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Published in:
11th International IEEE/EMBS Conference on Neural Engineering, NER 2023 - Proceedings

DOI (link to publication from Publisher):
10.1109/ner52421.2023.10123776

Publication date:
2023

Document Version
Accepted author manuscript, peer reviewed version

Classification of noxious and non-noxious event-related potentials from S1 in pigs using a convolutional neural network

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***Abstract*—The purpose of this study was to develop a novel objective measurement of nociception using brain signals. Using deep learning, pain markers can possibly be extracted from event-related potentials (ERP). Therefore, this study aimed to develop a convolutional neural network (CNN) to classify between noxious and non-noxious stimuli based on ERPs from micro-electrocorticography (μECoG) recordings in pigs. μECoG recordings were acquired from 13 experiments on 5 pigs. Subjects received electrical stimulation to the ulnar nerve, while μECoG recordings were acquired using a 32-channel microelectrode array placed on the dura above the primary somatosensory cortex. Each pig received three sets of both noxious and non-noxious stimulations. The μECoG recordings were transformed into short-time Fourier transforms, which were used as input to the CNN. ERPs were classified with an accuracy of 73.5% and AUC of the receiver operating characteristic curve at 0.72. Additionally, the model was better at predicting non-noxious responses (85%) compared to noxious stimuli (62%). In a further development process, the performance of the CNN model needs to be optimised and further research has to be conducted regarding the translation of the results from animal to human pain research.**

***Index Terms*—CNN, Pain detection, EEG, Pigs, ECoG**

I. Introduction

The subjective nature of pain is reflected in its assessment, where it is not possible to directly measure pain by a biological parameter since there are currently no known reliable biomarkers for pain. Therefore, the golden standard for pain assessment is a self-report, typically a numerical rating scale (NRS) or visual analogue scale (VAS). The NRS score requires the patient to make a self-report of their perception of pain between 0-10, while the VAS score requires the patient to point at a line between two points and measure the length of the line. Using a subjective measure leads to significant limiting factors, such as reliability and observer bias. [1], [2].

Pain measurement has become even more complex when conducting experiments on animals, since the subjective measurements used in humans cannot be transferred to animals, as animals cannot describe their pain experience. Therefore, scientists currently rely on evoked and spontaneous analysis to determine the effectiveness of an analgesic. This is suboptimal since there are two prominent issues; susceptibility to bias and validity of the biomarker. An objective biomarker of pain could be used as a complementary measure to the behavioural analysis and, therefore, possibly lead to improvements in the assessment and understanding of pain mechanisms in animals. [3]–[5]. Since pain perception takes place in the brain, it is only natural to try to obtain objective measures of pain through electrophysiological recordings of cortical activity.

Novel methods such as deep learning are increasingly being used to obtain objective biomarkers in electrophysiological signals. Deep learning has made a significant impact on neuroscience and neural engineering in recent years. It is widely used in brain-computer interfaces (BCI), where its classifying ability is used to interpret and classify brain signals based on event-related potentials (ERPs) from a variety of external stimuli. [6]–[8]. These signals share the complexity of those seen when inducing noxious stimuli and recording EEG in the brain [9]; however, deep learning has rarely been used as a classifier for pain-induced potentials in the brain [10].

Therefore, the purpose of this study was to investigate whether a convolutional neural network (CNN) architecture can be developed to classify noxious and non-noxious stimuli from electrocorticography (ECoG) signals in pigs.

II. Methods

A. Experiment

13 experiments in 5 pigs were used for this study, with the average weight of 30 $\pm$ 4.6 kg. This experiment was approved by the Danish Veterinary and Food Administration under the Ministry of Environment and Food of Denmark (protocol number: 2020-15-0201-00514).

The pigs were anesthetised, after which an electrical stimulation was applied through two cooner wires implanted subcutaneously under the right ulnar nerve, approximately 3 cm above the carpus. A craniotomy was performed frontal to the coronal and lateral to the sagittal suture line, and a 32-channel μECoG (E32-1000-30-200, Neuronexus, Ann Arbor, USA) was implanted on top of the dura over the primary somatosensory cortex (S1) region. The ERPs were recorded using a TDT system (Pre-amplifier SI-8, Processor RZ2, Data streamer RS4, Workstation WS8 Tucker-Davis Technologies, Alachua, FL, USA). Finally, data were sampled at 6 kHz.

The stimulation amplitudes were separated into non-noxious and noxious stimulation, inducing stimulations at two times the motor threshold and ten times the motor threshold, respectively. Each measurement set consisted of 100 non-noxious and 100 noxious stimuli at a frequency of 1Hz. Three sets were recorded at an interval of 10 minutes. The motor threshold was found by increasing the stimulation amplitude from 50 μA in steps of 200 μA. Once a motor response was observed, the amplitude was decreased in steps of 50 μA until no movement was observed. Then it was again increased by 50 μA until the threshold was found. The stimulation waveform was an asymmetric rectangular charge-balanced biphasic pulse with the secondary phase having an amplitude of 10% of the primary phase and an inter-pulse interval of 10 ms. A programmable stimulator (STG4008, Multichannel Systems, Reutlingen, Germany) was used.

B. Pre-processing

The data was filtered using a high-pass filter at 1 Hz (10th-order Butterworth) and a low-pass filter at 250 Hz (4th-order, Butterworth). Line noise (50 Hz) was removed with a 16th order Butterworth with cut-off frequencies of 48 Hz and 52 Hz. Line noise was filtered up to the fourth harmonic. Every filter was applied using forwards and backwards filtering, where the mentioned filter orders are the effective orders. Lastly, noisy channels were removed based on visual inspection applied to pre-processed data.

After filtering the data, a short-time Fourier transform (STFT) was performed, resulting in an image-like output, which is a favourable input format for a CNN architecture. The parameters for the STFT were: Hanning window with 50% overlap, a window size of 350 data points per window. The resulting image had a pixel length of 26.19 ms (x-axis) and 17.24 Hz (y-axis) (see Fig. 1). Subsequently, the amplitudes were normalised in the range of 0 – 1 by dividing all amplitudes by the maximum amplitude independently for each STFT. Normalisation was performed to obtain a faster convergence of the CNN. The images were then interpolated (spline, zoom factor of two) to obtain a higher temporal and spatial resolution. Lastly, the average was computed for every 25 STFTs to remove some of the neural variability from the recordings and enhance the similarities based on the additive theory [11] (See Fig. 1). The pre-processing steps were performed in Python (version 3.9.7, 2022).

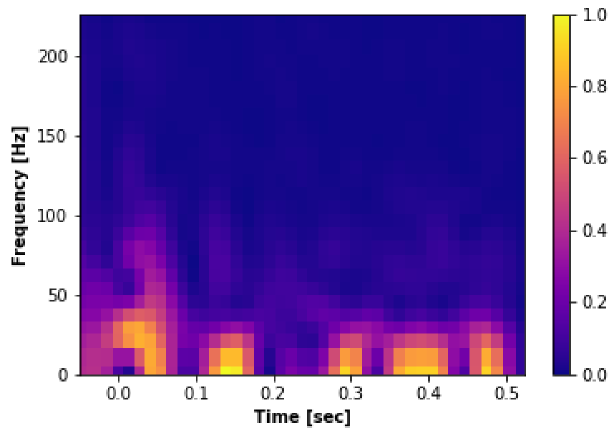

Fig. 1. Example of the final STFT with a mean of 25 epochs and a cut-off frequency of 250 Hz.

C. CNN architecture

The architecture used in this study consisted of two convolutional layers, two pooling layers, a flattening layer, two fully-connected and an output layer (Fig. 2). The two convolutional layers had zero padding and ReLU as activation functions. Additionally, the first convolutional layer had four feature maps and a kernel size of 5 x 5 pixels, and the second convolutional layer had eight feature maps and a kernel size of 3 x 3 pixels. After each convolutional layer, max pooling was applied. The first max pooling had a kernel size of 3 x 3 with a stride of 3, and the second max pooling had a kernel size of 2 x 2 with a stride of 2. After the second max pooling, the neurons were flattened in the flattening layer, which consisted of 120 neurons. The flattening layer was connected to the first fully connected layer, which consisted of 30 neurons. Furthermore, the first fully connected layer was connected to the second fully connected layer, which consisted of two neurons. Both fully connected layers applied sigmoid as an activation function. The output layer of the neural network had two neurons in accordance with the binary classification of noxious or non-noxious stimulation. Additionally, the output layer consisted of a softmax activation function in order to normalise the output and to obtain posterior probabilities. Through the training part of the neural network, dropout was applied. For the convolutional layers, a dropout rate of 50% was used and for the first fully connected layer, the dropout rate was 70%.

D. Training and optimisation

The chosen optimiser was a NAdam optimiser with a learning rate of 0.0002 and used binary cross-entropy as the

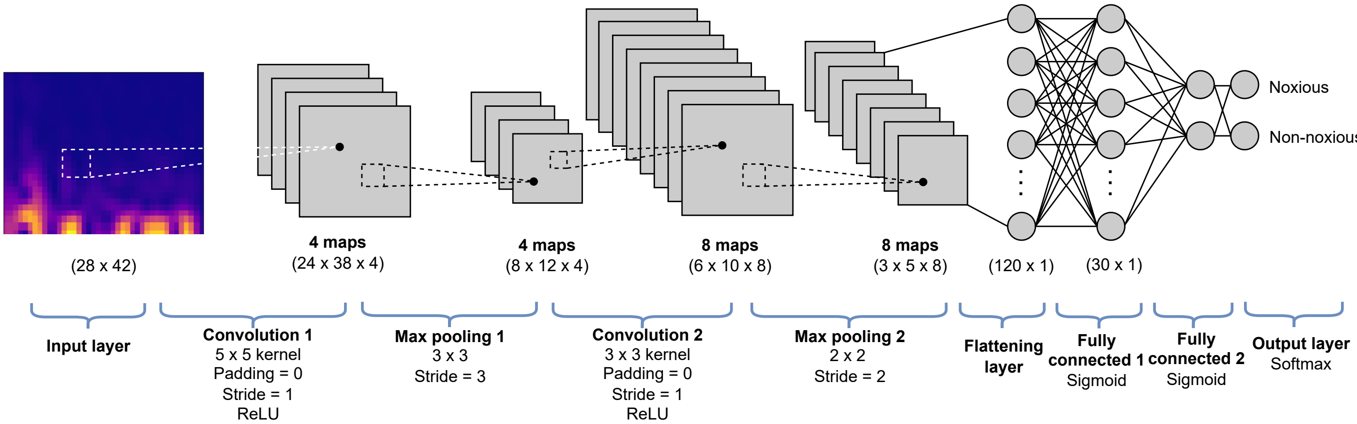

Fig. 2. CNN architecture developed for this study. The input layer consists of an STFT image, two convolutional layers, two max poolings, a flattening layer, two fully connected layers, and lastly an output layer. The input and output dimensions of the different layers through the network are indicated in parentheses '()'.

loss function. To reduce training time and avoid overfitting, a model checkpoint was used to save the best results, and early stopping was used if there was no decrease in validation loss for 100 epochs. The batch size was set to 50. The training, test, and validation data were divided into 60%, 20% and 20% of the data, ensuring that there was no overlap between experiments. The algorithm was created using the open-source PyTorch v1.11.0 framework. The hardware used to train was a NVIDIA GeForce RTX 3080 with CUDA 11.6.

E. Evaluation of CNN performance

CNN performance was evaluated using accuracy, F1-score, and receiver operating characteristic (ROC) area under the curve (AUC). Accuracy provides an overall performance measure, which is unweighted by the type of classification error.

$$Accuracy = \frac{TP + TN}{TP + FN + TN + FP} \tag{1}$$

F1-score is another way to measure a test's accuracy, which is calculated from the precision and true positive rate.

This can be calculated with the following

$$F1 = \frac{2TP}{2TP + FP + FN} \tag{2}$$

The ROC is a method to evaluate a binary classification algorithm in terms of the measures; true positive rate (TPR) and false positive rate (FPR). These measures can be used to plot the ROC curve that shows the performance of the binary classifier by plotting the TPR versus the FPR. [12].

An AUC can be computed to obtain a single performance metric of the system. According to [12]: "An AUC of 0.5 suggests no discrimination (i.e., ability to distinguish positive and negative samples), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding."

III. Results

The algorithm was better at predicting the non-noxious stimuli, with 85% correct predictions. It had a lower performance predicting noxious stimuli, where the network had 62% correct predictions. The accuracy and F1 score of the classifier was 73.5% and 70.1%, respectively. Using the CNN model to perform binary classification between noxious and non-noxious stimulations on the test data, an AUC of the ROC curve at 0.722 was achieved (see Fig. 3).

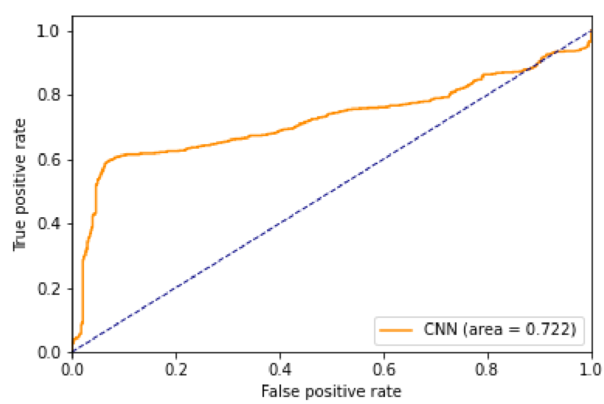

Fig. 3. The ROC curve showing the performance of the classifier. The orange lines represents the unique TPR and FPR, while the blue dashed line represents the line of no-discrimination. The AUC of the ROC curve was 0.722.

As seen in Fig. 3, the ROC is mostly above the line of no-discrimination. Above a FPR of 0.9 the ROC curve regresses below the line of no-discrimination. The optimal threshold is the point of the curve closest to (0,1), which in those results are placed at a TPR around 0.6.

IV. Discussion

In this study, a CNN architecture was developed to classify noxious and non-noxious stimulations given to the ulnar nerve in pigs. As input, a STFT was calculated from the µECoG signals. An accuracy of 73.5% was achieved when using the test data to predict between noxious and non-noxious stimuli. This was compared to the F1-score of 70.1%, which had a minimal difference, because the training data was balanced. However, the slight difference in accuracy can be explained by the balance of positive and negative predictions. This is also seen in the confusion matrix when comparing the prediction rates of TP and TN, where TP is 0.62, while the TN is 0.8. This explains the difference seen between F1-score and accuracy.

The lower accuracy of the noxious compared to non-noxious stimuli predictions can be explained by nerve fiber recruitment. Non-noxious stimuli are assumed to activate predominantly Aβ fibers, while noxious stimulis activate both Aβ and Aδ fibers. The brain signatures of noxious and non-noxious stimuli have therefore substantial overlap, making them difficult to distinguish from each other. Therefore, a method to stimulate only nociceptive fibres could help improve the classifier performance. [13].

Similar studies have been conducted using ERPs of different types of stimuli. One study used several different architectures to compare with their network. They used the Hilbert spectrum as input to a general CNN and received an accuracy of 73.02% which is similar to our study [14]. However, the authors found that using a CNN combined with a Bi-Long short-term memory (LSTM) could further improve the results, resulting in an accuracy of 91.3%. This was a general pattern in other studies, finding that a combination of general CNN and other neural networks architectures increased the classification accuracy. Another example is by [15], who have obtained an accuracy of 91.86% when using a CNN-LSTM algorithm. Another study combined different architectures in a Multi-Attention Convolutionl Recurrent mOdel (MACRO) using SE, SKNet, LSTM and SA to achieve better performance when classifying from a spatiotemporal input. Using MACRO, they achieved an AUC of ROC at 0.93, which is notably higher compared to our findings. [16]

Therefore a tendency is seen where CNN alone may not be sufficient to improve the performance of this study. Instead a combination of architectures, relevant to the given input, can be implemented to achieve a better performance.

The results indicate that it is still difficult to predict nociception in pigs. This speaks to the importance of an algorithm able to extract nociception related biomarkers, since pigs are unable to "confirm" when they are feeling pain. Such a biomarker needs to be both sensitive (able to detect pain at its lowest level) and specific (insensitive to other sensations). This will improve the outcomes of pre-clinical trials. It may further help humans who are unable to express themselves to receive pain relieving medication when needed. To further improve the algorithm, a look into what features are used to predict the noxious and non-noxious stimuli is needed. This could improve the understanding regarding which parts of the signals that are indicators for a nociceptive response. Ultimately this knowledge could further improve the algorithm and help in decoding the physiological response.

V. Conclusion

A CNN was developed to classify between noxious and non-noxious stimuli based on ERPs from µECoG recordings in pigs. Classification between noxious and non-noxious ERPs with an accuracy of 73.5% and an acceptable AUC of the ROC curve at 0.72 was achieved. The model was better at predicting non-noxious responses (85%) compared to noxious responses (62%).The CNN model can be further improved by combining CNN with one or more architectures.

VI. Acknowledgement

This work was funded by the Center of Neuroplasticity and Pain by the Danish National Research Foundation (DNRF121). We thank the staff at Aalborg University Hospital for assistance during the animal experiments.

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