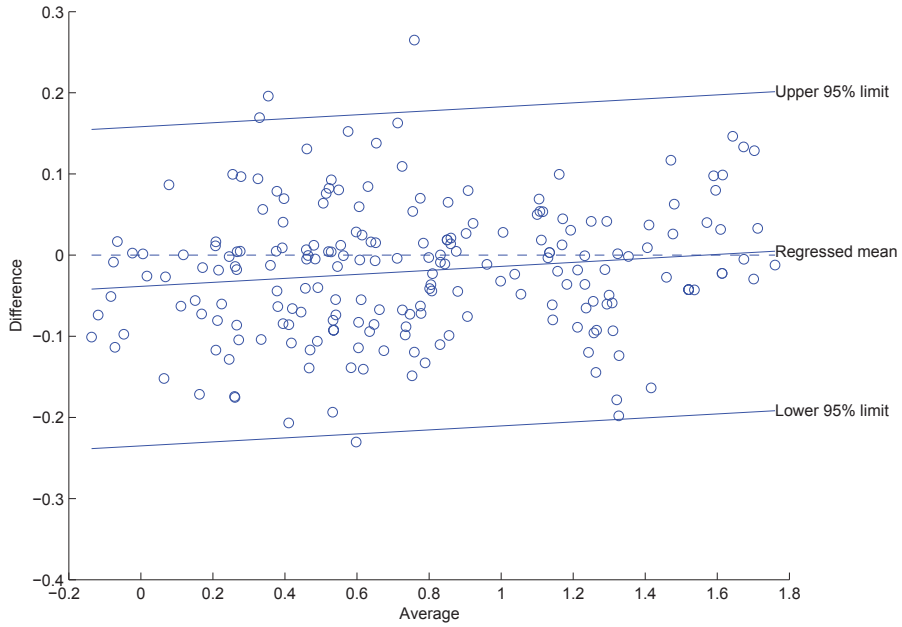


Figure 13.4: *Bland-Altman plot for A_{Beta}. It shows the mean between paired samples on the x-axis and the difference between them on the y-axis.*

CHAPTER 14

Individual analysis

The results from the group analysis was used to determine individual analysis. The wavelet feature A_{Beta} was the only feature correlating with the subjective bone-scores, and these were therefore chosen for the individual analysis.

The individual analysis used A_{Beta} for all sweeps as features for classification between placebo and buprenorphine treatment. Figure 14.1 shows the performance curves for all subjects, plotted against their subjective pain scores.

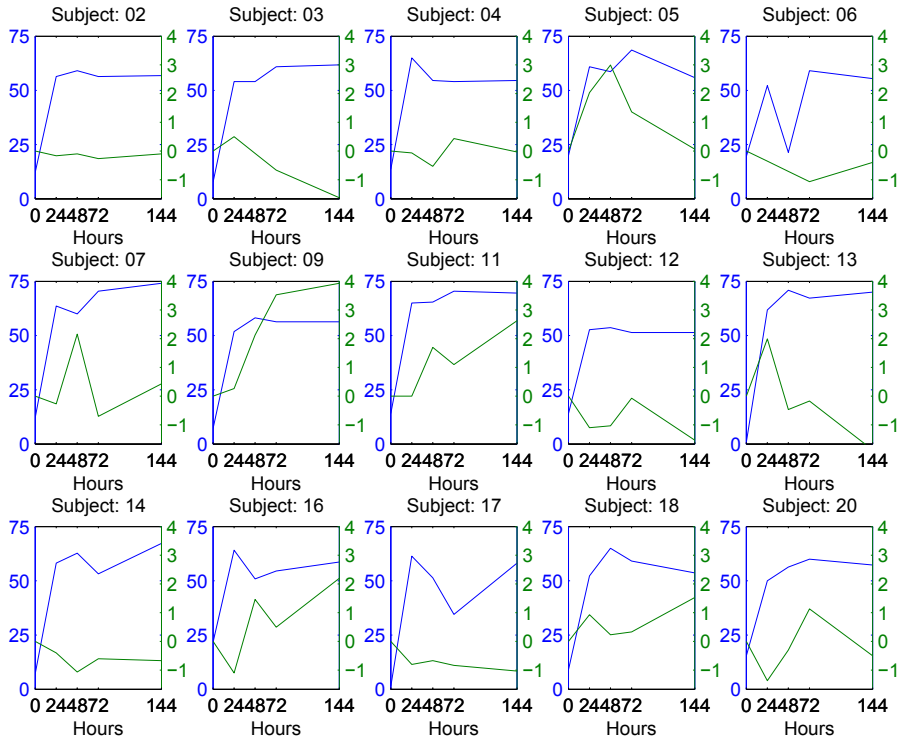


Figure 14.1: *Figure comparing the classification performances with the subjective bone-associated scores. Units on the left y-axis (blue) are given in percentages of correctly classified samples. Units on the right y-axis (green) are given in MPa.*

Afterwards correlation between the performance curves and the bone-associated pain scores where checked. Results of the correlation are shown in table 14.1.

Subject	Bone pain
2	-0.70
3	-0.39
4	-0.08
5	0.57
6	-0.44
7	0.04
9	0.67
11	0.58
12	-0.62
13	-0.15
14	-0.82
16	0.08
17	**-0.88**
18	0.38
20	0.05

Table 14.1: *Correlations between the bone-associated pain scores and the performance curves when classifying using the A_{Beta} feature. Statistically significant ($P < 0.05$) correlations are marked in bold.*

PART IV

Synthesis

CHAPTER 15

Discussion

This study investigated single-sweep pharmacological-EEG before and during treatment with placebo or buprenorphine administered through a transdermal patch. It was found in the group analysis that treatment with buprenorphine caused an increase in beta-band activity (12 - 32 Hz) which correlated to the subjective scores for bone-associated pain (P = 0.008) as well as the measured plasma concentrations of buprenorphine in the blood stream (P = 0.02).

The results in this study are reasonable compared to previous findings that indicate that buprenorphine targets receptors related to bone-associated pain [Andresen et al., 2010].

Choice of features

This study implemented features which were new or not commonly used in EEG analysis.

Features from TMP showed siginificant differences in the ANOVA test, but the features did not correlate to the analgesic effect. The results reported in this work from TMP resulted from calculating common atoms for all subjects. The weakness of this approach is due to the fact that the atoms have to match signals from all subjects at the same time the fit to each individual signal will be poor due to the difference in EP morphology between patients. This is illustrated in figure 15.1 where the atom decomposed for all subjects at once clearly shows a poor fit.

Another method was also tried where different atoms where decomposed for each subject, but with similar results. The problem with this approach is that atoms between subjects can vary greatly and therefore results between subjects are not comparable.
Another drawback of the MP method is that there is no preselection of which frequency band is to be analyzed. This means that e.g. for one subject the 3^{rd} atom might be high-frequency, whereas the 3^{rd} atom for another subject might be low frequency. For MP to be improved for analysis of EEG, a higher degree of control over the atoms being decomposed is needed. This can be acheived by making restricted dictionaries, that only decompose the signal into components within certain frequency ranges. Several restricted dictionaries could be made, one for each frequency band to be analyzed. Another

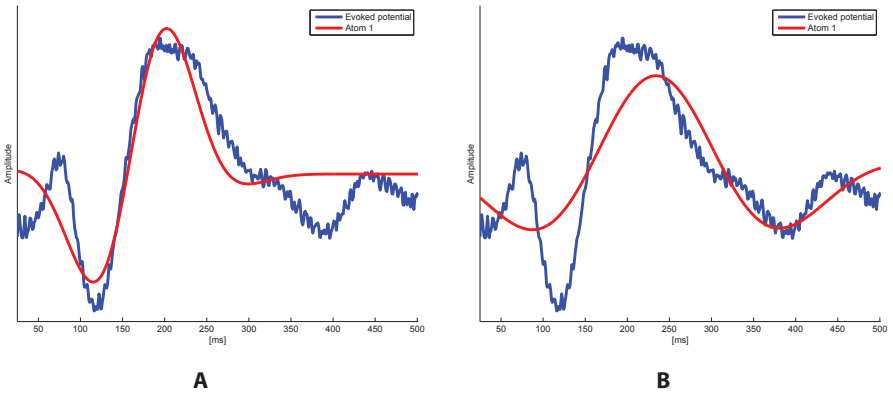


Figure 15.1: *Illustration of the an evoked potential and its first atom using the two different approaches for matching pursuit.* ***A*** *shows the atom from decomposing atoms individually for each subject.* ***B*** *shows the atom from decomposing common atoms for all subjects. It is clear that the fit of the atom in* ***A*** *is better. However this approach makes atoms inconsistent between subjects.*

possible solution is to bandpass filter the signal into the different frequency bands before decomposition in MP.
Both methods has the advantage that only predefined frequency band will be analysed, which would grant a higher level of control and make MP more comparable to existing methods.

Analysis of EEG using CWT is already common [Graversen et al., 2011]. However features from CWT are usually the spectral indicies, which reflect the overall energy within each frequency band. This study implemented a new feature, attempting to mimic MP with the added benefit of being able to choose frequency bands by finding the latency and amplitude of the most dominant waveform in each frequency band. This approach can be vulnerable, since the feature is based on a single value from the entire wavelet decomposition, as opposed to all values for the spectral indicies. It is very possible that the spectral indicies are better features for this application, since the latencies did not show differences between treatments.
Features were found that correlated to the analgesic effect. However, the feature should still be validated by comparison to the more established method of using spectral indicies, to determine the advantages and disadvantages of the method.

Group analysis

The group analysis revealed that all A_{band} features showed significant differences between treatments. Correlation with analgesic effect revealed that the rise in A_{Beta} correlated with the rise in PTT for bone-associated pain as well as the plasma concentrations.

Previous analysing pharmacological-EEG have found that treatment with analgetics induce slower EEG oscillations [Graversen et al., 2011]. It appears that this study shows the opposite, but this is due to the difference in methods. Closer inspection of the extracted features revealed that even though the A_{Beta} feature increases, the slow-frequency bands show even greater increases in activity. Therefore the distribution of energy still moves to the lower frequency bands, which makes the results consistant with previous findings.

Individual analysis

The individual analysis using SVM revealed one significant correlation (P = 0.05) between SVM performance and bone-associated pain scores. The fact that performances from only one subject correlated with a relatively high P-value indicate that the findings do not indicate a general tendency. Upon further inspected of the patient with a significant correlation (subject 17) on figure 14.1 it becomes clear that the correlation does not reflect the desired result. The subject does not gain increased pain tolerance, in fact pain tolerance is actually lower during buprenorphine treatment than placebo. The correlation is therefore purely due to chance.

There is another problem present in the results from the SVM. It is clear from inspection of figure 14.1 that most performance curves start much lower than 50 %. This means that when classifying between baselines(which have been baseline corrected to have a mean value of 0) where the expected output should be very close to 50 %, the SVM manages to perform worse than random assignment of samples to classes. This is an unacceptable problem, and means that the results from the SVM can not be trusted in this case.
Several attempts were made to resolve the error. Three different implementations of the SVM were tested for this purpose. Random, normally distributed data was generated as features to test the different implementations, with varying means. Results from this test showed that all implementations performed as expected. However, when the generated data was replaced with actual data from the study all implementations failed.
It is hard to say where the error lies, and it was not resolved during the project period. The problem could be an interaction between the actual data, which is not perfect normally distributed and the implementations. However further testing is needed to draw definite conclusions.

Methodoligy

It is worth noting that single sweep analysis could be an important tool in the EEG analysis, since it prevents the loss of data due to the averaging process [Domnick et al., 2009]. This seems to be especially important for this study, since the changes found in the beta band are high-frequency and might have been removed in the averaging process.

The stimulation was performed at the PDT for the patient each time recordings were performed. This could be a problem for the results, since the observed differences in the EEG could be caused by increased stimulation current instead of the analgesic effect. However, had the stimulation been performed using a fixed current, the subject might not have found the stimuli to be painful during treatment with buprenorphine, due to the analgesic effect. Also, it brings further credibility to the results that no features correlated with the electrical stimulation current. Had a significant correlation been present it would be likely that the differences in EEG where due to the increased stimulation intensity, rather than the analgesic effect.

Before correlation with the plasma concentrations were performed, the values from 24 hours after treatment initiation was removed. This is done to account for the delay before analgesic effect is present. This effect can be seen in figure 13.2B, where the plasma concetrations rise during the first 24 hours of treatment. However this is not the case for A_{Beta} or the bone-associated pain scores. The correction therefore seems reasonable since the plasma concentration 24 hours after treatment initiation does not reflect in the subjective scores for bone-associated pain.

In this study the plasma concentrations of buprenorphine in the blood was investigated. Norbuprenorhine, the metabolite of buprenorphine also has an analgesic effect and therefore might also affect the EEG [Andresen et al., 2010]. It is possible that norbuprenorphine is affecting the EEG at lower frequencies, causing the low-frequency features to not correlate with the plasma concentrations. However since this is not reflected in subjective pain scores this effect is of less interest.

The study used only the Cz electrode for analysis. It is possible that the analgesic effect is reflected better at other electrodes. Other studies have used a more frontal electrode (Fz), since the depth-of-anesthesia is measured based on the EEG of frontal electrodes [Kortelainen et al., 2009].

CHAPTER 16

Conclusion

This study investigated the effect of buprenorphine treatment through pharmacological-EEG. Features new to EEG analysis were tried using both MP and CWT. The group analysis found features from the CWT to be superior, probably due to the increased control over the analysis in the CWT.

It was found that the significantly increased activity in the beta band correlated with the analgesic effect of morphine in the bone-associated pain scores, as well as the measured plasma concentrations of buprenorphine in the blood stream. The results are reasonable since previous studies have determined buprenorphine to be especially effective against bone-associated pain [Andresen et al., 2010]. Previous pharmacological-EEG studies have found slowing of the EEG oscillations which match the results of this study since the activity in the low-frequency bands rise more than in the high-frequency bands [Graversen et al., 2011].

It was attempted to utilize performance measures obtained with an SVM to correlate to the clinical scores on an individual level. However despite numerous attempts with different SVM implementations the classification never performed as espected when using real data. More work is needed to identify the problem preventing the SVM from performing as expected.

The results from this study brings a better understanding of the mechanisms involved regarding the analgesic effect of buprenorphine. In the future they might be used in clinical trials to monitor the analgesic effect of the analgetic [Graversen et al., 2011; Staahl et al., 2009]. Future work should focus on testing the effects on actual patients instead of healthy volunteers. Furthermore the methods for feature extraction should be tested against more established methods, to determine their reliability.

References

M. Akin. Comparison of wavelet transform and fft methods in the analysis of eeg signals. *Journal of Medical Systems*, 26, 2002.

T. Andresen, C. Staahl, A. Oksche, H. Mansikka, L. Arendt-Nielsen, and A. Drewes. Effect of transdermal opioids in experimentally induced superficial, deep and hyperalgesic pain. *British Journal of Pharmacology*, 2010.

T. Andresen, C. Staahl, A. Oksche, H. Mansikka, L. Arendt-Nielsen, and A. M. Drewes. Effect of transdermal opioids in experimentally induced superficial, deep and hyperalgesic pain. *British Journal of Pharmacology*, 2011.

G. Atkinson and A. M. Nevill. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. *Sports Medicine*, 1998.

H. Breivik, B. Collett, V. Ventafridda, R. Cohen, and D. Gallacher. Survey of chronic pain in europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain*, 10, 2006.

C. Cortes and V. Vapnik. Support-vector networks. *Machine Leaming*, 20, 1995.

C. Domnick, M. Hauck, K. L. Casey, A. K. Engel, and J. Lorenz. C-fiber-related eeg-oscillations induced by laser radiant heat stimulation of capsaicin-treated skin. *Journal of Pain Research*, 2, 2009.

P. Durka. *Matching Pursuit and Unification in EEG Analysis*. Artech House, 2007.

P. Durka, A. Matysiak, E. M. Montes, P. V. Sosa, and K. Blinowska. Multichannel matching pursuit and eeg inverse solutions. *Journal of Neuroscience Methods*, 2005.

C. Graversen, S. S. Olesen, A. E. Olesen, K. Steimle, D. Farina, O. H. G. Wilder-Smith, S. A. W. Bouwense, H. van Goor, and A. M. Drewes. The analgesic effect of pregabalin in patients with chronic pain is reflected by changes in pharmaco-eeg spectral indices. *British Journal of Clinical Pharmacology*, 2011.

S. K. Hanneman. Design, analysis, and interpretation of method-comparison studies. *AACN advanced critical care*, 2008.

B. B. Hubbard. *The World According to Wavelets*. A K Peters, Ltd., 1996.

O. Ivanciuc. Applications of support vector machines in chemistry. *Reviews in Computational Chemistry*, 23, 2007.

N.-H. Jensen and P. Sjøgren. *Praktisk klinisk smertebehandling*. Munksgaard Danmark, 2009.

M. Karlsson and A.-C. Berggren. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 pg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: A 12-week, randomized, openlabel, controlled, parallel-group noninferiority study. *Clinical Therapeutics*, 31, 2009.

J. Kortelainen, M. Koskinen, S. Mustola, and T. Seppänen. Effects of remifentanil on the spectrum and quantitative parameters of electroencephalogram in propofol anesthesia. *Anesthesiology*, 2009.

M. Misiti, Y. Misiti, G. Oppenheim, and J. M. Poggi. *MatLab Wavelet Toolbox Users Guide*. 2011.

T. V. Perneger. What's wrong with bonferroni adjustments. *British Medical Journal*, 316, 1998.

S. Sanei and J. Chambers. *EEG Signal Processing*. John Wiley and Sons, Ltd, 2007.

G. N. Schmidt, E. Scharein, M. Siegel, J. Müller, S. Debener, R. Nitzschke, A. Engel, and P. Bischoff. Identification of sensory blockade by somatosensory and pain-induced evoked potentials. *Anesthesiology*, 2007.

B. H. Smith and N. Torrance. *ABC of Pain*. Blackwell Publishing Ltd., 2012.

C. Staahl, A. E. Olesen, T. Andresen, L. Arendt-Nielsen, and A. M. Drewes. Assessing analgesic actions of opioids by experimental pain models in healthy volunteers - an updated review. *British Journal of Clinical Pharmacology*, 2009.

G. Varrassi, G. Müller-Schwefe, J. Pergolizzi, A. Orónska, B. Morlion, P. Mavrocordatos, C. Margarit, C. Mangas, W. Jaksch, F. Huygen, B. Collett, M. Berti, D. Aldington, and K. Ahlbeck. Pharmacological treatment of chronic pain - the need for change. *Current Medical Research & Opinion*, 26, 2010.

WHO. *Cancer Pain Relief with a guide to opioid availability*, 1996.