Artificial intelligence for pain classification with the non-invasive pain monitor Anspec-Pro

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Abstract

Background: **Reliable measurement of perioperative pain is still an ongoing problem. Pain monitors are commercially available, but to date are not commonly used clinically. Anspec-Pro was developed as a new pain monitor device by Ghent University in 2018. The validation study compared this monitor to the commercially available and validated MedStorm pain monitor. Although the results were comparable with the validated monitor, the absolute results were debatable.**
Objectives: **The data were reanalyzed by means of artificial intelligence (AI), examining the correlation and prediction between the measured data and clinical parameters, to explore if this delivers complementary information that assists pain assessment.**
Design and setting: **A cohort study at Ghent University Hospital.**
Methods: **During two monitoring periods, data were collected from patients while measuring pain with Anspec-Pro. Patients were monitored in the preoperative period and during their postoperative recovery. Measurements by Anspec-Pro were processed with AI, more specifically with a convolutional neural network (CNN), and classified into pain classes. CNN's were trained both with offline (training prior to monitoring) and online (offline training followed by real-time retraining with incoming data) training methods. Performance was assessed with Receiver Operating Characteristic (ROC) curves.**
Main outcome measures: **Pain values as quantified by Anspec-Pro and NRS values as reported by the patients.**
Results: **Data from 11 patients were used for analysis. Good device performance was seen with offline training with all data and with online retraining every seven minutes with device output and an NRS from the last seven minutes.**
Conclusions: **CNN online training with recent patient data led to good algorithm performance. Hence, our results indicate that there is a potential for AI to deliver useful information that can be used in complementary models of monitoring devices.**
Trials registration: **At clinicaltrials.gov (Identifier: NCT03832764).**

Keywords: **Pain Measurement, Artificial Intelligence, Convolutional Neural Network, Analgesia, Pain Monitor.**

Introduction

The development of pain monitoring devices is a hot topic in today's clinical research. It may bring meaningful opportunities in the perioperative setting, including helping to control intraoperative stress responses, preventing postoperative pain and the development of closed-loop systems for the administration of analgesics[1]. This is particularly the case since perioperative pain is associated with

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Written informed consent was obtained from all included patients.
The trial was registered at clinicaltrials.gov (Identifier: NCT03832764, principal investigator: Martine Neckebroek, February 6, 2019).

higher morbidity, leading to prolonged hospital stay and higher healthcare costs[2].

The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'. They emphasize its individual and subjective nature and the dissimilarity with nociception, i.e. the process in the nerve system to process a pain stimulus[3,4]. This subjective nature is a major problem in the quantification of pain. In contrast, nociception and the physiological responses to it (e.g. spinal reflexes and autonomic responses, including changes in heart rate, vasomotor tonus, respiratory rate and pupillary diameter) are objective[1,5].

Pain quantification depends on the patients level of consciousness. In awake patients, we use self-report with scoring systems like Numeric Rating Scale (NRS) or Visual Analogue Scale (VAS)[6,7]. In anesthetized patients, we largely depend on monitored variables and clinical observations, e.g. hypertension, tachycardia, hyperventilation and movement.8 Scoring systems have been developed for this purpose[6,9,10].

Commercially available pain monitoring devices are largely based on the measurement of physiological responses to nociception, including an increased hart rate, peripheral vasoconstriction, pupillary dilation and increases in skin conductance[1]. Examples of existing monitoring devices are Analgesia Nociception Index (Mdoloris Medical Systems, Loos, France), MedStorm (MedStorm innovations AS, Oslo, Norway), AlgiScan (IDMed, Marseille, France), Nociceptive Flexion reflex TreShold (NFTS) Paintracker (Dolosys GmbH, Berlin, Germany), Surgical Pleth Index (GE Healthcare, Helsinki, Finland), qCON 2000 monitor (Quantium Medical, Barcelona, Spain) and Nociception Level Index (NOL) (Medasense, Ramat Gan, Israel)[1,11-14]. However, these devices are not widely used because of inconclusive study results, lack of clinical studies, confounding factors or complex set-up[1,11].

Anspec-Pro is a new pain monitoring device developed by Ghent University. It is based on the measurement of changes in skin impedance. This method can also be found in the MedStorm pain monitor. The innovative part is that the emitted signal consists of 29 frequencies instead of one single frequency, as is the case with MedStorm. This leads to more data available for analysis and possibly a better estimate of pain[15-17].

It was previously studied in one cohort study with awake, postoperative patients, where it was compared to the MedStorm pain monitor[18]. It was concluded that Anspec-Pro and MedStorm had a similar performance because there was no significant difference in the AUC (Area Under the Curve) of their ROC curves. However, the absolute results pointed to a poor performance since both ROC curves had an AUC near 0,5[18]. Therefore, the data collected with Anspec-Pro were reanalyzed, quantifying pain in another way, i.e. the use of Artificial Intelligence (AI) for processing the data monitored with Anspec-Pro. Furthermore, an attempt is made to achieve a more individualized pain assessment by recalibration of the AI algorithms with patient specific data. If AI could detect changes in tissue bioimpedance which correlate to NRS and if these changes would occur earlier than the reported NRS, projections could be made upon the expected pain levels in the near future and a more suitable pain management could be applied.

AI is defined by Kaplan and Haenlein as 'a system's ability to correctly interpret external data, to learn from such data, and to use those learnings to achieve specific goals and tasks through flexible adaptation'[19]. Depending on the specific system, AI can use cognitive, emotional and social intelligence to fulfill these tasks. Interest in AI systems is rapidly increasing and they are used widely in business, education and other parts of society. Its added value has clearly been demonstrated in daily life[19].

Our objectives are to examine if data analysis with AI can deliver complementary information that can lead to a more accurate pain assessment.

Methods

Data were extracted from the original trial, a cohort study conducted at Ghent University Hospital between 24 April 2018 and 22 June 2018. This study was approved by the Ethics Committee of Ghent University Hospital (Address: Corneel Heymanslaan 10, 9000 Ghent Belgium; Protocol code: EC/2017/1517; Chairperson: prof. dr. D. Matthys; Date of approval: 13 February 2018) and written informed consent was obtained from all subjects participating in the trial. The trial was registered at clinicaltrials.gov (Identifier: NCT03832764, principal investigator: Martine Neckebroek, February 6, 2019). This manuscript adheres to the applicable STROBE guidelines. More information about patient enrollment, inclusion and exclusion criteria and randomization can be found in our previous publication[18].

Pain was assessed at two distinct moments: before surgery in the waiting room (monitoring during 14 minutes) and after surgery in the Post Anesthesia Care Unit (PACU) (monitoring during 140 minutes). Pain was measured in two ways: continuously with the monitoring device and intermittently by asking the patient to report an NRS value every seven minutes.

Primary outcome parameters were, as in the first study, postoperative pain scores, i.e. pain values as quantified by Anspec-Pro and NRS as reported by the patient. Secondary end points were vital parameters (heart frequency (HF) and mean arterial pressure (MAP)) and assessment of subjective conditions like alertness, agitation, well-being, energy level and nausea. Other factors that were registered to take into account for interpretation of the results were Glasgow Coma Scale (GCS), patient movements, location of the electrodes (left or right hand), administered drugs (with time and dose) and the patient's medical history.

The pain monitoring devices used in this study are based on the measurement of changes in skin impedance. The underlying physiological principle is the fact that emotional sweating, which can be caused by pain, is activated by sympathetic nerves in the skin. Each time these skin sympathetic nerves are activated, palmar and plantar sweat glands are filled up and skin conductance increases. Next, the sweat is reabsorbed and skin conductance decreases again. This causes changes in skin conductance.

The Anspec-Pro pain monitor is a new monitoring device that was developed by Research Group DySC (Dynamical Systems and Control) at Ghent University. It quantifies pain by measuring changes in skin conductance after emitting a signal, just like the MedStorm pain monitor. The innovative part of Anspec-Pro is that the emitted signal consists of 29 distinct frequencies between 100 Hz and 1500 Hz with 50 Hz intervals, whereas other pain monitors like MedStorm emit only one frequency. This method is based on the fact that frequency affects pain detection, because each tissue molecule has a different response to a given frequency. The measurement requires three electrodes connected to

Fig. 1 — Clinical set-up of Anspec-Pro.
Anspec-Pro is connected to the patient with three electrodes that are placed at the palm of the hand. One electrodes emits the signal and the other two detect the signal. Anspec-Pro is further connected to a laptop that processes and displays the measurements (Figure obtained from Neckebroek et al.[18]).

the palmar skin, as shown in Figure 1. In our previous analysis, Anspec-Pro measurements were used to calculate a value of the complex skin impedance, which would correlate with pain intensity[15-17].

In our new analysis, data collected with Anspec-Pro were reanalyzed and pain quantification was done in a different way, with the aim of obtaining complementary information that could possibly lead to a more accurate pain assessment.

For this purpose, an AI algorithm classified pain by analyzing Anspec-Pro's measurements. In this study, deep learning is used, a part of AI that uses artificial neural networks to mimic the human brain, with a convolutional neural network (CNN), an artificial neural network commonly used for the analysis of visual data. Spectrograms displaying the spectrum of the electrical power (the rate at which electrical energy is transferred) of the skin as a function of time and emitted frequency are used as input for the CNN (Figure 2). These spectrograms are generated with the data collected with Anspec-Pro. More information on the generation of spectrograms can be found in Ghita et al.[16]

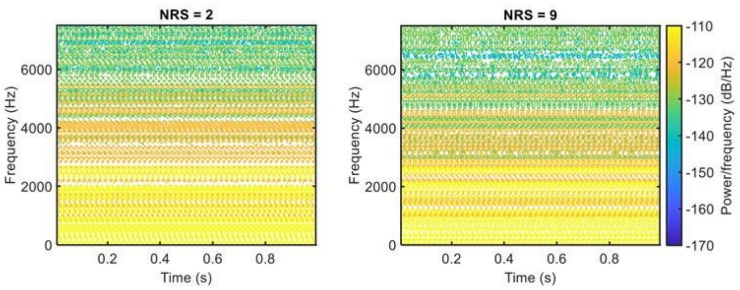

Fig. 2 — Example of two spectrograms generated at moments that differ in pain intensity.We generate a spectrogram by displaying the spectrum of the electrical power of the skin as a function of time and emitted frequency over one second. The x-axis represents time, the y-axis represents the emitted frequency. The color code displays the ratio of power over emitted frequency. There is a clear difference between the two spectrograms that were generated at moments that differ in pain intensity (NRS 2 versus NRS 9) in the same patient. NRS – Numeric Rating Scale.

In this analysis, pain intensity was categorized into four pain classes, instead of reporting single NRS values. These classes are: (I) no pain (NRS 0 – 1), (II) mild pain (NRS 2 – 3), (III) moderate pain (NRS 4 – 6) and (IV) severe pain (NRS 7 – 10). In future research, a bigger number of classes could be used to describe pain intensity more precisely.

In this deep learning algorithm, spectrograms were classified in pain classes by linking them to the NRS value reported at the same moment. Throughout the training of the CNN, the pain intensity predicted by the CNN is compared to the reported NRS value and subsequently the algorithm is adjusted to achieve a prediction as accurate as possible. This way, the CNN is trained to classify the spectrograms into pain classes. Both offline and online training algorithms were used.

In offline training, the training data are first collected over certain period of time. After collection of these training data, the AI model is trained with them. After training and during the use, the AI model is not updated anymore with the new data that it is presented with, it can’t learn anymore. In our trial, the CNN was trained with several subsets of the complete postoperative dataset collected with Anspec-Pro. These subsets were: (I) the patients with the best correlation between the Anspec-Pro index and the reported NRS in our previous analysis, (II) the patients with the worst correlation between the Anspec-Pro index and the reported NRS in our previous analysis, (III) all patients, (IV) the first 25% of data of all patients, (V) the first 50% of data of all patients and (VI) the first 75% of data of all patients. These distinct subsets were used in order to check if using less data for training would affect the accuracy of pain predictions. In this training, each spectrogram was presented multiple times to the CNN for providing sufficient training. After finishing the training, the CNN was tested with the remaining data that weren’t used for the training; for subset III (training with all data), the CNN was tested with the same data as used for training. A new spectrogram was generated from the test data every minute and presented to the CNN, resulting in 140 estimated pain levels for each test patient (one per minute). A mean value was calculated from seven consecutive estimates, firstly to lower the impact of outliers and secondly to be able to compare the result to the NRS values that were reported only every seven minutes (unlike the continuous monitoring by Anspec-Pro).

In online training, the data that are acquired over time can be used to update the AI model in real-time, at the moment that data are obtained. In other words, learning occurs as data come in. The model is updated after learning from each individual input to the system. In our online training algorithms, the CNN was first trained offline with subset I (the subset of patients with the best correlation between the Anspec-Pro index and the reported NRS), before starting patient monitoring (i.e. testing with the remaining data). Then, during patient monitoring, patient-specific spectrograms delivered by Anspec-Pro and NRS values reported by the patient were used in real-time to retrain the CNN, to individualize pain assessment. A fixed part of the CNN was always kept unchanged throughout the retraining to keep the CNN from becoming unfavorable sensitive to the individual patient. Summarized, in online training, algorithms that have a self-learning ability when new information is presented are used. Three algorithms were used for online retraining.

In the first online retraining algorithm, the preoperative data were used for retraining. Ten spectrograms with the accompanying NRS value were randomly selected from to preoperative dataset to partly retrain the CNN before starting the postoperative monitoring. During the postoperative monitoring, no retraining occurred.

In the second algorithm, the CNN was retrained with cumulative data from all past spectrograms, leading to a larger and larger dataset for training. The CNN was retrained every seven minutes, when a new NRS value was reported by the patient and linked to all spectrograms generated in this period. In the third algorithm, the CNN was, similarly to the second algorithm, retrained every seven minutes when a new NRS value was reported, but instead of keeping all collected data, only the data from the last seven minutes were used for retraining.

Statistical analysis

Performance of the CNN’s was evaluated by using ROC (Receiver Operating Characteristic) curves. The ROC curves were built using sensitivity (true positive predicted value rate) and false-positive rate:

sensitivity = true positive/positive
false positive rate = 1 – specificity = 1 – (true negative/negative)

where true positive is the number of correctly predicted occurrences of the specific class, positive is the number of the genuine occurrences of the class, true negative is the number of correctly predicted absences of the specific class and negative is the number of genuine occurrences of different classes to the specific one. An AUC (Area Under the Curve) of 0,5 would mean the CNN is randomly guessing the pain class, an AUC of 1 means that every spectrogram would be classified correctly. An

AUC above 0,8 was considered a successful result. In addition, a confusion matrix is presented for some of the CNN's. A confusion matrix is a table used to visualize the performance of an algorithm in deep learning, more specifically in statistical classification. The rows represent the reported pain classes and the columns represent the predicted pain classes. The shown number is the number of times that the CNN classifies a spectrogram f from the reported pain class in the predicted pain class.

Results

The inclusion of patients started on 24 April 2018. Of all patients screened and included in the trial, eleven were assigned to the arm monitored with Anspec-Pro. Data collected in this arm were reanalyzed. Our previous publication displays an extensive description of the original inclusions.18 Demographics and other characteristics of the Anspec-Pro arm are shown in Table I.

The CNN's ability to classify pain intensity into the proper pain class was evaluated by building ROC curves.

First, the ROC curves for the CNN's trained offline with six distinct subsets of data were composed (Figure 3A and Figure 4). The best performing CNN is the one trained with all available data (subset III), attaining an AUC above 0,88 for all pain classes (Figure 3A). Furthermore, the confusion matrix for this CNN shows a predominantly correct classification in pain classes, illustrated by the highest number of predictions in the diagonal (Figure 3B).

Table I. — Patients characteristics and clinical data.

Characteristic	Anspec-Pro (n = 11)
Biometric data	
Age (y)	34,90 (12,46)
Height (cm)	167,45 (10,01)
Weight (kg)	69,72 (13,38)
BMI (kg.cm^{-2})	24,81 (4)
Gender n (%)	
Male	1 (9,1)
Female	7 (63,6)
Transgender male	3 (27,3)
Surgery type n (%)	
ORL	3 (27,3)
Abdominal	2 (18,2)
Gynecology/Urology/Orthopedics	5 (45,5)
Breast surgery	1 (9,1)
ASA class n (%)	
I	3 (27,3)
II	8 (72,7)
III	0

Values are mean (SD), respectively count (%) from total number of patients of the Anspec-Pro group; Abbreviations: BMI – Body Mass Index; ORL – Otorhinolaryngology; ASA – American Society of Anesthesiologists physical status.

The performance of the other offline trained CNN's is remarkably lower. Training with subset I, the patients with the best correlation between Anspec-Pro and NRS, shows ROC curves with an AUC close to 0,5 for all pain classes, indicating a weak performance (Figure 4B). Training with subset II, the patients with the worst correlation between Anspec-Pro and NRS, displays similar ROC curves and AUC values (Figure 4A). Training with subset IV, the first 25% of data of all patients, shows better ROC curves with all AUC values above 0,5 and even an AUC above 0,8 for severe pain, however, for the other pain classes, AUC values remain below 0,8 (Figure 4C). Training with subset V, the first 50% of data of all patients, shows variable results, but all pain classes have an AUC below 0,8 (Figure 4D). For training with subset VI, the first 75% of data of all patients, AUC values vary between 0,5 and 0,8 (Figure 4E).

The ROC curves for the online retraining algorithms are shown in Figure 5A-C. For the first algorithm, the AUC is below 0,5 for mild and moderate pain and between 0,66 and 0,7 for no pain and severe pain (Figure 5A). The confusion matrix shows that mild and moderate pain are frequently underestimated in this algorithm (Figure 5D). In the second algorithm, a limited improvement can be seen for the AUC for mild and moderate pain (AUC = 0,62) and for no pain and severe pain (AUC between 0,71 and 0,74) (Figure 5B). The third algorithm has the best results with an AUC above 0,81 for all pain classes (Figure 3C) and predominantly correct classifications in the confusion matrix (Figure 5F).

Discussion

In this study, the data from our previous trial were reanalyzed using AI for pain classification, to explore if this can deliver complementary information that aids in better pain assessment.

In a first phase, training occurred offline. An AUC of at least 0,8 for every pain class was only seen when the CNN was trained with all available data and tested with the same data. This could possibly lead to overfitting of the CNN to the training data, with the risk of declining performance when new data are presented for pain classification. When the CNN was trained with smaller datasets, AUC values were lower than 0,8 and often even close to 0,5. From a clinical point of view, this means that, in this analysis with this population, offline training

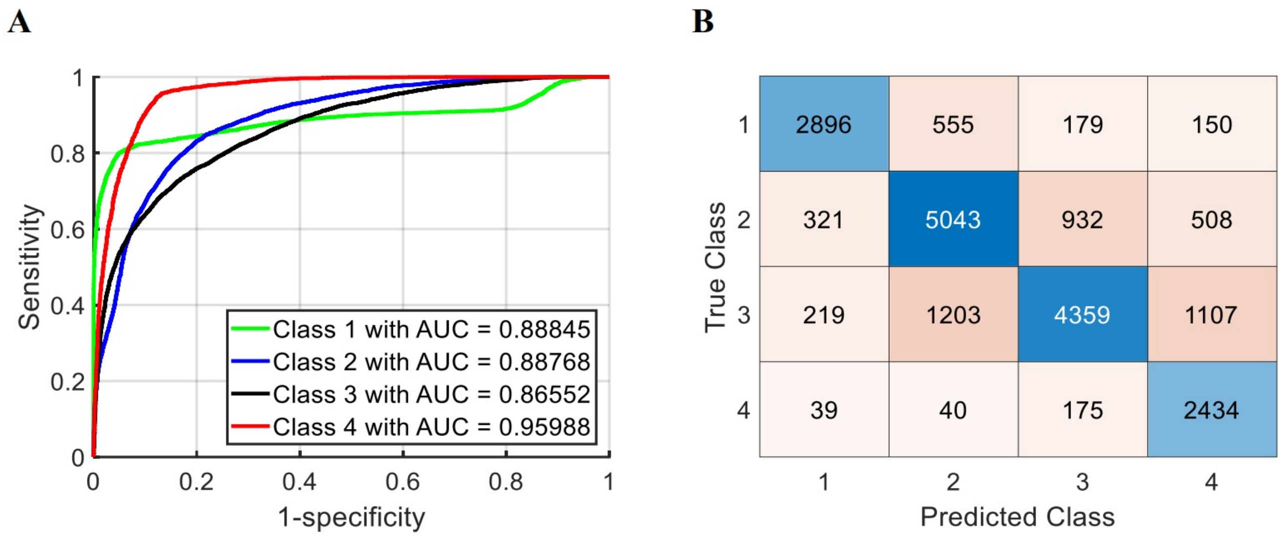

Fig. 3 — Performance of the CNN trained offline with all data.
(A) Receiver operating characteristic (ROC) curves and area under the curves (AUC) shown for each pain class. For all pain classes, an AUC above 0,86 is obtained, which is considered a good result. The drawback of this AI algorithm is that it was trained and tested with the same data. This could possibly lead to overfitting of the CNN to the training data, with the risk of declining performance when new data are presented for pain quantification.

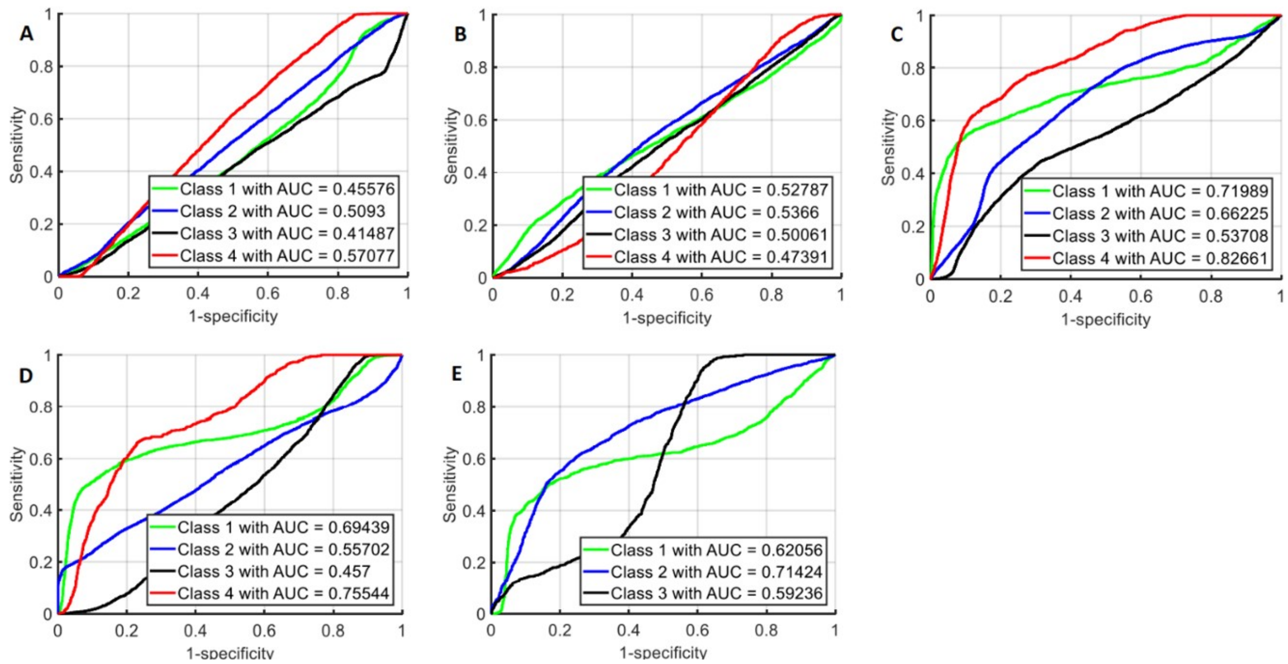

Fig. 4 — Receiver Operating Characteristic (ROC) curves with Area Under the Curve (AUC) for the other offline trained CNN's.
(A) CNN trained with data from the patients with the worst correlation between the Anspec-Pro index and the reported NRS in the first analysis. The low AUC values correlate with bad performance of this AI algorithm. (B) CNN trained with data from the patients with the best correlation between the Anspec-Pro index and the reported NRS in the first analysis. The low AUC values correlate with bad performance of this AI algorithm. (C) CNN trained with the first 25% of data of all patients. Only class 4 (severe pain) has an AUC above 0,8, other classes don't. This means that this AI algorithm can only be trusted when it indicates severe pain in the patient. (D) CNN trained with the first 50% of data of all patients. All AUC values are below 0,8, correlating with insufficient performance of this AI algorithm. (E) CNN trained with the first 75% of data of all patients. All AUC values are below 0,8, correlating with insufficient performance of this AI algorithm. AUC – Area Under the Curve.

alone was insufficient to quantify pain accurately in 'unknown' monitored patients.

In a second phase, real-time online training was provided. With the first algorithm, the AUC values for mild and moderate pain were close to 0,5 with predominantly an underestimation of pain. A possible explanation could be that the CNN was retrained with data obtained at a moment without pain and thus would underestimate pain in the following period. A slightly better performance was seen with the second algorithm, but the AUC values for mild and moderate pain remained rather low. With the third algorithm, specificity and sensitivity for classification of pain sharply increased, with AUC values above 0,8 for all pain classes.

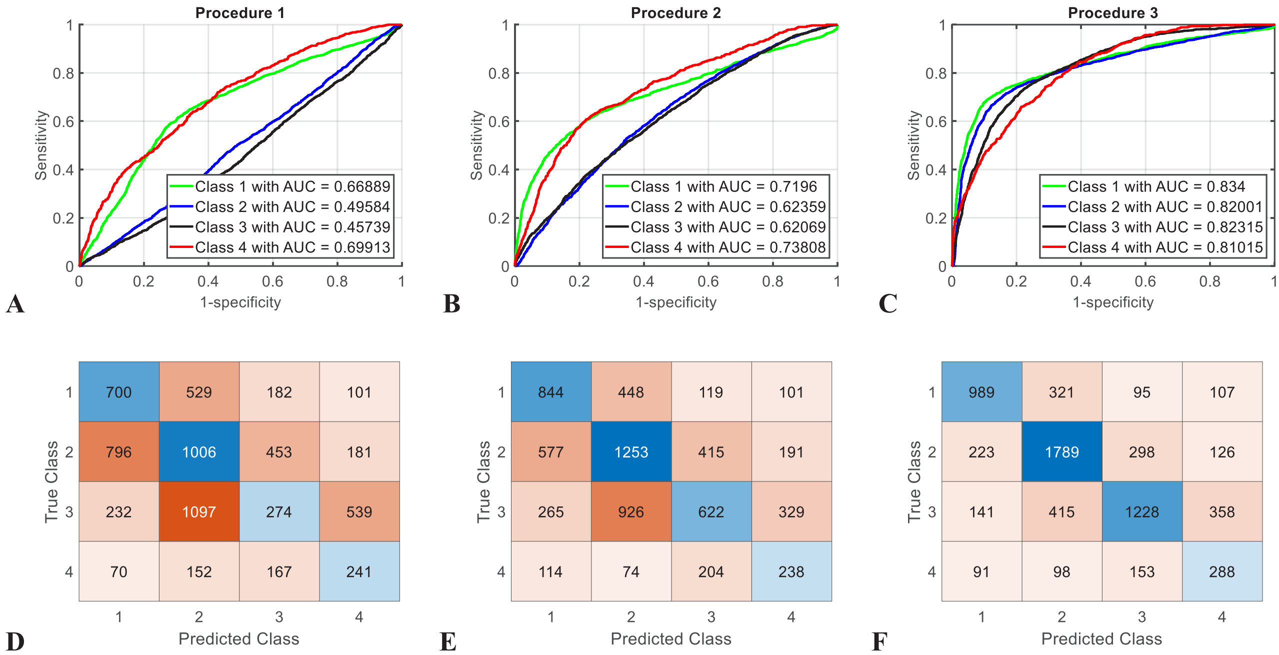

Fig. 5 — Performance of the online retrained CNN's presented by Receiver Operating Characteristic (ROC) curves with Area Under the Curve (AUC) and confusion matrices.
(A,D) ROC curves with AUC and confusion matrix for the CNN retrained using algorithm 1 (retraining with preoperative data). All AUC values are below 0,8, correlating with insufficient performance of this AI algorithm. This is most outspoken for the pain classes mild and moderate pain, as shown by AUC values below 0,5. The confusion matrix makes clear that in these classes, pain is predominantly underestimated. A possible explanation could be that the CNN was retrained with data obtained at a moment without pain and thus would underestimate pain in the following period. (B,E) ROC curves with AUC and confusion matrix for the CNN retrained using algorithm 2 (retraining with all postoperative data). All AUC values are below 0,8, correlating with insufficient performance of this AI algorithm. (C,F) ROC curves with AUC and confusion matrix for the CNN retrained using algorithm 3 (retraining with postoperative data from the last seven minutes). For all pain classes, an AUC above 0,81 is obtained, which is considered a good result.
AUC – Area Under the Curve.

The good performance of online training algorithm 3 could offer an opportunity to develop a reliable device for the continuous monitoring of awake and cooperative patients. In our trial, NRS reporting and retraining occurred every seven minutes, but in clinical practice, this could be done at any moment the patient reports an NRS value. This raises the question at what time interval, between the reported NRS values, the performance starts to decline. This is particularly important because if this interval would be too short, the input of NRS values could be labor intensive and compromise the use of the algorithm. Future research could focus on device performance as a function of the time interval since the last reported NRS value. Another limitation we make with this algorithm is that it can only be used in the postoperative period and not during surgery in a sedated patient, since the patient needs to be able to report NRS values for the online training.

Some factors that can attenuate the performance of Anspec-Pro (and MedStorm) can be identified. Sympathetic tone is not only affected by pain, but by multiple other factors too, e.g. emotions, awaking after anesthesia, fluid balance or age dependent changes in autonomic tone. All of these can affect sympathetic tone and thus lower specificity for pain. On the other hand, pain is defined as a personal experience and this experience could differ between individuals even after the same pain stimulus. This way, measuring sympathetic tone rather than nociception could offer an advantage by possibly taking the emotional aspects of pain in a conscious patient into account.

Since this was a proof of concept study, only a small dataset was available for analysis. Nevertheless, it can be concluded that there is a large interindividual variability in pain responses, which limits the potential use of offline training algorithms. This is shown in this analysis by the fact that offline training only resulted in a good performance when the device was trained and tested with the same data. Future research could focus on how big a training population needs to be to train a reliable offline trained device or could examine if performance of an offline trained device is better when trained and used in particular patient populations. However, even with big training populations, the question remains if offline training alone will ever be sufficient to develop a reliable device for monitoring of big populations.

On the other hand, a considerable intra-individual variability exists, as shown by the worse performance of online retraining algorithm two compared to algorithm three. This indicates the need for continuous real-time retraining with recent data, which is possible in cooperative patients.

Furthermore, this population contains a large variety of surgical procedures, decreasing the similarity of the subjects of this already small population. Additionally, the presence of three transgender males in the population is noted, making it less representative of the general population.

It should be mentioned that at this moment, a scale to express pain intensity as assessed by Anspec-Pro has not been developed yet. In this analysis, pain intensity was categorized into four classes (no pain, mild pain, moderate pain and severe pain). In future research, there is a possibility to expand this classification and narrow the classes in order to describe the measured pain intensity more precisely.

We mentioned that if the changes in tissue bioimpedance that are detected with AI would occur earlier than the reported NRS, projections could be made upon expected pain levels in the near future. However, this analysis does not provide sufficient information to draw conclusions upon this topic. This predictive aspect needs further exploration in future research.

To conclude, our results indicate that there is potential for AI to deliver useful information that can be used in complementary models of monitoring devices. Additional research on this topic is highly recommended.

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