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Prediction of postoperative opioid analgesia using clinical-experimental parameters and electroencephalography

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Abstract

Background: Opioids are often used for pain treatment, but the response is often insufficient and dependent on e.g. the pain condition, genetic factors and drug class. Thus, there is an urgent need to identify biomarkers to enable selection of the appropriate drug for the individual patient, a concept known as personalized medicine. Quantitative sensory testing (QST) and clinical parameters can provide some guidance for response, but better and more objective biomarkers are urgently warranted. Electroencephalography (EEG) may be suitable since it assesses the central nervous system where opioids mediate their effects.

Methods: Clinical parameters, QST and EEG (during rest and tonic pain) was recorded from patients the day prior to total hip replacement surgery. Postoperative pain treatment was performed using oxycodone and piritramide as patient-controlled analgesia. Patients were stratified into responders and non-responders based on pain ratings 24 h post-surgery. Parameters were analysed using conventional group-wise statistical methods. Furthermore, EEG was analysed by machine learning to predict *individual* response.

Results: Eighty-one patients were included, of which 51 responded to postoperative opioid treatment (30 non-responders). Conventional statistics showed that more severe pre-existing chronic pain was prevalent among non-responders to opioid treatment ($p = 0.04$). Preoperative EEG analysis was able to predict responders with an accuracy of 65% ($p = 0.009$), but only during tonic pain.

Conclusions: Chronic pain grade before surgery is associated with the outcome of postoperative pain treatment. Furthermore, EEG shows potential as an objective biomarker and might be used to predict postoperative opioid analgesia.

Significance: The current clinical study demonstrates the viability of EEG as a biomarker and with results consistent with previous experimental results. The combined method of machine learning and electroencephalography offers promising results for future developments of personalized pain treatment.

1. Introduction

Opioids are the primary analgesic drugs used to treat moderate to severe pain, including pain after surgery (Liu and Wu, 2007). However, treatment of postoperative pain remains in many cases unsatisfactory, leading to unnecessary suffering (Dolin et al., 2002; Sommer et al., 2008; Maier et al., 2010; Drewes et al., 2013). Furthermore, inadequate analgesia carries the risk of developing persistent long-term pain (Kehlet et al., 2006; Gerbershagen et al., 2009; VanDenKerkhof et al., 2012). Better understanding of the inter-individual differences in pain processing is paramount to achieve improved and personalized opioid treatment (Bruehl et al., 2013). However, there is no method to determine if opioid treatment will provide analgesic relief in the postoperative setting. Some studies have focused on quantitative sensory testing (QST), but with contradictory results (Grosen et al., 2013). This indicates a need for improvement in the ability to accurately predict analgesic effect of opioids (Grosen et al., 2013).

Pain processing can be investigated using imaging techniques such as magnetic resonance imaging (Ahmedzai, 2013). However, electroencephalography (EEG) is more clinically feasible to assess pain processing as it has a considerably lower cost and can be used directly at the patient's bedside or in the outpatient clinic. Furthermore, EEG can assess inter-individual differences in pain processing by predicting the experience of pain within a single subject (Schulz et al., 2011). For instance, EEG recorded during rest was used to predict pain perception during experimentally induced pain (Nir et al., 2012) and in the clinic to asses analgesic efficacy (Graversen et al., 2012). We have previously shown that EEG during tonic pain is more reliable and superior to resting EEG for prediction of analgesic efficacy in healthy volunteers (Gram et al., 2014, 2015). The present study now aims to investigate EEG for prediction of analgesic efficacy in clinical population.

We *hypothesized* that risk factors for analgesic inefficacy of postoperative opioid treatment could be identified preoperatively. Additionally, we hypothesized that EEG could be used as an objective biomarker for predicting analgesic efficacy. Thus, the *aims* of this study were to (1) determine the effect of the postoperative pain treatment, (2) investigate risk factors associated with non-response to analgesic treatment and (3) predict the analgesic response based on the pre-operative EEG (during rest and tonic pain) on an individualized basis in patients undergoing hip replacement surgery. Unlike previous EEG prediction studies which used the spectral content within predefined frequency bands (Gram et al., 2015) to evaluate brain rhythmicity, we also applied a functional connectivity evaluation which considers the brain as a large inter-connected network and investigates the interactions between different cortical regions (Hardmeier et al., 2014). We also applied machine learning methods which have the ability to assess the interaction between several EEG features at once without making *a priori* assumptions about the data (Gram et al., 2015).

2. Methodology

The study was conducted at the Pain Clinic, Center for Anesthesiology, Emergency and Intensive Care Medicine at the University Hospital Göttingen, Germany and the Orthopedic University Hospital of the Medical School Hannover, Germany. The study was approved by the Ethical committees of the University Hospital of Göttingen (No 19/2/13) and conducted according to the recommendations of the Declaration of Helsinki.

2.1 Study subjects

Patients admitted to the Orthopaedic University Hospital Annastift in Hannover for total hip replacement were recruited between April and August 2013.

Inclusion criteria were patients above 18 years of age and able to give informed consent. Exclusion criteria were (1) severe neurological disease, which might interfere with the EEG recordings or experimental pain testing (including dementia); (2) Severe psychiatric disease such as major depression or schizophrenia or active drug abuse; (3) High dose of preoperative opioid therapy (>30 mg/day oral morphine equivalent). In case of post-operative delirium making the subject unable to complete the study due to disorientation or inability to answer questionnaires, the subject was excluded.

2.2 Study outcomes and risk factors

Response to post-surgical analgesic treatment was assessed using a response score based on the results of patients outcomes assessed by the 'Quality Improvement in Postoperative Pain Management' Questionnaire (QUIPS), which is a validated German outcome measurement instrument for postoperative quality control, see below (Meissner et al., 2008).

Predictors for insufficient analgesic response were investigated and included clinical patient characteristics and standardized assessment of the preoperative pain symptoms, QST parameters, conditioned pain modulation (CPM) effect and EEG during rest and cold pain. Clinical patient data included age, sex and body mass index (BMI) while parameters on the preoperative pain condition included pain duration, chronic pain grade (Von Korff et al., 1992), Mainz Pain Staging System (MPSS) (Schmitt and Gerbershagen, 1990), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy, 2005) as well as pain rated on passive rotation of the hip. QST parameters included heat and cold pain thresholds.

2.3 Study procedures

Fig. 1 shows the experimental setup. Patients were examined one day prior to their operation. Patients were told to refrain from smoking and from drinking coffee and other caffeine-containing beverages 2 h prior to the clinical testing.

All clinical testing were conducted between 15:00 and 18:00 on the preoperative day by the same examiner. The clinical testing commenced with familiarization of the cold pressor test and the experimental evoked pain conditions applied. Patients were placed on a bed in a semi-recumbent position, and the EEG cap was mounted on their head with conducting gel inserted for each electrode.

2.4 Perioperative pain management

The patients preoperative pain medication (type and dosage) was noted and the Medication Quantification Score (MQS), which is a reliable and validated score for quantifying analgesics, was calculated in order to obtain a comparable metric for all different analgesics (Masters Steedman et al., 1992). It enables characterization of analgesics when many analgesics are involved and doses are irregular, as is the case for the patient group in this study. It was calculated for each non-opioid and opioid based on weights assigned by medication class and dosage level (level 1 = sub-therapeutic dosage and/or on demand, level 2 = lower 50% of the therapeutic dose range, level 3 = upper 50% of the therapeutic dose range, level 4 = *supra*-therapeutic dose) using the 1998 detriment weights (Stormo et al., 1998). The detriment weights are summed by the dosage level to provide the final score. To provide a quantitative index for analgesics usage suitable for statistical analysis these scores were summed.

In the evening before and morning prior to surgery, all patients were pre-medicated with 20–30 mg dipotassium chlorazepat. General anaesthesia was performed according to the local clinical standards,

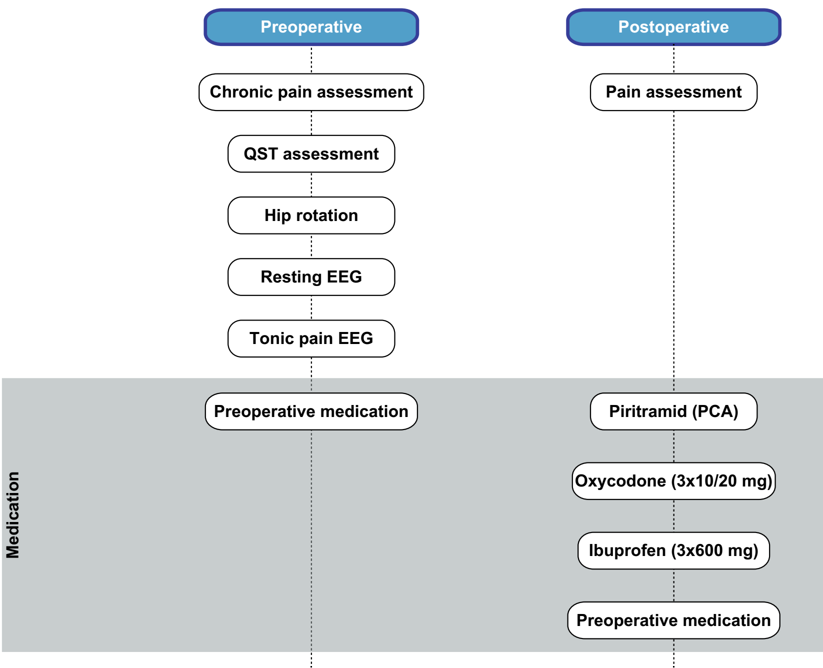

Figure 1 Experimental setup and study procedures. PCA, Patient-Controlled Anaesthesia; QST, Quantitative Sensory Testing.

with remifentanyl (1–1.5 μg/kg/3 min) and propofol (1–2 mg/kg). Orotracheal intubation was facilitated by 0.5 mg/kg atracurium. Propofol (3.5–4.5 mg/kg/h) and remifentanyl (0.15–0.25 μg/kg/min) were used for maintenance of anaesthesia. During the implantation of the femoral shaft, intravenous injection of 0.1 mg/kg piritramide and 15 mg/kg metamizol (or paracetamol, if contra-indicated) were administered.

In the recovery phase, patients received 10 or 20 mg slow-release oxycodone (10 mg if their weight was below 60 kg and age above 70 years, otherwise 20 mg was given) along with 600 mg ibuprofen. Pain was titrated using intravenous piritramide bolus application of 3.75 mg until pain intensity was 3 or below on a numerical rating scale (NRS; 0 = no pain und 10 = worst imaginable pain) (see section on pain assessments). Then patients received patient-controlled analgesia (PCA) with piritramide for 24 h (Perfusor fm PCA, B. Braun; single dose 2 mg, lockout 10 min, limit 30 mg/4 h) at a NRS of 3 or below and as soon as they were able to operate the PCIA system. On the ward, oxycodone (twice a day) and ibuprofen (three times a day) was administered according to the first dosage and followed a standardized postoperative pain treatment protocol (Erlenwein et al., 2012).

Then the 24 h opioid dose was calculated as oral morphine equivalent (ME; conversion factor to morphine: piritramide 1.5, hydromorphone 0.13, oxycodone 0.75, intravenous vs. oral morphine 3:1).

2.5 Chronic pain assessments

Before surgery, patients indicated their duration of pain, and their chronic pain grade was assessed (Von Korff et al., 1992). This grading system divides patients into four grades of chronic pain based on their pain intensity and disability, which can be summarized as:

(1) Grade I: low pain intensity, low disability
(2) Grade II: high pain intensity, low disability
(3) Grade III: high disability – moderately limiting
(4) Grade IV: high disability – severely limiting

The chronic pain grades I and II are based on the pain intensity, but only for patients with a low disability following their pain. Grades III and IV consists of patients with a certain degree of disability from their pain, and therefore disregards the pain intensity, but solely looks at how limiting the pain is (Von Korff et al., 1992).

Furthermore, the clinician assessed the patient's pain profile using the Mainz Pain Staging System (MPSS), which divides patients into three pain stages of increasing pain chronicity (Schmitt and Gerbershagen, 1990; Frettlöh et al., 2003).

2.5.1 Passive hip rotation

A test was performed to assess the magnitude of evoked pain with passive rotation of the hip scheduled for replacement. First, the leg was brought into a 90° flexed position, with the knee flexed at 90° at the same time, and then slowly rotated interiorly until the patient reported the first onset of pain (pain detection threshold). Then, the passive rotation was continued until the pain threshold was reached and this position was maintained for 30 s. Afterwards the patients were asked to rate the evoked hip pain on a NRS.

2.6 Quantitative sensory testing (QST)

Perceived pain intensity was rated on a NRS (0 = no pain und 10 = worst imaginable pain).

2.6.1 Heat pain threshold

Heat pain assessments were performed with 9 cm^2 Peltier Thermode, 10 cm proximal to the wrist of the right volar forearm, using a 'Thermo Tester' (TSA II NeuroSensory analyser, Medoc Ltd, Ramat Yishai, Israel). The temperature was gradually increased from a baseline of 32 °C baseline at a rate 1 °C/s to a maximum temperature of 52 °C. The subjects were instructed to press a button when the heat stimulus became painful and this was documented as the heat pain threshold. Four consecutive assessments were performed and the average of the last three threshold estimations was retained for further analysis.

2.6.2 Cold pressor test

Patients were instructed to submerge their non-dominant hand in water until the wrist was covered (~8 °C) and keep it submerged for 2 min. The temperature of the water was controlled. The maximum pain intensity perceived during the test was rated on a NRS.

2.6.3 Conditioned pain modulation (CPM)

A CPM paradigm was utilized to investigate the generation of descending pain modulation. The CPM can be measured by application of a test-stimulus (in this case heat pain threshold), during and following the application of a conditioning stimulus (in this case the cold pressor test). An increase in the pain threshold after application of the conditioning stimulus indicates the presence of descending pain modulation (Pud et al., 2009).

In this study, heat pain threshold was repeated at 120 s after the cold pressor test was initiated. This was performed to assess the conditioned pain modulation of each patient. The difference between the heat pain threshold at baseline and 120 s after initiation of the cold pressor test was determined and expressed as a percentage to quantify the CPM effect.

2.7 Post-operative pain

The outcome quality of post-operative pain management was assessed with the QUIPS questionnaire which is a validated German outcome measurement instrument for post-operative quality control, and the national register currently includes more than 400,000 patients from around 200 hospitals. It consists of three questions asking for (1) pain intensity during movement, and (2) the least and worst pain over the last 24 h, all rated on the NRS. Furthermore, it includes (3) questions about patients′ pain intensity and postoperative functional restrictions (mobilization, coughing/deep breathing, night-sleep, yes/no) (Meissner et al., 2006, 2008). The first 24 h were chosen since it was the most standardized period in the post-surgery treatment, with some patients commencing rehabilitation after 24 h, while other remained on bed-rest. The questionnaire is in German, but a translation of the questions to English is available (Meissner et al., 2008). Hence, it has served as model for the internationally used PAIN OUT questionnaire, which is available in various languages (Zaslansky et al., 2014, 2015).

Since there is no validated definition for a positive opioid response in a perioperative setting, we developed a ‘response score’ to determine analgesic response after surgery based on various patient′s reported outcome-items used in the QUIPS questionnaire. Points indicating an overall successful pain management were awarded up to a maximum of 10 by the following criteria:

(1) Maximal pain NRS $< 5 = +2$ points
(2) Pain on movement NRS $< 5 = +2$ points
(3) Minimum pain NRS $< 3 = +2$ points
(4) No pain on mobilization = +1 point
(5) No pain when coughing = +1 point
(6) No pain when waking up = +1 point
(7) No effect on mood = +1 point

Definition of cut-off points was based on typical intervention thresholds for postoperative pain management (e.g. pain on movement or maximal pain of 5) (Maier et al., 2010; Rothaug et al., 2013). Interaction of pain with function was included to derive a clinically meaningful response. Patients with a score of 5 or higher were considered opioid responders, those with scores of 4 or lower non-responders to opioids.

2.8 EEG recordings

EEG was acquired using a 34-channel cap (34ch prewired cylindrical Ag/AgCl electrodes, MEQNordic A/S, Jyllinge, Denmark) and amplified on a Nuamp system (NuAmp, Neuroscan, El Paso, TX, USA) and recorded for later analysis. The cap was placed symmetrical in a standardized position 3 cm above the nasium. Electrode gel was applied into each of the recording channels to reduce the electrode impedance below 5 kΩ. Recordings were performed in a dimmed light room with all unnecessary electrical equipment turned off to avoid 50 Hz contaminations. Sampling frequency was 1000 Hz.

First resting EEG was acquired and patients were instructed to minimize eye movements and refrain from talking. Open or closed eyes were alternated between in four sequences of 2.5 min, starting with eyes open. For this study, only the first recording of 2.5 min eyes open was used.

EEG during the cold pressor test was commenced as soon as the patient immersed their hand into the water. The first 60 s of recording after hand immersion was used for analysis to avoid artefacts induced by the conditioned pain modulation procedure.

2.9 Pre-processing

The data was pre-processed with Neuroscan software (Neuroscan 4.5, Neuroscan) in the following steps: (1) zero-phase shift notch filtering (49–51 Hz) using a finite impulse-response filter with a slope of 24 dB/octave; (2) zero-phase shift band-pass filtering (1–80 Hz) using a finite impulse-response filter with a slope of 12 dB/octave; (3) blinded visual inspection of data quality for all channels using linked-ear reference. Channels with abnormal signals were discarded and replaced by signals interpolated from neighbouring electrodes; (4) Re-referencing to the average electrode.

2.10 Spectral analysis

Spectral indices were calculated using Matlab 2012a (The Mathworks, Inc., Natick, MA, USA) in order to obtain the relative EEG amplitude. Calculations were performed using a wavelet transform as this has a superior time-frequency resolution than the more common Fourier transform (Akin, 2002). The continuous wavelet transform was applied to EEG from each channel using the complex Morlet wavelet as a mother wavelet function with a bandwidth of 10 Hz and a centre frequency of 1 Hz. Scales for the mother wavelet was chosen to match frequencies ranging from 1 to 32 Hz with a 0.5 Hz between-scale frequency interval. The absolute values of the obtained wavelet coefficients were used for analysis and divided into the following standardized frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–32 Hz). The wavelet coefficients were averaged over time and scales contained within each frequency band were summed together to yield the absolute activity within each frequency band. The relative activity was calculated separately for each channel by dividing each frequency band with the total energy of all bands and multiplying by 100. The values then represent the percentage of total amplitude contained in each frequency band.

2.11 Functional connectivity analysis

Functional connectivity is a new approach within EEG, but has been used within structural and functional magnetic resonance imaging (Hardmeier et al., 2014). Functional connectivity considers the brain as a complex network of inter-connected nodes (Hardmeier et al., 2014). Several methods exist for estimation of functional connectivity within EEG analysis and most methods work by investigating the phase-relationships between EEG signals for different electrodes, where electrodes with similar phases are thought to be exchanging information (Nolte et al., 2008). The phase-lag index (PLI) is based on a consistent lag between instantaneous phases between two signals and thus ignores most zero-phase phase-relations in order to discard volume conduction noise (Nolte et al., 2008).

The PLI was calculated for the same frequency bands as used for the spectral analysis, using the implementation from The Neurophysiological Biomarker Toolbox (NBT) (http://www.nbtwiki.net/). The signal was divided into time windows and the PLI was calculated for each window. Lastly, the results for all time windows were averaged. The window width was set to twice the sampling frequency (2000 samples) as this provides a frequency resolution of 0.5 Hz, which is equal to the spectral analysis. The band-pass filter was a 1st order butterworth filter (Lehembre et al., 2012).

2.12 Machine learning analysis

A support vector machine (SVM) was used for the machine learning approach. The SVM is a binary classifier which optimizes the decision threshold between two groups without any *a priori* assumptions about the data (Cortes and Vapnik, 1995). The SVM was chosen over other machine learning classifiers since it has previously been used for other prediction studies in pain medicine (Graversen et al., 2012; Olesen et al., 2013a).

To avoid over-fitting, the most discriminative features were selected using the criteria for joint mutual information, as this criterion has been found to provide the best selection for data sets with a limited number of samples (Brown et al., 2012). For both resting EEG and EEG during cold pain, features were selected using the joint mutual information criterion and subsequently used for SVM classification. The number of features to be used was determined by investigating the accuracy of the classifier by gradually increasing the number of features up to 15. Accuracy was defined as the ratio between correctly classified subjects and total number of subjects in percentage. The number of features that yielded the highest accuracy on both study days was chosen for the final analysis due to the importance of reliability in the classifier. Classification was performed using the libSVM toolbox (version 3.20) for Matlab (Chang and Lin, 2011). A linear kernel function was used to avoid over-fitting of the data (Gong et al., 2011). The cost parameter C of the SVM was set to 1. Classification accuracy was determined using leave-one-out cross-validation which consisted of removing one subject before performing feature selection and training the SVM classifier using all remaining subjects. The subject that was removed was then used to test the predictive capability of the classifier. This was repeated until all subjects had been left out, to assess the overall accuracy of the classifier (Gong et al., 2011; Graversen et al., 2011; Gram et al., 2015). Accuracy, positive predictive value and negative predictive value of the classification were calculated.

Lastly, the feature selection method was applied to the complete data set, in order to indicate which features were most useful for classification.

2.13 Statistical analysis

All data are reported as mean ± standard deviation unless otherwise stated. Logistic regression was used to determine the capability of different clinical variables to predict post-operative analgesia. Significant predictors in univariate analysis were included in a multivariate analysis and bootstrapping (1000 samples) was used for internal validation of the multivariate estimates. Analysis of Multichannel EEG was carried out using a mixed analysis of variance (ANOVA) model with electrode (i.e. electrode 1 through 34) as within-subjects factor and responder group (i.e. responder vs. non-responder) as between-subjects factor. The *F*-test results were corrected for identity covariance matrix by the Greenhouse–Geisser method to take into account possible intragroup correlations. Additionally, data were analysed using the previously described machine learning approach. SVM classifications were analysed using chi-square. *P*-values below 0.05 were considered statistically significant.

3. Results

Out of 175 patients screened for the study, 112 was eligible for the study and signed the informed consent (24 patients declined to participate, 1 was below 18 years of age, 1 was already participating in another study, 1 due to replacement of both hips in the same surgery, 1 because informed consent could not be obtained, 13 for planned spinal anaesthesia during surgery, 4 due to high preoperative opioid use, 1 due to drug abuse and 17 due to a history of neurological conditions). Out of the 112 patients who signed the informed consent, 81 were included in the final analysis (15 excluded because surgery was cancelled or consent was withdrawn, 3 because PCA was not administered, 1 due to postoperative delirium, 1 because of sevoflurane anaesthesia, 1 because of basal-bleeding history, 1 due to insufficient time to complete measurements and 9 patients for having one or more unusable EEG recordings due to poor quality). Demographics and clinical characteristics of the final 81 patients (36 males and 45 females) are reported in Table 1.

3.1 Response to post-operative analgesic treatment

Fifty-one patients (63%) were classified as opioid responders and 30 (37%) were classified as opioid non-responders based on the response score from the QUIPS questionnaire. Details of the two groups are reported in Table 2. Mean score was 8.4 ± 1.3 for the responder group and 3.5 ± 1.5 for the non-responder group ($p < 0.001$).

Table 1 Demographical and clinical characteristics of patients scheduled for total hip replacement. Since some patients had missing data, the percentage of patients is given in a separate column for each parameter.

		Patients, *n* (% of total cohort)
Age (years)	64.5 ± 12.5	81 (100%)
Male sex, *n* (%)	36 (44%)	81 (100%)
BMI (kg/m^2)	28.1 ± 5.0	79 (98%)
WOMAC	54.6 ± 18.3	65 (80%)
Hip-pain duration, *n* (%)		81 (100%)
0–6 months	12 (15%)	
6–12 months	11 (14%)	
1–2 years	19 (23%)	
2–5 years	20 (25%)	
More than 5 years	19 (23%)	
Chronic pain grade, *n* (%)		78 (96%)
Grade I–II	32 (41%)	
Grade III–IV	46 (59%)	
MPSS, *n* (%)		81 (100%)
Stage I	34 (42%)	
Stage II	26 (32%)	
Stage III	21 (26%)	
Preoperative MQS – non-opioids	5.1 ± 4.5	79 (98%)
Preoperative MQS – opioids	0.6 ± 1.6	81 (100%)

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; MPSS, Mainz Pain Staging System; MQS, Medication Quantification Scale.

3.2 Prediction of post-operative analgesia

3.2.1 Group-wise analysis

3.2.1.1 Clinical variables. Clinical and demographic characteristics, pain medications and QST results stratified on responders and non-responders are reported in Table 2. Chronic pain grade ($p = 0.007$) and MPSS stage ($p = 0.01$) were associated with the postoperative analgesic response groups. Non-responders predominantly belonged to more severe chronic pain grades (III and IV) and were skewed towards MPSS stage III (high pain chronicity). Furthermore, responders experienced more pain during the hip rotation test compared to the non-responders ($p = 0.03$). In contrast, none of the QST parameters were associated with post-operative analgesia response (all $p > 0.1$). Results from the multivariate analysis (Table 3) revealed that only the chronic pain grade ($p = 0.02$) remained an independent predictor of postoperative analgesic response and the association remained significant after internal bootstrapping validation. Using the chronic pain grade to classify patients into response

Table 2 Baseline parameters for the included patients, divided into groups of responders (N = 51) and non-responders (N = 30) to post-operative analgesic treatment with oxycodone and piritramide.

	Responders (N = 51)	Non-responders (N = 30)	OR (95% CI)	p-Value
Age (years)	64.2 ± 10.4	64.9 ± 15.7	1.05 (0.73–1.51)	0.81
Male sex, n (%)	25 (49%)	11 (37%)	0.60 (0.24–1.52)	0.28
BMI (kg/m^2)	28.1 ± 4.6	28.1 ± 5.7	1.00 (0.91–1.09)	0.98
WOMAC	51.6 ± 18.9	60.0 ± 16.2	1.03 (1.00–1.06)	0.082
Hip-pain duration, n (%)				
0–6 months	7 (14%)	5 (17%)	1.00	
6–12 months	8 (16%)	3 (10%)	0.53 (0.10–3.03)	0.47
1–2 years	12 (24%)	7 (23%)	0.82 (0.19–3.58)	0.79
2–5 years	13 (25%)	7 (23%)	0.75 (0.17–3.28)	0.71
More than 5 years	11 (22%)	8 (27%)	1.02 (0.24–4.41)	0.98
Chronic pain grade, n (%)				
Grade I–II	26 (53%)	6 (21%)	1.00	
Grade III–IV	23 (47%)	23 (79%)	4.33 (1.50–12.50)	0.007[a]
MPSS, n (%)				
Stage I	25 (49%)	9 (30%)	1.00	
Stage II	18 (35%)	8 (27%)	1.23 (0.40–3.82)	0.71
Stage III	8 (16%)	13 (43%)	4.51 (1.41–14.46)	0.011[a]
Pain on hip rotation (NRS)	5.2 ± 2.0	6.2 ± 1.9	1.33 (1.02–1.72)	0.034[a]
Preoperative MQS – non-opioids	4.6 ± 4.6	5.9 ± 4.3	1.06 (0.96–1.18)	0.24
Preoperative MQS – opioids	0.4 ± 1.3	0.8 ± 1.9	1.14 (0.86–1.52)	0.36
Post-surgery patient-controlled analgesia – opioid equivalents (mg)	114.5 ± 41.2	123.1 ± 47.5	1.00 (0.99–1.02)	0.39
Cold pressor pain (NRS)	6.1 ± 2.3	6.9 ± 2.5	1.16 (0.94–1.42)	0.17
Heat pain threshold (°C)	47.0 ± 2.9	46.3 ± 3.7	0.93 (0.81–1.07)	0.34
Pressure pain threshold (kPa)	71.7 ± 20.4	68.0 ± 22.2	1.01 (0.99–1.03)	0.45
Conditioned pain modulation (%)	2.8 ± 4.3	2.8 ± 4.2	1.00 (0.90–1.12)	0.96

BMI, Body Mass Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; MPSS, Mainz pain staging system; NRS, Numerical Rating Scale; OE, Opioid equivalent units; MQS, Medication Quantification Score.
[a]$p < 0.05$.

Table 3 Multivariate analysis of risk factors associated with inadequate post-operative analgesia identified using logistic regression. Internal validation performed with 1000 bootstrap samples.

	Multivariate analysis		Internal validation	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Chronic pain grade, n (%)				
Grade I–II	1.00			
Grade III–IV	3.74 (1.21–11.53)	0.022[a]	3.74 (1.07–13.14)	0.04[a]
MPSS, n (%)				
Stage I	1.00			
Stage II	1.14 (0.34–3.83)	0.83		
Stage III	1.99 (0.54–7.30)	0.30		
Pain on hip rotation (NRS)	1.26 (0.95–1.68)	0.11		

MPSS, Mainz Pain Staging System; NRS, Numerical Rating Scale.
[a]$p < 0.05$.

groups (Responders: Grade I and II and non-responders: Grade III and IV) yielded an accuracy of 63% (positive predictive value = 81%; negative predictive value = 50%).

3.2.1.2 Resting EEG. No differences in *resting EEG* were found between responders and non-responders for spectral EEG indices (all $p > 0.1$) or functional EEG connectivity (PLI) (all $p > 0.1$). The topographical plots are shown in Fig. 2 for the spectral indices and functional connectivity in Fig. 3.

3.2.1.3 EEG during cold pain. There were no differences in spectral EEG indices (all $p > 0.3$) or functional connectivity (all $p > 0.1$) between responders and non-responders *during cold pain*. The topographical illustration of the EEG spectral indices for responders and non-responders is shown in Fig. 4 while the topography of the functional connectivity is illustrated in Fig. 5.

3.2.2 Individual subject analysis (machine learning)

3.2.2.1 Resting EEG. Machine learning analysis was unable to distinguish between responders and non-responders with any number of resting EEG features

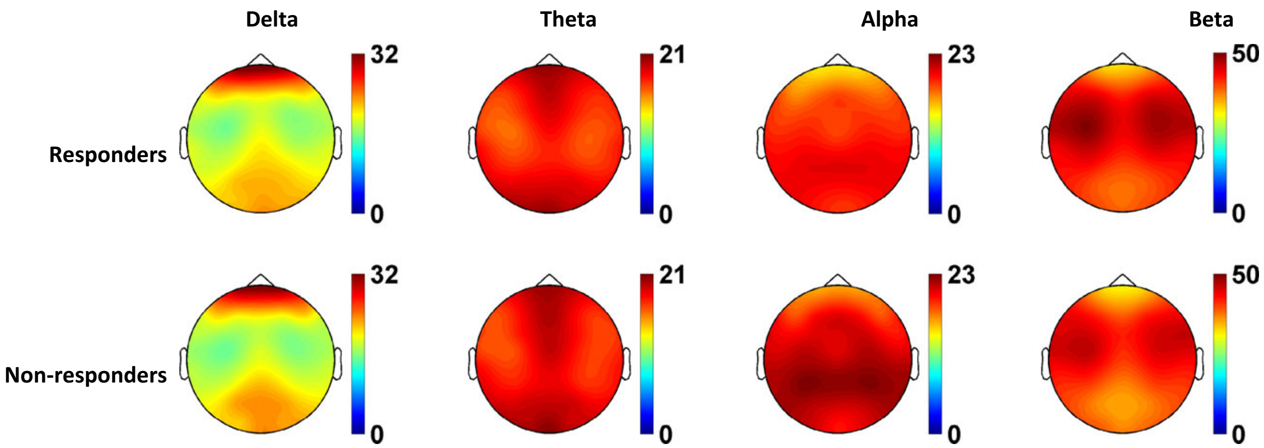

Figure 2 Topographical illustration of the spectral indices calculated from the resting electroencephalography in the four frequency bands; delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–32 Hz). Activity is colour coded with higher levels of activity represented in red and yellow colours, while lower activity is represented by blue. Responders to opioid treatment appear to have slightly decreased alpha activity, and increased beta activity.

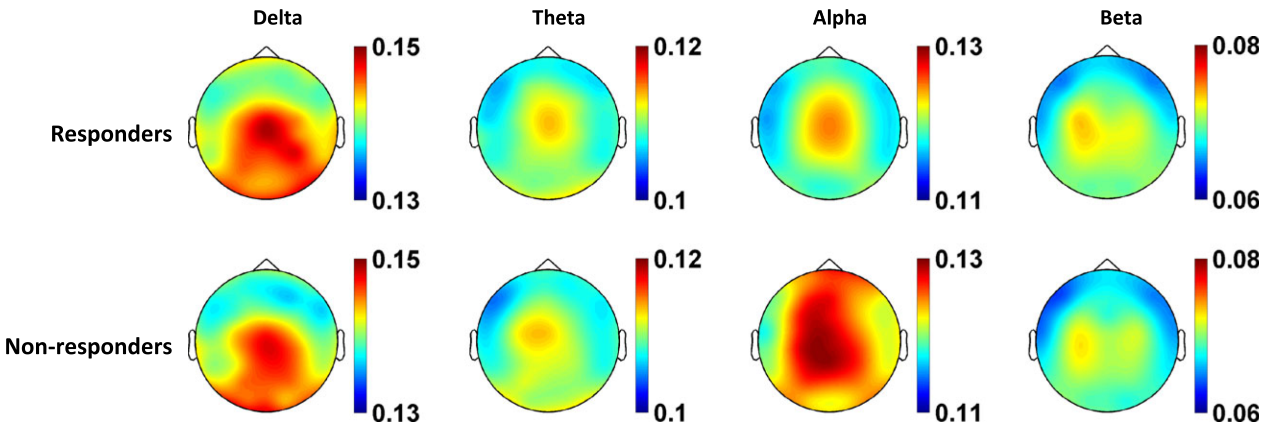

Figure 3 Topographical illustration of the phase-lag index calculated from the resting electroencephalography in the four frequency bands. The colour code shows red and yellow for electrodes that have stronger average connections to all other electrodes, while blue colours represent electrodes, which are poorly connected. Responders to opioid treatment appear to exhibit decreased connectivity of the alpha band compared to non-responders.

(spectral EEG indices and functional connectivity) (maximum accuracy = 58%; p = 0.2).

3.2.2.2 EEG during cold pain. Machine learning analysis discriminated between responders and non-responders when selecting features freely from both spectral indices and functional connectivity measures derived from the EEG. The most accurate classification was achieved using only one feature from the entire data set. This was the delta spectral index band from frontally placed FP1 electrode with an accuracy of 65% (positive predictive value = 76%; negative predictive value = 53%; p = 0.009).

To ensure that the results were not related to the stratification of subjects, the analysis was also repeated by stratification based on opioid consumption within the first 24 h after surgery. The cut-off value for opioid consumption was set at 65 mg morphine equivalent units, resulting in 45 patients in the high dose opioid group (i.e. >65 mg morphine) and 37 patients in the low dose opioid group. Here, it was not possible to discriminate between responders and non-responders (maximum accuracy = 57%; p > 0.05).

4. Discussion

This study aimed to investigate response to postoperative analgesic treatment with opioids and investigate factors associated with insufficient response.

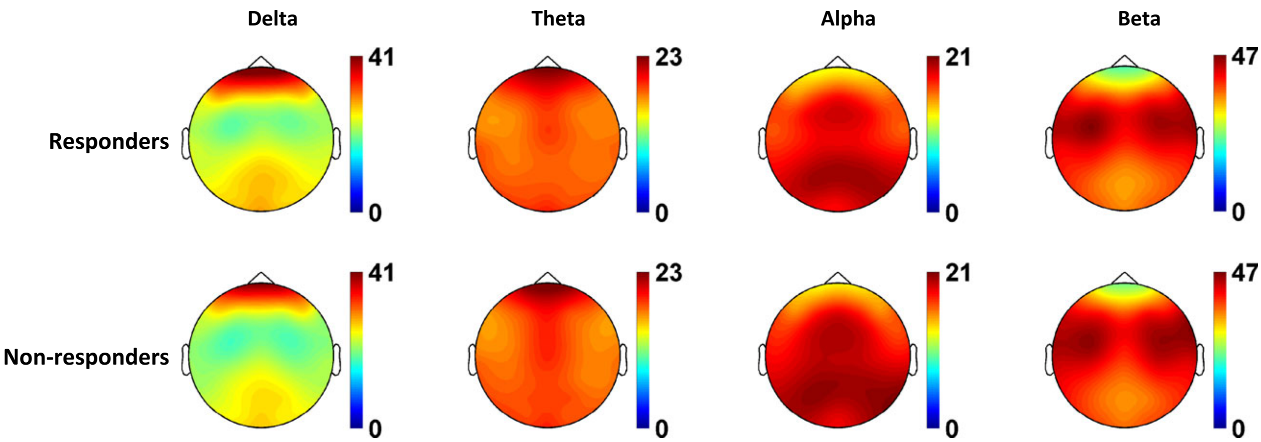

Figure 4 Topographical illustration of the spectral indices calculated from electroencephalography during cold pain, in the four frequency bands. Activity is colour coded with higher levels of activity represented in red and yellow colours, while lower activity is represented by blue. Increased delta activity appears to be present for responders to opioid treatment.

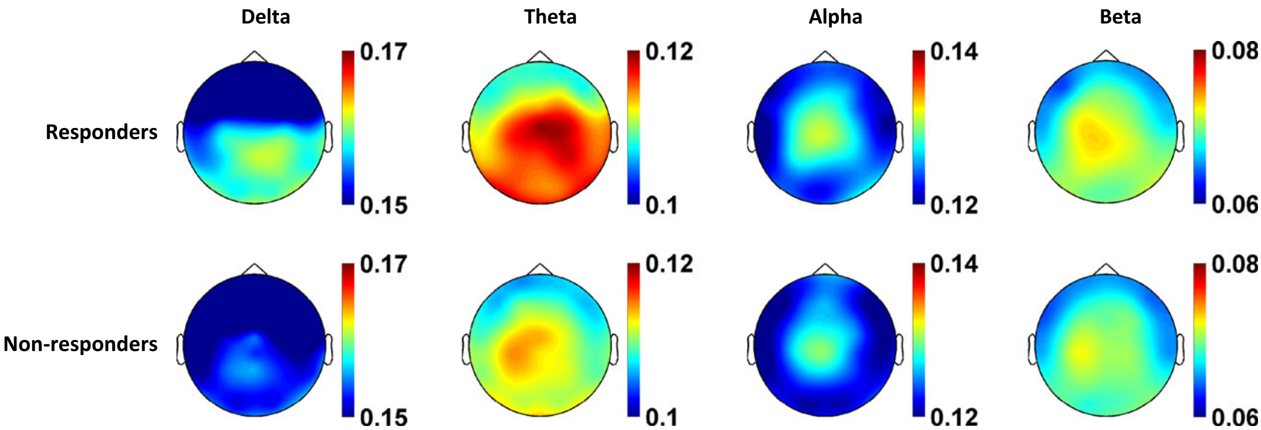

Figure 5 Topographical illustration of the phase-lag index calculated from the electroencephalography during cold pain, in the four frequency bands. The colour code shows red and yellow for electrodes that have stronger average connections to all other electrodes, while blue colours represent electrodes, which are poorly connected. Responders to opioid treatment seems to present with increased connectivity in the delta and theta bands compared to non-responders.

Severity of the pre-surgical chronic pain condition was a factor associated with post-surgical insufficiency of analgesic treatment, while QST measures were not related. In a first for clinical studies, it was possible to predict analgesic efficacy based on the pre-operative EEG recordings using machine learning, with similar accuracy to the chronic pain grade. Consistent with previous research, tonic painful EEG proved to be useful in contrast to resting EEG for prediction of opioid analgesia (Gram et al., 2015).

4.1 Methodological considerations

For a measurement to be of value within personalized medicine, reliability over longer time periods is a requirement (Bruton et al., 2000; Cannon et al., 2012). This study used spectral analysis and PLI of EEG during both rest and tonic cold pain, which are reliable, and therefore useful as a biomarker for prediction of analgesic efficacy (Gram et al., 2014; Hardmeier et al., 2014).

The only previous study on prediction of analgesic effect of opioids using EEG was performed on healthy volunteers using an experimental pain model (Gram et al., 2015). The current study is clinical and as such, suffers from confounders such as anxiety, and existing medication (Olesen et al., 2012). Firstly, patients were suffering from preoperative chronic pain, which influences EEG (Sarnthein et al., 2006; Olesen et al., 2011). Secondly, patients were already on analgesics before inclusion, which could also affect the EEG (Malver et al., 2014). Since pre-existing analgesic use could not be controlled for, this might have interfered with classification accuracy. On the other hand, since there was no difference in premedication analgesics between the groups and pre-operative opioid doses were low this is likely not of major importance. Lastly, the pain evoked in experimental pain models in our previous study is standardized between subjects, whereas the post-surgical pain is not, even when using a standardized operative procedure. Although the procedure is the same for all patients, there will always be variation in duration and complexity during surgery, which might affect postoperative pain. All these factors could explain why classification accuracy was lower in this clinical study.

It was not possible to distinguish between responders and non-responders based on the resting EEG which is consistent with previous research in where the tonic painful EEG was found superior to resting EEG for prediction of analgesic efficacy (Gram et al., 2015). Thus, it seems that the predictive biomarkers in the EEG are only present when subjects experience pain. Previously, tonic pain was shown to result in increases in the delta band, with a simultaneous suppression of the alpha band. This was also seen in this study, but to a lesser degree than previously reported (Gram et al., 2014). The water temperature for the cold pressor test was higher than in previous studies (range = 1–7 °C) (Mitchell et al., 2004). However, perceived pain during the cold pressor test (~6 NRS) was experienced as intense. It is therefore unlikely that water temperature alone accounts for low accuracy. However, future studies should attempt to use lower temperatures for the cold pressor test.

Within recent years, the gamma band of the EEG has received increasing attention within pain research. While large components of the EEG signal in evoked brain potentials have been shown to be closely related to the saliency of the stimulus rather than pain *per se* (Iannetti et al., 2008), the gamma band contains features specifically associated with pain perception (Zhang et al., 2012; Tiemann et al., 2015). However, most research on the gamma band was done on evoked brain potentials, where potentials contaminated by noise are easily rejected unlike in continuous EEG signals. This study utilized the cold pressor test for evoking pain, since tonic pain models have been shown to more closely mimic the unpleasantness of chronic pain (Rainville et al., 1992). The cold pressor test introduces electromyography artifacts into the gamma band, due to wincing facial expressions that accompanies prolonged and unpleasant tonic pain (Dowman et al., 2008). Taken together, despite its potential relevance for pain, the gamma band was excluded in this analysis to avoid the noise from muscle activity which could potentially also affect the results.

Patients were stratified into two groups based on a combined score of clinical pain ratings in order to account for problems associated with PCA, namely that both pain scores and analgesic consumption varies in a related way in the post-operative setting (Dai et al., 2013). Therefore, the identification of the optimal method of combining pain scores with analgesic consumption is a major focus point for research in analgesic studies (Dworkin et al., 2008; Turk et al., 2008). Attempts have been made to develop integrated scores which encompass both metrics (Silverman et al., 1993), but no method has received widespread acceptance and their validity remains unknown (Grosen et al., 2013). The stratification based on clinical response from the QUIPS questionnaire resulted into a response rate of roughly 65% which is consistent with this type of procedure (Maier et al., 2010). It could be argued that opioid consumption should have been incorporated into the response score. However, the fact that stratifying based on opioid consumption did not yield higher prediction accuracies indicates that the stratification method is not the main reason for the relatively low accuracy.

It should also be noted that the opioid medication in this study consisted of a combination of piritramide and oxycodone, which might affect individual patients differently (Drewes et al., 2013). Therefore, several sub-groups might exist within these two response groups, complicating stratification. However, it was not ethically feasible to alter the routine treatment in this study. To further investigate response or non-response to individual opioids, future studies could attempt to treat using only one opioid.

4.2 Prediction of post-operative analgesia

Clinical parameters relating to the pre-surgical pain state was associated with post-operative analgesia. Hence, a higher proportion of severe pre-surgical chronic pain grades were associated with poor post-operative analgesia. This corresponds well to the literature which consistently shows pre-operative pain is a strong predictor of acute post-operative pain (Sommer et al., 2008; Gerbershagen et al., 2010;

Pinto et al., 2015). Since the responder score in this study is based on the post-operative pain ratings it follows that the pre-surgical pain would be related to this score.

Several studies have investigated prediction of analgesia based on QST and some results have been promising (Grosen et al., 2013). Heat and cold pain was included in this study as QST predictors, and neither proved effective for prediction. This could be due to central sensitization in the patients, for which opioids have limited effect (Olesen et al., 2013b).

A dysfunctional descending inhibition (as assessed by CPM paradigms) has previously been associated with development of post-operative pain in different clinical settings including pain after thoracic and gastrointestinal surgeries (Yarnitsky et al., 2008; Ip et al., 2009). Overall, the CPM effect in patients was weak in both responders and non-responders and this observation likely reflects a dysfunctional descending inhibition.

Group-wise statistical analysis of the EEG data revealed no differences between responders and non-responders, while machine learning was able to discriminate between responder groups at the individual patient level with an accuracy of 65%. This result is comparable to the predictive accuracy of chronic pain grade (63%), but is likely more robust as it is obtained with an objective method. The positive predictive value of EEG based classification was 76%. Hence, if patients had been treated according to the machine learning results based on preoperative EEG during cold pain, response rate to piritramide and oxycodone would have been 76% compared to the actual 65% response rate in this study. The remaining patients would have been treated with an alternative treatment, although only 53% were actually non-responders, meaning that there were a higher proportion of false negatives. However, in a personalized medicine scenario where the EEG and SVM model would be used to decide which patients to switch to secondary analgesic treatment the patients falsely classified as non-responders could still respond to the alternative treatment. Since this study included no alternative treatment, the actual response rate in a personalized medicine scenario could not be determined.

The relative delta content from a frontally placed electrode (FP1) was selected as the most discriminate feature. This is comparable with previous research in healthy volunteers where frontal delta activity was mainly selected by a machine learning approach (Gram et al., 2015). However, in this study only one feature was selected in comparison to the previous 7 features.

5. Conclusions

The novel use of EEG in combination with machine learning allowed for discrimination between responders and non-responders to postoperative analgesic opioid treatment. This shows EEG to be a potential important part in personalized pain medicine, with the potential to reduce suffering and persistent post-operative pain. The use of EEG in daily clinical work is becoming more and more feasible with new devices emerging, offering drastically reduced mounting times while retaining the quality of recordings (Schiff et al., 2016). Future studies should work towards optimization of the methods together with inclusion of more variables in combination with the EEG.

Author contributions

A.M.D., M.P., F.P., D.F., M.R. and J.E. initiated and carried out the study. M.R. and J.E. performed the preoperative assessments. M.G. designed and carried out the EEG analysis. M.G. carried out the machine learning analysis. M.G., S.S.O. and A.M.D. evaluated results and drafted the manuscript. All authors were involved in reading and approving the final manuscript.

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