

## Objectively measuring pain using facial expression: is the technology finally ready?

Article (Accepted Version)

Dawes, Thomas Richard, Eden-Green, Ben, Rosten, Claire, Giles, Julian, Governo, Ricardo, Marcelline, Francesca and Nduka, Charles (2018) Objectively measuring pain using facial expression: is the technology finally ready? *Pain Management*, 8 (2). pp. 105-113. ISSN 1758-1869

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/73147/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

### **Copyright and reuse:**

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

## **Objectively measuring pain using facial expression: is the technology finally ready?**

TR Dawes, B Eden-Green, C Rosten, J Giles, R Governo, F Marcelline, C Nduka

*Department of Anaesthesia, Queen Victoria Hospital, East Grinstead, West Sussex, RH19 3DZ, UK; thomas.dawes@nhs.net*

*Department of Anaesthesia, Queen Victoria Hospital, East Grinstead, West Sussex, RH19 3DZ, UK; beden-green@nhs.net*

*School of Health Sciences, University of Brighton, Falmer, BN1 6PP; C.E.Rosten@brighton.ac.uk*

*Department of Anaesthesia, Queen Victoria Hospital, East Grinstead, West Sussex, RH19 3DZ, UK; Julian.Giles@qvh.nhs.uk*

*Brighton and Sussex Medical School, University of Sussex, Brighton, BN1 9PX; R.Governo@bsms.ac.uk*

*Brighton and Sussex Library and Knowledge Service, Royal Sussex County Hospital, Brighton BN2 5BE, UK; francesca.marcelline@bsuh.nhs.uk*

*Department of Plastic and Reconstructive Surgery, Queen Victoria Hospital, East Grinstead, West Sussex, RH19 3DZ, UK; cnduka@gmail.com*

### **Practice Points**

1. Facial expression is a key pain-related behaviour that may unlock the answer to an automatic objective pain measurement tool.
2. Several facial movements occur frequently when describing the facial expression of pain.
3. The facial expression of pain shows consistency across ages, genders, cognitive states and different types of pain and may correlate with self-report of pain.
4. Computer imaging has introduced a novel approach to assessing pain perception, via the automatic recognition of specific facial expressions attributed to pain. This has some intrinsic limitations, including as the detrimental effect from participant movement.
5. Facial electromyography is an alternative method to detect facial muscle activity. Its ability to measure muscle tone may demonstrate an improved correlation to pain intensity, but the concept has not been proven.
6. If facial electromyography or other technology could be refined to accurately measure pain intensity, it could be combined with advances in sensor technology and artificial intelligence to create a field rich for research and technical innovation and, ultimately, clinical use.

## **Abstract**

Currently clinicians observe pain-related behaviours and use patient self-report measures in order to determine pain severity. This paper reviews the evidence when facial expression is used as a measure of pain. We review the literature reporting the relevance of facial expression as a diagnostic measure, which facial movements are indicative of pain, and whether such movements can be reliably used to measure pain. We conclude that although the technology for objective pain measurement is not yet ready for use in clinical settings, the potential benefits to patients in improved pain management, combined with the advances being made in sensor technology and artificial intelligence, provide opportunities for research and innovation.

## **Key words**

Pain  
Objective measure  
Automatic  
Facial expression  
Computer-image analysis  
Electromyography

How pain is ultimately perceived is the result of a complex interplay of sensory, cognitive, social and emotional drivers that vary between individuals [1]. Since the experience and the manifestation of pain, including verbal reports, can be ascribed as highly subjective, there is a genuine desire in searching for diagnostic tools that provide more objective measures. To date, clinicians have relied upon observing pain-related behaviours to grade a patient's extent of suffering. Facial expression exemplifies one of these pain-related behaviours and there is a growing interest in its objective measurement. The focus of this article is to review current advances in technology working towards an objective measure of pain through facial expression. The ability to record the pain experience in such a way would bring a myriad of clinical advantages. These include improved assessment of pain in non-communicative patients, better targeting of potential treatments and more accurate assessment of their efficacy. It may also enhance our understanding of pain, thereby assisting towards new pharmacological and non-pharmacological analgesic breakthroughs.

While the practice of observing facial expression is a common method for clinicians to assess the presence or absence of pain [2], its interpretation can be influenced by numerous factors, such as age and dementia [3]. In addition, similar studies demonstrate that healthcare professionals exposed to a high number of painful facial expressions over time develop an exaggerated bias. This attitude shift, labelled a 'recalibration' phenomenon, signifies the desensitization of healthcare professionals to the severity of pain being experienced by the patients. Moreover, several other factors can influence this judgment bias, such as ethnicity, associated motivations including opiate seeking behaviour or the general likeability of the observed individual [4-6]. Overall, healthcare professionals observing facial expression are at risk of underestimating patients'

pain and can, as a result, undertreat it.

Pain measurement tools can aid the clinician in estimating a patient's pain. A wide range are available including those for different ages (e.g. Preverbal Early Verbal Paediatric Pain Scale and Doloplus-2 Scale), clinical environments (e.g. Critical Care Pain Observation Tool) or cognitive states (e.g. Abbey Pain Scale), but most remain un-validated and lack reliability data [7-12]. Rather than objectively measuring facial expression, pain measurement tools often infer information from the patients' expressions [3,11,13,14]. In general, it seems the fewer facial characteristics that are empirically described in the tool (e.g. 'clenched teeth' vs. 'Grimace; brows drawn together, eyes partially closed, squinting'), the less reliable and more variable the pain estimates [12,15]. However, unless formally trained in assessing facial activity, assessor-mediated variability is likely to result from subjective interpretation of discrete facial movements.

Emerging technology capable of recording facial muscle movement opens the opportunity for acquiring data that is unaffected by exposure bias or interpretation variation. More importantly, in the context of pain assessment, automatic facial expression recognition is being explored as a method to provide an objective measure of pain perception. Examples of such tools include computer image analysis [16–24] and facial electromyography techniques [25], although the latter is still in its infancy.

The aim of this narrative review is to explore current methods being developed to measure facial expression of pain and the feasibility of their clinical use. A summary of the literature exploring facial expression of pain and its usefulness as a marker of pain is included. Available articles were identified by structured computerized searches of MEDLINE and CINAHL databases using search terms FACE, FACIAL EXPRESSION, FACIAL MUSCLES, FACIAL PAIN, PAIN, EMOTIONS, STIMULUS, VISUAL ANALOGUE SCALE, PAIN MEASUREMENT, TOOL and SCORE. The date range was initially limited to 2000 onwards to provide studies detailing the most recent advances. However studies with historical significance before this date were reviewed and have been included where relevant.

### ***How are facial expressions measured?***

Ekman and Friesen devised the Facial Action Coding System (FACS) [26] which describes facial movements in terms of 46 action units (AUs) resulting from underlying muscle activity. Although described as an objective measurement of facial activity, the FACS is limited to what is clearly visible to observers and ignores subtle or invisible changes (i.e. muscle tone). It is also open to a degree of assessor interpretation and takes over 40 hours to learn and accurately use.

***Which facial movements display the expression of pain?***

Researchers attempted to describe the adult and infant facial expression of pain (FEP) in terms of the FACS and initially 12 AUs were identified [27–31]. But these occurred inconsistently and in several combinations. In later studies the concept of a core expression of pain (CEP) began to develop, with a group of AUs frequently being observed in response to a painful stimulus (see figure 1) [25,32–35]. Table 1 summarizes the studies that demonstrate this concept and the facial AUs involved. Facial actions involving AU4, AU6/7 and AU9/10 occur the most consistently. Note that as previously described, AU 6 and 7 and AU 9 and 10 are paired as the facial activity and muscular bases of the movements are similar [31]. It is also the author’s opinion that AU 43 (eyes closed) or AU 45 (blink) could be used interchangeably, based upon assessor interpretation.

Study	Description	Facial Actions (AU)				
		4	6/7	9/10	25-27	43 (or 45)
Grunau & Craig (1987) [29]	‘pain expression’	✓	✓	✓	✓	
Prkachin (1992) [31]	‘general pain expression’	✓	✓	✓		✓
Peters et al (2002) [28]	‘core facial actions’	✓	✓	✓	✓(27)	
Wolf et al (2005) [25]	‘key muscles’	✓	✓		✓ (25)	
Kunz et al (2007) [34]	‘pain-relevant AU’	✓	✓	✓		
Prkachin & Solomon (2008) [32]	‘core pain expression’	✓	✓	✓	✓	
Kunz et al (2008) [33]	‘pain-relevant AU’	✓	✓	✓		✓ (45)
Rahu et al (2013) [35]	‘core facial actions’	✓	✓	✓ (9)		✓

Table 1. Summary of studies suggesting the concept of a CEP and the associated AUs. AU, action unit; CEP, core expression of pain.

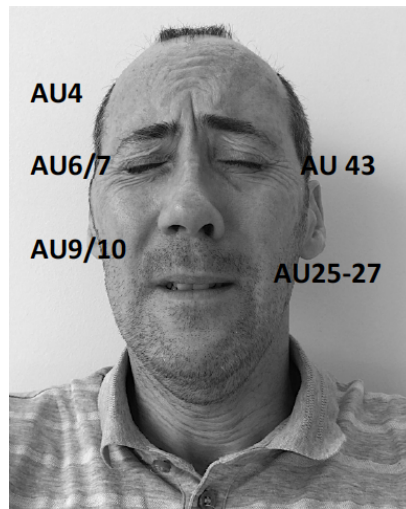


Figure 1. Model demonstrating the AUs making up the CEP. AU 4, brow lower; AU 6/7, eyes tighten; AU 9, nose wrinkle; AU 10, upper lip raise; AU 25-27, mouth opening lips part; AU 43, eyes close. AU, action unit; CEP, core expression of pain.

On initial comparison of the AUs forming the CEP to those seen in other emotions, the combination appears distinct [36]. However, there is considerable overlap in the AUs involved in the facial expressions of CEP, sadness and anger. This could make distinction of these emotions difficult.

### ***Can facial expressions of pain reliably measure pain?***

The above select literature supports the argument that FEP may be a sensitive marker of pain, in following the notion of a CEP. However, to be of greatest benefit to all pain sufferers, FEP needs to be reliable across different patient age groups, genders, cultures and types of pain. In addition, for FEP to be used as a method to estimate pain intensity, a correlation between FEP and self-reported levels of pain must exist.

Our analysis of the literature identified several studies that report a significant correlation between facial expression and self-reported pain. Prkachin and Mercer (1992), observed a direct relationship between the intensity of active AUs (5 point system) during painful shoulder movements with self-reported sensory and affective pain scales [30]. In addition, Kunz and colleagues (2004) demonstrated a significant relationship between an increasing pressure stimulus and both self-report and facial expression of pain [37]. Moreover, Prkachin and Solomon (2008) described the CEP as a reliable phenomenon with good short-term reproducibility giving it stability as a potential measure of pain [32]. These authors further found that pain facial expression and self reports of pain were significantly related. Finally, Peters and colleagues (2002) also found that combining the most consistently occurring facial actions from the Neonatal Facial Coding System (NFCS) into a single index increased specificity for pain assessment in the neonatal post-operative period [27]. This suggests reducing

the facial expressions of pain to the core expression of pain, and defining the intensity of these AUs, could produce a reliable measure of pain. However, several studies also demonstrated no significant correlation between facial expression and self-reported pain [27,38,39]. This discrepancy in findings may be the result of the attempt to define the multidimensional experience of pain in a uni-dimensional way.

Studies to date reveal that FEP is not significantly affected by age [28,29,33], gender [14,29,40,39], dementia [34,39] or different types of experimental pain [30]. AUs associated with the CEP remain predominant in the majority of these studies. In contrast, though, any evidence that FEP is mirrored across different ethnicities is lacking [14].

Interestingly, evidence suggests that sedation may not affect FEP. The work by Rahu's group (2013) demonstrated that patients who were sedated with opioid, benzodiazepine or propofol retained the core expression of pain. [35]. These results suggest that FEP could be useful in measuring pain in sedated patients.

### ***What technology is available to detect FEP?***

The majority of work for the automatic recognition of FEP has revolved around computer image analysis. Measurement of facial activity from still images or video recordings requires several sequential processes. Initially basic analysis involves face localization, tracking and adjustment for head pose and illumination. Secondly, feature extraction aims to convert pixel data to that representative for variations in shape, colour and texture. Finally, classification, or expression recognition, is simply facial action detection by recognizing active AUs [23,41].

One method that enables automatic recognition of active AUs is based on machine-learning techniques and makes use of artificial intelligence algorithms. Once the initial images have been adjusted and converted, the relevant facial feature data are filtered and input into machines which have learnt to recognise AUs through training on large databases of FACS-labeled images [23,42,43]. An alternative method tracks manually-marked feature points across sequential images, allowing an estimation of pain intensity: the greater the distance moved by the feature point, the more intense the AU [44,45].

Table 2 summarizes published studies where technology designed to detect FEP has been applied to investigative research. Studies using computer-based systems to recognise FEP were largely conducted in neonates or children. In a 2006 study, three face classification techniques were trained and tested on photographs to assess the ability of the system to differentiate between painful and non-painful facial expressions [19]. The best system classifier in this study had an 88% recognition rate. Although an early form of machine-based facial recognition, it highlighted some of the clinical feasibility issues associated with

this method, particularly the temporal uncoupling that occurs when still images are taken and individually processed by hand before analysis. A 2015 study used the Computer Expression Recognition Toolbox (CERT) [23] to develop a model that could detect and measure post-operative pain in children that had undergone an appendectomy [21]. The CERT is trained on 5 large databases [23] and was used on this occasion to identify 14 pain-related AUs from video recordings. The model demonstrated good accuracy in detecting the presence of pain, but estimating its intensity was only moderately correlated to self-report [21]. Issues highlighted from this study were that children had to be positioned and remain relatively still in front of a camera to enable capture of suitable images. Lighting also had to be optimized. Although accurate in detecting pain, correlation with reported pain intensity was limited and it highlighted problems with using this technology in a clinical environment.

A 2015 study assessed the ability of newly developed software, based on the principle of facial point tracking, to recognize 5 NFCS identified pain-related facial actions in neonates [46]. The sensitivity and specificity of the software to detect pain was 100% when assessed using images obtained during a painful procedure. However, the concordance of the software with the painful situation was assessed using only 90 out of the 5644 images obtained and equated only to the presence or absence of pain, rather than intensity. As with the previous studies, participant movement is poorly tolerated and with software dependent on analyzing distance moved by tracked points, this becomes even more intolerant to participant or camera movement [46].

Study	Technology detecting FEP	Subjects	Stimulus	Study findings	Limitations of technology
Wolf (2005) [25]	Facial electromyogram (measuring 9 facial muscles)	10 male adults	Laser pulses	Significant activation of 2 groups of facial muscles – orbicularis oculi/ corrugator supercilii and mentalis/depressor anguli oris	Only a pilot study. No described correlation between pain intensity and muscle activity.
Brahnam(2006) [19]	Machine recognition of facial expression from photographs	26 Caucasian neonates (13 boys)	Transport, air stimulus, friction, heel puncture	88% automatic recognition rate of pain vs. non-pain states	Not clinically practical – each image needs manually processing prior to analysis
Heiderich (2015) [46]	Automatic recognition of NFCS using facial point tracking from sequential still images	30 neonates	Intramuscular injection, heel lancing, venipuncture	100% sensitivity and specificity of automatic detection of pain during painful procedure	Intolerant to camera movement once images calibrated. Unable to detect pain intensity.
Sikka (2015) [21]	Computer vision machine learning-based technique	50 children (5-18 years)	<24 hours post laparoscopic appendectomy	Good-excellent detection of pain vs. no-pain. Moderate correlation between pain-intensity estimate and self-report.	Frontal camera with 15° tolerance. Moderate ambient lighting needed. Intolerant to rapid subject motion.

Table 2. Studies where automatic facial recognition of pain has been applied to investigative research. FEP, facial expression of pain; NFCS, Neonatal Facial Coding System.

Progress has been made in an attempt to develop computer software capable of overcoming the issue of non-frontal facial alignment [20,24]. However,



movement error remains a limitation, making its use in the clinical setting questionable. Another fundamental limitation is the fact that computer image analysis still relies on the assumption that muscle contraction causes visible facial movements. As Ekman queried in his paper first describing the FAC, it ignores the invisible movements such as muscle tone that may give more detailed information about pain intensity [26].

### ***Facial EMG and the evidence for its practical use.***

An alternative method to detect facial muscle activity is facial EMG (fEMG). As reviewed by Dimberg (1990), consistent fEMG reactions occur in response to different visual emotional stimuli, allowing emotions of fear, happiness and anger to be distinguished [47]. However, until recently there have not been any studies identifying FEP through muscle activity detectable by fEMG [25].

Dimberg highlighted the advantages of fEMG in detecting facial muscle actions from fEMG studies [47]. Firstly, fEMG signal is instantaneously detected and recorded and not reliant upon large amounts of time to interpret facial activity or process videoed facial images. Secondly, fEMG provides an objective measurement of muscle activity. This compares favourably with computer image analysis that, as previously described, uses software trained on databases of manually and therefore subjectively labeled images. Thirdly, fEMG allows detection of muscle activity that is too small to be seen visibly. The potential relevance of this is demonstrated by the fact that invisible facial muscle activity is detected during imagery of different emotions [47]. But it remains unknown if intensity of muscle activity translates to a sensitive measure of pain intensity. Lastly, an advantage that fEMG has over current methods of computer image analysis is that the participant's face does not have to be kept in alignment with the camera or at a set distance. This could make it a feasible tool for use in the clinical setting.

There has only been one study measuring FEP by fEMG methods (see table 2). Wolf's group (2005) conducted a pilot study to test a new EMG method in which the recording of facial muscle activity was related to the previously identified AUs making up expression of pain [25]. Where fEMG methods had previously been unsuccessful in reaching a balance in sufficient sensitivity and selectivity, this study was able to record activity in 9 facial muscles simultaneously. As a result participants exposed to a painful stimulus showed significant activities in corrugator supercilli (AU4) and orbicularis oculi muscle (AU7) as well as muscle groups initiating mouth movement (mentalis and depressor anguli oris). Encouragingly, these authors found that the facial pattern of pain differed from that demonstrated in their previous work exploring facial expressions associated with joy, disgust and appetite [48]. However, as previously mentioned, the distinction of CEP from anger and sadness may be more challenging.

### ***What potential problems can be foreseen using facial EMG techniques?***

The process of recording fEMG signals is composed of 3 stages including electrode selection and placement, EMG recording and signal conditioning [49]. Electrodes can either be needle or surface type. However, needle electrodes are invasive and therefore unsuitable for routine use so will not be considered further. Surface electrodes, in turn, are non-invasive, safe and easy to use, but may irritate and thus be poorly tolerated. In addition they are prone to crosstalk from other surrounding muscles, making it difficult to measure signals from specific muscles. However, crosstalk can be considerably improved by filtering out EMG signals originating from distant muscles and, as seen in the study by Wolf et al, fEMG technique can overcome the issue of selectivity [25]. Correct electrode placement is required to measure the appropriate muscle activity and to minimise crosstalk. As the optimal placement is in the midline of the muscle belly, anatomical variations in facial muscles may be a complicating factor that needs to be addressed [50]. Also, to minimize inaccuracies in data acquisition, an expert in facial anatomy and fEMG would be required.

During EMG recording, the small amplitude signals can easily be affected by extrinsic electrical noise. Many forms of such noise can be found in the clinical environment, such as those created by electrostatic, electromagnetic radiation or noise from power-lines and electrical equipment. In addition, noise can also result from what is defined as motion artifact, generally caused from the electrode moving over the skin.

Measures to overcome some of these potential artifacts include signal conditioning or the application of filters. The former is the final part of the EMG recording process and its role is to clean up the EMG and improve the signal to noise ratio. Filters, in turn, are applied to remove background electrical interference and allow signal amplification in the range of frequencies at which the facial muscles operate [49]. It is yet to be proved, however, whether these techniques are able to eliminate noise sufficiently when attached to a moving patient.

### **Conclusion**

A combination of 4 facial movements makes up the CEP. This combination appears unique to the experience of pain, differentiating it from other key facial expressions, although some overlap with emotions such as sorrow or anger may exist. As the FEP does not appear to be affected by factors such as participant age, gender, or the presence of dementia or sedation, the CEP may have universal application. Although the identification of the FEP is a sensitive marker for the presentation of pain, evidence of a correlation between FEP intensity and reported pain intensity is currently limited.

This review has focused on novel systems of measuring facial expressions as an example of objectively assessing pain, namely the FACS system. While novel, this elaborate system requires prolonged specialist training to become proficient in its use prior to being able to confidently identify and code facial movements.

Although it is an improvement upon simple observation of facial expressions, it can be open to interpretation error. Furthermore, it is limited somewhat by only being able to score facial movements that are clearly visible and attempting to grade the intensity of the AU by sight alone adds further to the subjectivity of the measure.

Despite its drawbacks, automated recognition of FEP has been used in investigative research. The underlying principle is to replace a human facial action coder with a computer-based system, relying on the automatic recognition of facial movements that are interpreted from optimally processed images. This should minimise interpretation error, which in turn improves data quality. Unfortunately, before computer-based FEP recognition can be reliably introduced into the clinical setting, its limitations need to be overcome. It is intolerant to participant movement and the systems were trained on human-coded databases, which are inherently limited. Like the operator-based systems, computer-based systems can only measure visible movements and the ability to measure pain intensity is weak. The accuracy of these systems further decreases if other expressions of emotion and speech are introduced [51]. It is likely that computer systems for image analysis could eventually be developed to overcome patient movement. However, its underlying principle for measuring the FEP and correlating it to pain intensity could remain fundamentally flawed, limiting it to provide a binary measure only i.e. pain or no-pain state.

Theoretically, fEMG reveals several advantages as a method for detecting FEP in the clinical setting over computer image analysis: it is a purely objective measure of facial activity; it is able to detect changes in muscle tone as well as gross facial movements; it is not reliant on a correct orientation between participant and camera to work. However, due to the paucity of work on fEMG in the clinical setting to detect FEP, these advantages have not yet been demonstrated. Facial EMG may be subject to similar issues of movement intolerance, limited ability to measure pain intensity and performance degradation associated with speech movements or other non-pain expressions. In addition, anatomical variations both in the size of faces and in the precise location of the muscles are further issues that would need to be tackled. Novel machine learning algorithms and multi-sensor arrays have improved the spatial resolution of fEMG, which partially address these technical issues [52].

### **Future Perspective**

Technology continues to improve and evolve. If future research were to demonstrate its ability to accurately measure pain intensity, its application would be wide-ranging. First, it would allow improvements in pain measurement and treatment in non-communicative patients. This could extend from infants and adults with cognitive impairment to patients in the post-operative period and those on intensive care who are sedated.

Secondly, it could be incorporated into perioperative closed-loop delivery systems, such as those delivering anaesthesia. The last decade has seen increasing interest in this area with the aim to automate administration of anaesthesia, titrating it against the recorded depth of anaesthesia, thus freeing the anaesthetist to concentrate on the management of perioperative physiology

[as exemplified by 53]. Depth of anaesthesia measurement uses bispectral index (BIS), whereas intra-operative pain measurement, currently relies on haemodynamic information as an indirect measure of pain [54]. This method is obviously limited by the effect of pharmacological or surgical interventions on the cardiovascular parameters. A method, which could detect pain intensity, albeit in a non-paralysed patient, through facial muscle tone, could significantly improve closed-loop anaesthesia delivery systems.

Advances in sensor technologies such as capacitive sensing, signal processing and miniaturisation are enabling novel applications in research, healthcare and beyond [55]. In particular, there is great potential for wearable sensing systems to enable multimodal data acquisition allowing behavioural and physiological signals to be fused. Furthermore, advances in machine learning algorithms have enabled much more accurate detection of facial expressions and novel technologies are currently being developed with the aim of measuring facial muscle activity through sensors embedded into wearable devices [56].

In summary, the technology for objective pain measurement is currently far from ready for use in the clinical setting. However, the potential benefits to patients in improved pain management, combined with the advances being made in sensor technology and artificial intelligence, make this field a rich area for continued research and technical innovation.

## References

1. Tracey I, Mantyh PW. The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*. 55(3), 377–391 (2007).
2. Prkachin KM. Facial pain expression. *Pain Manag*. 1(4), 367–76 (2011).
3. Hadjistavropoulos T, Herr K, Prkachin KM *et al*. Pain assessment in elderly adults with dementia. *Lancet Neurol*. 13(12), 1216–1227 (2014).
4. Kaseweter KA, Drwecki BB, Prkachin KM. Racial differences in pain treatment and empathy in a Canadian sample. *Pain Res. Manag*. 17(6), 381–384 (2012).
5. De Ruddere L, Goubert L, Prkachin KM, Louis Stevens MA, Van Ryckeghem DML, Crombez G. When you dislike patients, pain is taken less seriously. *Pain* 152(10), 2342–2347 (2011).
6. Kappesser J, Williams AC, Prkachin KM. Testing two accounts of pain underestimation. *Pain* 124(1–2), 109–116 (2006).
7. Schultz A, Murphy E, Morton J, Stempel A, Messenger-Rioux C, Bennett K. Preverbal, Early Verbal Pediatric Pain Scale (PEPPS): development and early psychometric testing. *J. Pediatr. Nurs*. 14(1), 19–27 (1999).
8. Hølen JC, Saltvedt I, Fayers PM, Hjermstad MJ, Loge JH, Kaasa S. Doloplus-2, a valid tool for behavioural pain assessment? *BMC Geriatr*. 7, 29 (2007).

9. Abbey J, Piller N, De Bellis A *et al.* The Abbey pain scale: a 1-minute numerical indicator for people with end-stage dementia. *Int. J. Palliat. Nurs.* 10(1), 6–13 (2004).
10. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. *Am. J. Crit Care* 15(4), 420–427 (2006).
11. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A. Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. *Paediatr. Anaesth.* 17(8), 720–733 (2007).
12. Sheu E, Versloot J, Nader R, Kerr D, Craig KD. Pain in the elderly: validity of facial expression components of observational measures. *Clin. J. Pain* 27(7), 593–601 (2011).
13. Schiavenato M. Facial expression and pain assessment in the pediatric patient: The primal face of pain. *J. Spec. Pediatr. Nurs.* 13(2), 89–97 (2008).
14. Schiavenato M, Byers JF, Scovanner P *et al.* Neonatal pain facial expression: Evaluating the primal face of pain. *Pain* 138(2), 460–471 (2008).
15. Chang J, Versloot J, Fashler SR, McCrystal KN, Craig KD. Pain Assessment in Children: Validity of Facial Expression Items in Observational Pain Scales. *Clin. J. Pain* 31(3), 189–197 (2014).
16. Bartlett MS, Hager JC, Ekman P, Sejnowski TJ. Measuring facial expressions by computer image analysis. *Psychophysiology* 36(2), 253–263 (1999).
17. Pantic M, Rothkrantz LJM. Machine understanding of facial expression of pain. *Behav. Brain. Sci.* 25(4), 1–3 (2002).
18. Fasel B, Luetin J. Automatic facial expression analysis: A survey. *Pattern Recognit.* 36(1), 259–275 (2003).
19. \* Brahnam S, Chuang CF, Shih FY, Slack MR. Machine recognition and representation of neonatal facial displays of acute pain. *Artif. Intell. Med.* 36(3), 211–222 (2006).  
\* *In this study computer-based FEP recognition technology is used in the clinical setting demonstrating its practical use.*
20. Ashraf AB, Lucey S, Cohn JF *et al.* The painful face - Pain expression recognition using active appearance models. *Image Vis. Comput.* 27(12), 1788–1796 (2009).
21. \* Sikka K, Ahmed AA, Diaz D *et al.* Automated Assessment of Children's Postoperative Pain Using Computer Vision. *Pediatrics* 136(1), 1–8 (2015).  
\* *In this study machine learning-based FEP recognition technology is used in the clinical setting demonstrating its practical use.*
22. Pantic M, Patras I. Dynamics of facial expression: Recognition of facial actions and their temporal segments from face profile image sequences. *IEEE Trans. Syst. Man, Cybern. Part B Cybern.* 36(2), 433–449 (2006).

23. Littlewort G, Whitehill J, Wu T *et al.* The computer expression recognition toolbox (CERT). In: *2011 IEEE International Conference on Automatic Face and Gesture Recognition and Workshops, FG 2011*. 298–305 (2011).
24. Kaltwang S, Rudovic O, Pantic M. Continuous pain intensity estimation from facial expressions. In: *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 368–377 (2012).
25. \* Wolf K, Raedler T, Henke K *et al.* The face of pain - A pilot study to validate the measurement of facial pain expression with an improved electromyogram method. *Pain Res. Manag.* 10(1), 15–19 (2005).  
\* *This is the only study describing the use of fEMG in measuring the pre-visible muscle activity associated with the facial expression of pain.*
26. \* Ekman P, Friesen W V. Facial Action Coding System: A Technique for the Measurement of Facial Movement. *Environ psych and nonverb behavior.* 1(1), 56–75 (1976).  
\* *This article reports the first description of the Facial Action Coding System (FACS) that forms the basis of our understanding of the muscular basis of facial expressions.*
27. Craig KD, Patrick CJ. Facial Expression During Induced Pain. *J. Pers. Soc. Psychol.* 48(4), 1080–1091 (1985).
28. Peters JWB, Koot HM, Grunau RE *et al.* Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. *Clin. J. Pain* 19(6), 353–363 (2003).
29. Grunau RVE, Craig KD. Pain expression in neonates: facial action and cry. *Pain* 28(3), 395–410 (1987).
30. Prkachin KM, Mercer SR. Pain expression in patients with shoulder pathology: validity, properties and relationship to sickness impact. *Pain* 39(3), 257–265 (1989).
31. Prkachin KM. The consistency of facial expressions of pain: a comparison across modalities. *Pain* 51(3), 297–306 (1992).
32. Prkachin KM, Solomon PE. The structure, reliability and validity of pain expression: Evidence from patients with shoulder pain. *Pain* 139(2), 267–274 (2008).
33. Kunz M, Mylius V, Schepelmann K, Lautenbacher S. Impact of age on the facial expression of pain. *J. Psychosom. Res.* 64(3), 311–318 (2008).
34. Kunz M, Scharmann S, Hemmeter U, Schepelmann K, Lautenbacher S. The facial expression of pain in patients with dementia. *Pain* 133(1–3), 221–228 (2007).
35. Rahu MA, Grap MJ, Cohn JF, Munro CL, Lyon DE, Sessler CN. Facial expression as an indicator of pain in critically ill intubated adults during endotracheal suctioning. *Am. J. Crit. Care* 22(5), 412–422 (2013).
36. Kohler CG, Turner T, Stolar NM *et al.* Differences in facial expressions of four universal emotions. *Psychiatry Res.* 128(3), 235–244 (2004).

37. Kunz M, Mylius V, Schepelmann K, Lautenbacher S. On the relationship between self-report and facial expression of pain. *J. Pain* 5(7), 368–376 (2004).
38. LeResche L, Dworkin SF, Wilson L, Ehrlich KJ. Effect of temporomandibular disorder pain duration on facial expressions and verbal report of pain. *Pain* 51(3), 289–295 (1992).
39. Hsu K-T, Shuman SK, Hamamoto DT, Hodges JS, Feldt KS. The application of facial expressions to the assessment of orofacial pain in cognitively impaired older adults. *J. Am. Dent. Assoc.* 138(7), 963–969 (2007).
40. Kunz M, Gruber A, Lautenbacher S. Sex Differences in Facial Encoding of Pain. *J. Pain* 7(12), 915–928 (2006).
41. Jiang B, Valstar M, Martinez B, Pantic M. A dynamic appearance descriptor approach to facial actions temporal modeling. *IEEE Trans. Cybern.* 44(2), 161–174 (2014).
42. Bartlett MS, Littlewort G, Lainscsek C, Fasel I, Movellan J. Machine learning methods for fully automatic recognition of facial expressions and facial actions. *2004 IEEE Int. Conf. Syst. Man. Cybern.* 1, 592–597 (2004).
43. Bartlett MS, Littlewort G, Frank M, Lainscsek C, Fasel I, Movellan J. Fully automatic facial action recognition in spontaneous behavior. In: *FGR 2006: Proceedings of the 7th International Conference on Automatic Face and Gesture Recognition*, 223–230 (2006).
44. Cohn JF, Zlochower AJ, Lien J, Kanade T. Automated Face Analysis by Feature Point Tracking Has High Concurrent Validity With Manual FACS Coding. In: *What the Face Reveals: Basic and Applied Studies of Spontaneous Expression Using the Facial Action Coding System (FACS)*. (2012).
45. Pantic M, Patras I. Detecting facial actions and their temporal segments in nearly frontal-view face image sequences. *2005 IEEE Int. Conf. Syst. Man. Cybern.* 4, 3358–3363 (2005).
46. \* Heiderich TM, Leslie AT, Guinsburg R. Neonatal procedural pain can be assessed by computer software that has good sensitivity and specificity to detect facial movements. *Acta. Paediatr.* 104(2), e63–e69 (2015).  
\* In this paper facial point tracking computer-based FEP recognition technology is used in the clinical setting demonstrating its practical use.
47. Dimberg U. Facial electromyography and emotional reactions. *Psychophysiology* 27(5), 481–494 (1990).
48. Wolf K, Mass R, Ingenbleek T, Kiefer F, Naber D, Wiedemann K. The facial pattern of disgust, appetite, excited joy and relaxed joy: An improved facial EMG study. *Scand. J. Psychol.* 46(5), 403–409 (2005).
49. Huang CN, Chen CH, Chung HY. The review of applications and measurements in facial electromyography. *J. Med. Biol. Eng.* 25(1), 15–20 (2005).
50. De Luca CJ. The use of surface electromyography in biomechanics. *Journal of Applied Biomechanics* 13(2), 135–163 (1997).

51. Aung MSH, Kaltwang S, Romera-Paredes B *et al.* The Automatic Detection of Chronic Pain-Related Expression: Requirements, Challenges and the Multimodal EmoPain Dataset. *IEEE Trans. Affect. Comput.* 7(4), 435–451 (2016).
52. Hamedi M, Salleh SH, Ting C, Astaraki M, Noor A. Robust Facial Expression Recognition for MuCI: A Comprehensive Neuromuscular Signal Analysis. *IEEE Trans. Affect. Comput.* 1-1. (2016).
53. Pasin L, Nardelli P, Pintaudi M, *et al.* Closed-loop delivery systems versus manually controlled administration of total IV Anesthesia: A meta-analysis of randomized clinical trials. *Anesth Analg.* 124(2), 456–464 (2017).
54. Hemmerling TM, Arbeid E, Wehbe M *et al.* Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: A randomized controlled trial. *Br. J. Anaesth.* 110(6), 1031–1039 (2013)
55. Fatoorechi M, Parkinson J, Prance RJ, Prance H, Seth AK, Schwartzman DJ. A comparative study of electrical potential sensors and Ag/AgCl electrodes for characterising spontaneous and event related electroencephalogram signals. *J. Neurosci. Methods* 251, 7–16 (2015).
56. McGhee JT, Hamedi M, Fatoorechi M *et al.* Towards a novel biometric facial input for emotion recognition and assistive technology for virtual reality. Presented at: *11th International Conference on Disability, Virtual Reality and Associated Technologies*. Los Angeles, California, USA. 20-22 September 2016.