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Facial muscle movements encoding pain – a systematic review

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Abstract

Facial expressions of pain are not undefined grimaces but they convey specific information about the internal state of the individual in pain. With this systematic review we aim to answer the question of which facial movements are displayed most consistently during pain. We searched for studies that used the Facial Action Coding System (FACS) to analyze facial activity during pain in adults, and that report on distinct facial responses (Action Units, AUs). Twenty-seven studies using experimental pain and 10 clinical pain studies were included. We synthesized the data by taking into consideration (i) criteria used to define whether an AU is pain-related; (ii) types of pain; and (iii) the cognitive status of the individuals. When AUs were selected as being pain-related based on a "pain>baseline" increase, a consistent subset of pain-related AUs emerged across studies: lowering the brows (AU4), cheek raise/lid tightening (AUs6_7), nose wrinkling/raising the upper lip (AUs9_10) and opening of the mouth (AUs25_26_27). This subset was found independently of the cognitive status of the individuals and was stable across clinical and experimental pain with only one variation, namely that eye closure (AU43) occurred more frequently during clinical pain. This subset of pain-related facial responses seems to encode the essential information about pain available in the face. However, given that these pain-related AUs are most often not displayed all at once, but are differently combined, healthcare-professionals should use a more individualized approach, determining which pain-related facial responses an individual combines and aggregates to express pain, instead of erroneously searching for an uniform expression of pain.

Keywords: facial expression of pain; facial pain responses; Facial Action Coding System; FACS; nonverbal communication

1. Introduction

The facial expression of pain has attracted considerable interest in experimental and clinical research based on an increasing awareness that it supports the communication of pain as a second signal system besides the verbal one [4,11] and thus can be used as another indicator of pain when self-report is missing (e.g. in patients with dementia [40]). Right from the start of research on facial expressions of pain, researchers tried to characterize how facial activity during the experience of pain looks like. The vision was to define a prototypical facial expression of pain, similarly to prototypical facial expressions having been suggested for different emotional states [6]. Groundbreaking research was conducted by Prkachin [51], who analyzed in a sample of 41 healthy students, which facial responses are displayed consistently across different types of experimental pain stimulation (pressure, temperature, electrical current and ischemia). Facial responses were analyzed using the Facial Action Coding System (FACS [8]), the gold-standard for facial expression research. The FACS is a fine-grained, objective and anatomically-based coding system that differentiates between 44 facial movements (Action Units). Coders are trained to apply specific operational criteria to determine the on- and offset as well as the intensity of the AUs. Using the FACS, Prkachin [51] suggested that there are four facial movements that are more steadily displayed across experimental pain modalities than other AUs, namely lowering the brows (AU4), cheek raise/lid tightening (AUs6_7), nose wrinkling/raising the upper lip (AUs9_10) and eye closure longer than 0.5 s (AU43). Prkachin and Salomon [52] further suggested that this set of facial movements is not only indicative for experimental pain but also for clinical pain. When studying facial responses in a group of 129 shoulder pain patients undergoing a range of painful movement exercises, the authors found that the same set of facial movements was displayed as has been previously found for experimental pain [51]. Mainly based on these two

studies, this subset is regarded as presenting the key components of the facial expression of pain [9,28,50].

Meanwhile, a substantial number of further studies have been conducted, investigating facial expressions of pain in various groups of individuals (e.g. young, old [31], patients with depression [41], individuals with intellectual disabilities [38]) and during various types of pain conditions (low back pain [17], chest pain [5], experimental pain [19]). At least parts of the above-described set of facial responses [51] have also been found to be associated with pain in these further studies. Nevertheless, there is also considerable variability between studies; with other facial movements also having been found to be pain-related. For example, "raising the chin" (AU17) [53] or even "oblique lip raising" (AU12, smiling) [34,35] have been recurrently found to occur while individuals are experiencing pain. Indeed, some studies even include up to 17 AUs as a set of pain-associated AUs [13]. One reason for the variability between studies is the difference in how studies defined whether an AU is pain-related. Overall, there are two main approaches. Approach one is to define an AU as pain-related when it occurs during pain above a critical frequency level (*"frequency of occurrence" criterion*) which is often set to 5% (e.g. [16]). Approach two is to define an AU as pain-related when it occurs (statistically) more frequently during pain compared to a non-painful baseline condition or more frequently in pain patients compared to pain-free controls (*"pain>baseline" criterion*) (e.g. [51]). Often, approach two is not conducted on all possible 44 AUs of the FACS system, but instead, authors use approach two consecutively after having used approach one to pre-select AUs that fulfil the *"frequency of occurrence"* criterion and then in a second step the *"pain>baseline"* criterion is used to define which of these pre-selected AUs are really pain-related (e.g. [20]).

The aim of this systematic review article is to examine the question of which facial movements are indeed pain-related by making use of the substantial number of primary studies that have analyzed facial responses during pain. Although it has been assumed that the above described subset [51] does include the most relevant pain-related facial movements, the meanwhile substantial empirical evidence being available has not yet been systematically used to scrutinize this assumption. We do so and take into consideration (i) the different criteria used to define whether an AU is pain-related. Moreover, given repeated doubts about the comparability of facial responses to clinical and experimental pain, we also consider (ii) different types of pain (clinical vs. experimental pain). Furthermore, given the increasing awareness of how important facial expressions are for pain assessment in individuals with cognitive impairments (e.g. dementia [40]), we also consider (iii) the cognitive status of the individuals being examined. Given that FACS is the most often used and best operationalized method to analyze facial expressions of pain, we limited our review to those studies using FACS, although other methods can also be utilized to assess facial communication of pain (e.g. not FACS-based automatic systems, observational pain scales).

2. Methods

The systematic review was performed following the "Preferred reporting items for systematic review and meta-analysis protocols" (PRISMA-P [46]).

2.1. Search strategy and study selection

Literature Search: An extensive search of literature published until April 2018 was conducted using the databases PubMed and PsycINFO. We set no restrictions with regard to the earliest year of publication. In our search, we combined with a logical AND keywords for pain (pain, nociception; with a logical OR) with keywords for facial expression (facial expression, facial

display, facial activity, facial expressiveness, facial response, FACS; connected with a logical OR)[1]. Given that we were interested in facial activity during pain in human adults, we excluded the following keywords by setting a NOT qualification: child, neonat*, animal. Additionally, reference lists from identified articles as well as reviews [59] and book chapters on facial expression of pain [4,23] were screened for missing articles. The systematic search was limited to articles published in English or German.

Eligibility criteria: We selected only those studies (i) that analysed facial responses using the Facial Action Coding System, (ii) that provide results on single Action Units, (iii) that include a minimum sample size of N=20, and (iv) that provided a clear description of statistics. We excluded non-original research, conference proceedings and doctoral theses. Two independent reviewers (the authors DM and MK) screened the titles and abstracts for the eligibility criteria. We retrieved full texts of all studies that were potentially relevant or could not be excluded based on the study title or abstract. In case of discrepancies/disagreement between the 2 reviewers, a third reviewer (author SL) was consulted and discrepancies/disagreements were resolved. The study selection process is displayed in Figure 1.

2.2. Information extraction

From each included study we extracted the following information:

- sample: patients or healthy participants, number of participants, age, sex, cognitive status
- type of pain: experimental pain (pressure, thermal, electrical, other[2]), clinical pain
- FACS coding: duration of sampling, how many and which AUs were FACS coded, AU information being coded (intensity, frequency, duration, apex)

[1] Precise search terms and combinations are available from the authors upon request.
[2] Procedures like "blood sampling" or "injections" were added to the experimental category, given that the short invasive procedure shares more similarities to experimental pain induction than to clinical pain states

- approach used to determine pain-related AUs: selecting AUs as being pain-related based on a "frequency of occurrence" criterion or on a "pain>baseline" criterion (see the Introduction section for further explanation).

The information was extracted by one reviewer (author DM) and documented in a data extraction form. All the extracted data were independently counter-checked by a second reviewer (author MK). In order to control for bias caused by the inclusion of multiple reports of the same study, authors were contacted in cases where an overlap of the sample was suspected and the duplicate sample was excluded (e.g. a healthy control sample [29] was greatly overlapping with the sample of another publication [31] and was, thus only included once). All ambiguities in data extraction (6% reviewer discrepancies) were double-checked and resolved.

2.3. Assessing the quality of studies

To assess the quality of the studies and the risk of bias, we graded the studies based on the following criteria (adopted from the Newcastle Ottowa criteria [58]), which were (i) reported gender distribution and age of the participants, (ii) specification of the type of pain and in case of experimental pain on the pain induction procedure, (iii) specification of the video recording (position of the camera, instruction for head positions), (iv) FACS coding (duration of video samples, software used, type of Action Units being coded), (v) reliability of FACS coding and (vi) the extent to which the study sample represents the true population under investigation (e.g. with regard to gender, education, severity and duration of chronic pain). Each criterion was judged as either "successfully fulfilled" (1), "partially fulfilled (0.5) or "not fulfilled" (0). The total possible quality score was 6.0.

2.4. Analyses

Our main aim is to find out which AUs prove to be pain-related across studies. Given that studies differ with regard to how they defined whether an AU is pain-related, we separately report findings for (i) *"frequency of occurrence" criterion* (% occurrence during pain has to surpass a certain threshold (often 5%)) and for (ii) the stricter criterion, "*pain > baseline*" or "*pain patients > pain-free controls*" comparisons (based on significant p-values or moderate effect sizes), respectively. Moreover, given the possibility that facial responses to pain might be affected by the "type of pain" being induced/experienced or by the "cognitive status" of the person, we compiled the AU findings separately for these 2 domains. In some studies more than one sample was investigated (e.g. patients with dementia and healthy controls [1]). In these cases, AU outcomes are reported separately for each sample (see Tables 1-3). Likewise, if studies used different types of experimental pain (e.g. pressure and heat pain [20]), the outcomes are also reported separately for each type of pain (see Tables 1-3).

AU findings are presented as descriptive frequency statistics.

3. Results

3.1. Characteristics of included studies

The initial literature search identified 2304 studies with 4 additional studies found through manual searching of reference lists. The study selection process is displayed in Figure 1. After excluding duplicates and screening the remaining abstracts and titles, 97 studies remained. After reviewing the full texts of these remaining articles, 60 articles were excluded. The reasons for exclusion are listed in Figure 1. Altogether 37 articles were retained for analyses, with 27 studies assessing facial responses during experimental pain (see Table 1) and 10 studies assessing facial responses during clinical pain (see Table 2). Most of the included studies (78%) reached a high quality score (≥ 5.0 out of 6.0) and the remaining studies (22%)

showed a good quality score (4.0 - <5 out of 6.0). Thus, we are confident that the reported outcomes are not biased by a lack of quality of the included studies.

Sample characteristics: Altogether, facial responses during pain were investigated in 2237 individuals. Most often experimental pain models were used to study facial responses. Indeed, facial responses during *experimental pain* were assessed in 1578 individuals (847 females, 668 males (for 63 participants gender information was missing)). Facial responses during *clinical pain* were assessed in 659 individuals (366 females, 293 males). Amongst the experimental pain models, thermal heat pain was used most often to elicit facial responses, followed by pressure pain (see Table 1). The gender distribution across studies was quite balanced; with a slight tilt towards more female participants (56% of the participants were female).

FACS coding: With regard to the FACS coding, most studies coded the whole set of 44 Action Units (84%), with only a few studies limiting the FACS coding to a set of Action Units that has previously been found to be associated with pain (e.g. two studies [9,28] only coded those AUs reported to be pain-related by Prkachin [51]). Moreover, in most studies AU frequency (87%) and AU intensity (93%) were coded, whereas only 25% of the studies coded AU duration. Interestingly, coding of AU duration was more common in clinical pain studies (50% of clinical pain studies coded the duration of an AU) and in experimental studies that used somewhat longer stimulation times (>5 seconds). Thus, the duration of an AU was supposed to hold more meaningful information when the painful stimulus or the pain experience is not limited to a few seconds. For analyses purpose, most studies combined those AUs that represent very similar facial movements into one aggregate AU, namely AU1 & AU2 were combined into AU1_2, AU6 & AU7 into AU6_7, AU9 & AU10 into AU9_10 and AU25 & AU26 & AU27 into AU25_26_27.

Definition of pain-related AUs: As mentioned above, the studies differ in their approach of how to define whether an AU is pain-related or not. Overall, five studies based their selection of pain-related AUs solely on their "frequency of occurrence" (see column "% occurrence" in Table 1 and Table 2). As soon as an AU was displayed in more than 5% (sometimes 1%) of the painful segments (or of the participants), it was classified as pain-related. The majority of studies (N=32) chose the more stricter criterion, namely that an AU had to be displayed more frequently during pain compared to a baseline condition or more frequently in pain patients compared to healthy controls, respectively, to be chosen as pain-related (see column "pain>baseline/ pain patients>controls" in Table 1 and Table 2). To determine the fulfilment of this criterion, T-Tests (p-values) or effect sizes (Cohen´s d) were computed and presented comparing AU occurrences between pain vs. baseline or pain patients vs. healthy controls, respectively. Interestingly, 23 out of these 32 studies used the stricter "pain>baseline/ pain patients>controls" criterion as a second step, after pre-selecting AUs which fulfilled the "frequency of occurrence" criterion in a first step and then computing which of these pre-selected AUs are really pain-related based on the stricter "pain>baseline/ pain patients>controls" criterion.

3.2. Pain-related facial responses

To give a better overview on which AUs are found to be pain-related across studies, we calculated separately for each AU in how many studies the given AU met the "frequency of occurrence" criterion as well as the "pain>baseline"/"pain patients>pain-free controls" criterion. These data are presented in Table 3. Out of the existing 44 AUs from the FACS system, we only included those AUs in Table 3 that fulfilled either the "frequency of occurrence" criterion or the "pain>baseline"/"pain patients >pain-free controls" criterion in at least one of the studies

3.2.1 Pain-related AUs: "frequency of occurrence" criterion

As can be seen in Tables 1 and 2 (column "% of occurrence") as well as in Table 3a, selecting AUs as pain-related based on their "frequency of occurrence" results in a large number of AUs which meet this criterion.

Overall: Across all samples and across all types of pain, there are 10 AUs which meet the "frequency of occurrence" criterion in at least 50% of the studies, namely AUs 1_2, 4, 6_7, 9_10, 12, 14, 17, 25_26_27, 43, 45 (see Table 3a, left column).

Clinical pain: When looking at the outcomes separately for clinical pain, the "frequency of occurrence" criterion was applied to select pain-related AUs in only four studies. Across these studies, the list of AUs meeting the "frequency of occurrence" criterion is quite extensive and includes 12 AUs (see Table 3a).

Experimental pain: When looking at the outcomes for experimental pain paradigms, the "frequency of occurrence" criterion was applied in 35 samples/paradigms. When comparing the overall experimental pain outcomes to the outcomes found for the different types of experimental pain, it becomes apparent that there are no systematic variations. Similar lists of AUs meet the "frequency of occurrence" criterion across experimental heat, pressure and electrical pain induction. The only difference seems to be that some of the lower face movements (AU12 (lip corner pull), AU14 (dimple) and AU17 (chin raise)) are observed in fewer studies using pressure stimulation compared to those using heat or electrical stimulation.

Clinical vs. experimental pain: There is a great overlap in AUs which meet the "frequency of occurrence" criterion in at least 50% of the studies using clinical pain and those using experimental pain (see Table 3a). The greatest differences are that more lip movements (AU18 (lip pucker), AU20 (lip stretch), AU24 (lip press)) are observed in clinical pain

conditions compared to experimental pain, and that closing of the eyes for longer than half a second (AU 43) seems more prevalent in clinical pain conditions.

Cognitive status of the individual: Comparing the AUs outcomes between individuals with and without cognitive impairments, it becomes apparent that the AU percentage numbers tend to be lower for individuals with cognitive impairments (see Table 3a, right column). Only six AUs meet the "frequency of occurrence" criterion in at least 50% of the studies that included individuals with cognitive impairment (compared to ten AUs in individuals without cognitive impairments).

3.2.2 Pain-related AUs: "pain > baseline" respectively "pain patients >pain-free controls" criterion

As can be seen in Tables 3b, there are far fewer AUs that meet this stricter criterion compared to the "frequency of occurrence" criterion.

Overall: Across all samples and across all types of pain, there were only four AUs which meet the "pain > baseline" criterion in at least 50% of studies/samples, namely AUs 4, 6_7, 9_10 and 25_26_27 (see Table 3b, left column).

Clinical pain: When looking at the outcomes separately for clinical pain, the list of AUs which meet the "pain > baseline" criterion or the "pain patients > pain-free controls" criterion, respectively is very comparable to the overall results, with the addition of one AU, namely closing of the eyes for longer than half a second (AU43).

Experimental pain: The findings for experimental pain are also very comparable to the overall results. Moreover, the same AUs meet the "pain > baseline" criterion when applying heat and pressure pain stimulation. Only the findings for electrical pain seem to differ, with more studies finding blinking (AU45) to be pain-related, which might be due to the sudden nature of this type of experimental pain stimulation eliciting startle responses. In the "others"

category (e.g. venepuncture, injection), only the brow lower movement (AU4) is consistently found to occur more often during pain compared to baseline.

Clinical vs. experimental pain: When comparing outcomes for clinical vs. experimental pain, there is only one difference, namely that closing of the eyes for longer than half a second (AU43) is found to be pain-related in 50% of the studies looking at clinical pain responses whereas only 22% of the studies using experimental pain find this facial movement to occur more frequently during pain compared to baseline.

Cognitive status of the individual: As can be seen in Table 3b (right column), the same AUs meet the „pain > baseline" criterion in more than half of the studies investigating facial responses during pain in individuals with as well as without cognitive impairments.

3.3. Summary

The stricter criterion "pain > baseline" resulted not only in smaller numbers of AUs to meet this criterion, compared to the "frequency of occurrence" criterion, but also in much more consistent results. The same set of AUs proved to be pain-related in at least 50% of the studies, regardless of observing facial responses during clinical or experimental pain and regardless of the cognitive status of the individual being observed. This subset is illustrated in Figure 2 and is composed of lowering the brows (AU4), cheek raise and lid tightening (AUs6_7), nose wrinkling and raising the upper lip (AUs9_10) and opening of the mouth (AUs25_26_27). There is only one substantial variation between clinical and experimental pain conditions, namely that half of the studies looking at clinical pain conditions found that individuals also show an increase in closing their eyes for longer than half a second (AU43, see Figure 2) when they are experiencing pain.

However, one has to keep in mind that this small subset of pain-related AUs (see Figure 2) does not occur consistently in all studies. As can be seen in Table 3b, not one single AU is found to be pain-related in all studies. Moreover, even if a study finds an AU to be pain-related on a group level, this does not mean that every individual displayed this AU more frequently during the experience of pain. Therefore, even if Figure 2 suggests that the combination of AUs is very stable and uniform, the actual combinations of pain-related AUs vary substantially between individuals and across episodes [24].

4. Discussion

The aim of this article was to examine the question of which facial movements are indeed indicative of pain by conducting a systematic review of the available empirical evidence. Thirty-seven studies, investigating facial responses during pain by use of the Facial Action Coding System (FACS) and separately reporting findings on single Action Units (AUs), were included. The findings on pain-related AUs were synthesized across studies by taking into consideration (i) the different criteria used to define whether an AU is pain-related, (ii) the different types of pain (clinical vs. experimental pain) and (iii) the cognitive status of the individuals being examined.

The role of criterion used to define whether a facial response is pain-related

Across the studies on facial responses during pain, there are two main approaches used when deciding which AUs to include as pain-related in the analyses. One approach is to include all AUs that were displayed above a critical frequency level during pain. Another, more stricter approach is to classify only those AUs as pain-related that were displayed more frequently or more intensely during pain compared to a baseline condition or observed in pain patients compared to pain-free persons by using statistical threshold criteria (e.g. certain effect sizes),

which helps to define what "more" means. In the included studies, the baseline condition was most often a non-painful stimulation procedure (in case of experimental pain stimulation), a resting phase or a comparison with pain-free individuals (in case of clinical pain). Most often, authors combined these approaches, classifying AUs as pain-related if they fulfil the "frequency of occurrence" (step 1) and the "pain>baseline" (step 2) criteria.

As this review demonstrates, selecting AUs as pain-related only based on their "frequency of occurrence" results in a rather large, fuzzy subset of AUs that lacks consistency across studies, across types of pain and across individuals with and without cognitive impairments. In contrast, when using the stricter criterion and defining AUs as pain-related only if they increase in intensity or frequency during pain, a much smaller and quite stable subset of facial responses was found across studies. Most agreement overall could be found for brow lowering (AU4) and cheek raise & lid tightening (AUs6_7). These facial movements were found to increase during pain in around 80% of the reviewed studies. Similarly high agreement across studies was also found for nose wrinkling and raising the upper lip (AUs9_10), with more than 70% of all studies finding this facial movement to increase during pain. The agreement for the facial movement "opening of the mouth" (AUs25_26_27) was a bit lower, with approximately 60% of the studies finding this movement to increase during pain. To reverse perspective, even the most frequent facial signals of pain could not be found in all studies. Thus, there is commonality between studies but not to a perfect degree, which also excludes the notion of a strict uniformity of facial expressions.

Given that the stricter criterion (pain>baseline) resulted in a much smaller and much more consistent subset of facial responses, this strongly suggests to always include a baseline or control group condition when conducting research on facial responses to pain, especially in those studies that look for group specific patterns in facial expressions of pain (e.g. patients with migraine, patients with schizophrenia). Including a baseline or control group allows

defining which facial responses are pain-indicative for the given type of pain and for the given sample of individuals being studied.

Clinical vs. experimental pain

This review corroborates previous assumptions, namely that facial responses elicited by experimental pain stimulation are very comparable to facial responses displayed during clinical pain conditions [52]. Especially when applying the stricter criterion (pain>baseline) it becomes apparent, that the core subset of pain-related facial responses was similarly displayed both during experimental and clinical pain conditions. There was only one variation, namely with regard to closing of the eyes for longer than half a second (AU43) (see also Figure 2). Whereas half of clinical pain studies found this facial response to be pain-related, only 20% of the studies using experimental pain corroborated this. Thus, closing of the eyes for longer than half a second might be especially indicative for clinical pain, and, thus, for pain states that might be of longer duration and of greater severity than experimental pain. In line with this, closing of the eyes (AU43) is based on activity of the orbicularis oculi muscle, the same muscle that underlies the pain-related cheek raise & lid tightening (AU6_7) [8]. Whereas contraction of the orbital part of the muscle results in AU6_7 (narrowing of the eye aperture), activity of the palpebral part results in AU43 (complete closing the eyes). Thus, in the context of pain, AU43 might occur as an intensification of AU6_7, signalling more severe or prolonged levels of pain that are more likely in clinical pain than in experimental pain settings [50].

With regard to differences between different types of experimental pain, the most variance occurred for electrical stimulation. Here, blinking (AU45) was found to increase during pain in 75% of the studies. It seems likely that this is due to the sudden, startling nature of this type of pain stimulation, resulting in more startle responses (the blink component of the startle-

reflex [39]) compared to other types of pain. Thus, when being interested in relevant facial responses during clinically ongoing pain, choosing an experimental pain protocol that uses electrical pain induction methods seems less ideal (with the exception of cases with attack-like clinical pain).

The role of cognitive status

One major reason for the increased interest in facial responses during pain is the notion that facial responses could serve as a substitute to self-report in individuals who are not capable to provide pain self-report due to cognitive impairments [12,40]. However, in order to use facial responses to assess pain in individuals with cognitive impairments, one must first investigate whether the facial encoding of pain might be altered due to the cognitive impairment. For this review, we could include nine studies investigating facial responses in individuals with cognitive impairments. The cognitive impairment was mostly due to dementia-related cognitive decline in samples of older individuals [1,14,15,29,32,36,45]. Across all nine studies, the same subset of facial responses proved to be pain-related (pain>baseline) in the majority of studies as was found for cognitively unimpaired individuals. Thus, this review gives clear evidence that the type of facial responses being displayed during pain is unaffected by the cognitive status of the individual (see also Figure 2). This is in line with those studies which directly compared facial responses to pain between individuals with and without dementia [1,29,36]. In all three studies, the authors found that individuals with dementia display the same AUs in response to experimental pain stimulation as individuals without dementia do. Even those individuals with more advanced stages of dementia, who were not able to provide a self-report of pain, displayed the same subset of pain-related facial responses [36]. The only difference found between groups was that individuals with dementia displayed

this subset of pain-related facial responses more intensely or more vigorously compared to individuals without dementia [1,29,36].

Comparing the findings to the "prototypical facial expression of pain"

As stated in the introduction, Prkachin and colleagues could show in two studies that there is a core subset of pain-related facial responses, which occurs across clinical and different types of experimental pain [51,52] and which has sometimes been referred to as the prototypical facial expression of pain [9,26,56]. Comparing this prototypical facial expression of pain to the subset of AUs that showed to be pain-related in at least half of the included studies of this review, it becomes apparent that the findings are very comparable. As demonstrated in Figure 2, three facial movements (brow lowering (AU4); cheek raise & lid tightening (AUs6_7); nose wrinkling and raising the upper lip (AUs9_10)) were found to be pain-related in the majority of the included studies. These three facial movements are identical to the core movements of the facial expression of pain as reported by Prkachin and colleagues [51,52]. However, there is also at least one crucial divergent finding. Whereas Prkachin and colleagues did not include the opening of the mouth (AUs25_26_27) in the subset of pain-related facial responses, our findings clearly suggest that this movement is one of the key facial movements because it was found to increase or become more frequent when individuals are experiencing pain. Both during experimental and clinical pain at least half of the studies found "mouth opening" to be pain related. Opening the mouth during pain could be a preparatory movement for pain vocalizations ("ouch", "ooh", "aah"). Based on this review, opening of the mouth should be included in the subset of pain-related facial responses. Another variation between the present review and Prkachins' findings is that one of the key movements of pain described by Prkachin and colleagues, namely closing of the eyes for longer than half a second (AU43), only proved to be pain-related in clinical pain conditions.

Variability despite a core subset

To avoid any erroneous ideas of a strong uniformity of facial expressions of pain, which might be suggested by postulating a core subset of facial responses to pain, the following arguments have to be considered. The facial responses of the core subset are more often displayed during pain than other facial responses and are more frequently displayed during pain compared to baseline conditions but they are far from being consistently displayed during each pain episode in each individual. Indeed, most often individuals do not show the whole subset of pain-related facial responses when experiencing pain but may only display a single facial movement or combine two or three of them [24]. One reason for this variability between individuals is due to people varying in their degree to which they facially express pain, with expressive vs. stoic variants. We learn to inhibit the facial display of negative affective states, including pain, following different social display rules [4], which in turn results into individually different learning histories. The degree to which we inhibit the facial expression of pain is – besides this learning history- also dependent on intra-individual factors (e.g. familiarity of social situations [19]) as well as on further inter-individual factors (e.g. general ability to inhibit automatic motor movements [18]); these factors can differentially affect the various facial muscles; with upper face muscles being more under automatic motor control compared to lower face muscles [54].

This intra- and inter-individual variability of facial expressions of pain does not contradict the assumption of a core subset of facial responses during pain given that this core subset provides a limited number of facial signals characteristic of pain, which can be individually and situationally combined and aggregated.

What does the recognition of variability mean for clinical practice, when relying on facial expression to assess pain in non-verbal individuals (e.g. individuals with dementia)? It is crucial that healthcare professionals become aware that facial expressions of pain vary between individuals and situations. Thus, when choosing an observational pain scale to assess pain in non-verbal individuals, which is clinically the necessary alternative to the time-consuming manual application of FACS, one should choose a scale that does not only include the general description of a prototypical facial expression of pain but instead include separate specific facial items that cover the facial signals characteristic of pain (e.g. PACSLAC [8], PAIC-15 [42]).

Moreover, given that these facial signals are not truly specific to pain states, but also occur in other emotional states, the risk of false positive pain judgements is quite high. Indeed none of the 4-5 pain-related facial movements is exclusively related to pain. The greatest overlap to other emotional states can be found with the facial expressions of disgust (sharing brow lowering (AU4), cheek raise & lid tightening (AUs6_7) and nose wrinkling & raising the upper lip (AUs9_10) [8, 33]) and anger (sharing nose brow lowering (AU4), cheek raise & lid tightening (AUs6_7) [8]. This overlapping facial phenomenology makes the consideration of the combination and aggregation of single facial signals necessary for successful distinction of emotional and pain states. Furthermore, the observations of facial expressions in clinical settings do not occur in isolation but are embedded in a context, which favors the assumption of certain emotional and pain states relative to others. In addition the facial expression is accompanied by other types of state-indicative behaviors (e.g. body posture, vocalizations), the consideration of which surely helps to improve the specificity of observations. The final perspective is the use of multi-sensor data recording with the facial responses being amongst the key variables as basis of automatic pain recognition, which can be individualized by machine learning algorithms [37,55].

Strengths and weaknesses

The review included studies with varying sample sizes, different sample characteristics, different intensities and different types of pain, different social settings, different stimulation protocols and different protocols for FACS coding. These variations have surely affected the outcomes (e.g. depending on the social setting, individuals tend to more or less inhibit their facial expression of pain [19,21]) and make it difficult to directly compare the studies. This high heterogeneity between studies at first glance was one of the main reasons why we decided to "only" conduct a systematic review instead of also performing a meta-analysis. In order to compile data into a meta-analysis the data have to fulfil stricter homogeneity requirements. Our aim was to give a first broad and comprehensive overview of the empirical evidence on facial responses during pain without being constrained to the methodological requirements of meta-analyses. The next step would be to perform a meta-analysis on a homogenous subgroup of the included studies. It is noteworthy, that despite the heterogeneity in methodology between studies, a quite stable subset of pain-related facial responses was found across studies.

However, the results are limited to the measurement of facial expressions by the Facial Action Coding System and it is not clear that other methods would produce the same results. Even though FACS is the gold-standard and the most widely used method in facial expression research, this method does have several limitations. Besides the enormous time effort it takes to train somebody in FACS coding (approximately 100 h), performing the FACS coding itself is also very time consuming, thus, limiting its usefulness for clinical practice. Moreover, although FACS coding is generally viewed as an objective description of facial activity (given its anatomical base) [8], it is based on human judgments and thus, has elements of subjectivity in it, despite of intra-rater reliability values being quite high (usually above 0.8). Furthermore, given that FACS coding is based on observable movements in the face, more subtle facial

activity remains unnoticed. The FACS coding is also limited in its possibility to capture the complex dynamics of temporal patterns in facial expressions. Some of these limitations can be overcome by alternative methods to analyse facial expressions of pain. Using surface electromyography (EMG), for example, allows to assess even very subtle changes in facial muscle activity. However, EMG performs poorly compared to FACS coding with regard to pinpointing the exact location of the facial muscle activity, given that it captures activity from neighbouring muscles [57]. More recent progress in computer vision technology has led to the development of automatic analyses of facial expressions, which are partially based on AU detection and partially use other forms of facial mapping. These approaches seem to promise an objective assessment of facial expressions of pain. However, they are more affected by illumination conditions, variation in head pose, errors in face mapping, wrinkles in the face, etc. compared to manual FACS coding [37]. Therefore, they cannot be used as valid alternatives (clinically or experimentally) for the time being but they hold great promise for the future, asking for further interdisciplinary cooperation between medicine, nurses, psychology, engineers and computer sciences. The present review may help to inform the necessary classification algorithms for pain recognition by providing knowledge about the critical elements of pain-relevant facial responses.

Conclusion

When reviewing the research on facial responses to pain (based on FACS coding), our semi-quantitative analyses revealed that there is a small subset of facial responses that is consistently found to be associated with pain. Corroborating previous findings, this subset is unaffected by the cognitive status of the individual and is very comparable between clinical and experimental pain states. However, despite this stable subset of pain-related facial responses, one has to keep in mind that this subset does not represent one uniform facial

expression of pain that can - at all time and in each individual - be observed in the presence of pain [24]. Instead this subset of pain-related facial responses seems to convey – as already stated by Prkachin [51] – "the bulk of information about pain that is available in facial expression" but not a uniform facial expression of pain. Thus, both for clinical and experimental pain assessment a more individualized approach should be preferred, which allows for determining the pain-related facial responses an individual combines and aggregates to express pain instead of erroneously searching for an uniform expression of pain in each sufferer's face.

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Figures

Figure 1: PRISMA flow chart

Figure 2: Pain-related facial responses
Illustration of those facial responses that proved to be pain-related based on the "pain>baseline" criterion in at least half of the included studies.

Tables

Table 1: Summary of studies included in the systematic review that investigated pain-related Action units (AUs) occurring during **clinical pain**

study	sample				pain	FACS coding			AU analyses		AUs found to be pain-related	
	patient group	N	age *in years*	sex *f/m*		duration	coded AUs	AU coding	baseline	defining pain-related AUs	% occurrence	pain>baseline or pain patients>controls
Craig et al. [3]	low back pain	120	42.7	60/60	motion exercise	8x 6s	44 AUs	fr /appex	resting	1% occurrence during pain & pain>baseline (p<0.005)	1,2,4,6,7,10,12,17,18,20,25,26,43,45	4,6,7,10,25,43
Dalton et al. [5]	chest pain	28	65.4	10/18	physical examination	6x 10s	44 AUs	fr /duration	none	prediction of true myocardial infarction		4,24,25
Hadjistavropoulos et al. [13]	post-surgical pain (knee replacement)	82	73.1	54/28	motion exercise	3x 1 min	44 AUs	fr /in / duration	less painful procedure	5% occurrence during pain & pain>baseline (p<0.05)	1,2,4,6,12,17,18, 20, 24,25,26,43,45	2,4,12,17,24,26,43
Hadjistavropoulos et al. [14]	elderly (cognitively impaired) patients undergoing physiotherapy	58	76.6	28/30	motion exercise	6x 1-2 min	17 AUs*	fr /in	less painful procedure	pain>baseline (p<0.05)		6_7
Hadjistavropoulos et al. [9]	cognitively healthy	52	75.5	36/16	physio-therapy examination	1x5min	6 AUs*	fr/in	resting	pain>baseline (p<0.05)		4,6_7,9_10
	dementia	48	82.5	33/15								4,6_7,9_10
Hill & Craig [17]	low back pain	40	32.6	17/23	motion exercise	2x 10s	44 AUs	fr /in / duration	resting	5% occurrence during pain & pain>baseline (p<0.05)	1_2,4,6_7,9_10,12, 14, 17,19,24,25/6/27,38, 42,43,44,45	4,9_10,25_26_27
LeResche & Dworkin [43]	temporomandibular disorder	28	30.0	28/0	clinical examination	8x 120	44 AUs	fr /in / duration	none	frequent occurrence during pain	4,6_7,9,10,20,25/26, 43/45	
Prkachin & Mercer [50]	shoulder pain	24	36.2	10/14	motion exercise	14x 5s	14 AUs*	fr /in	none	patients>controls (p<0.05)		4,6,7,26,41,43
Prkachin & Solomon	shoulder pain	129	42.2	66/63	motion exercise	32x >5s	11 AUs*	in	unaffected body side	affected>unaffected side (p<0.05)		4,6_7,9_10,12,20, 25_26_27,43

[52]												
Rahu et al. [53]	critically ill intubated patients	50	53.2	24/26	endo-tracheal suctioning	1x 30s	44 AUs	fr /in / duration	resting	pain>baseline ($p<0.05$)		1,2,4,6,7,9,17,25, 43,45

*the authors selected AUs based on previous publications that found a certain set of AUs to be pain-related
fr = coding AU frequency; in = coding AU intensity

Table 2: Summary of studies included in the systematic review that applied **experimental pain** to study pain-related Action Units (AUs)

study	**sample**				**pain**	**FACS coding**			**FACS analyses**		**AUs found to be pain-related**	
	group	**N**	**age *in years***	**Sex *f/m***	**Type and number of stimuli**	**duration**	**coded AUs**	**AU coding**	**baseline**	**Defining pain-related AUs**	**% occurrence**	**pain>baseline**
Beach et al. [1]	healthy	33	78.5	21/12	pressure 8x 5s	8x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.35)	1_2,4,6_7,9_10, 25_26_27,45	4, 6_7
	patients: dementia	35	74.4	25/10							1_2,4, 6_7,9_10, 25_26_27,45	4, 6_7,9_10, 25_26_27
Craig & Patrick [2]	healthy	72	18.7	72/0	temp. (cold pressor) max. 6min	5x 10s	44 AUs	fr /in / appex	non-painful stimulation	5% occurrence during pain & pain>baseline (p<0.05)		6_7, 10, 12, 25, 26/27, 43/45
Hadjistavropoulos et al. [10]	patients: frail elderly	26	78.2	14/12	injection	1x 10s	44 AUs	fr /in	no-stimulation	5% occurrence during pain	4,5,6,7,10,17,18, 20,27,43,44,45,50	
Hadjistavropoulos et al. [15]	patients: (cognitively impaired) elderly inpatients	59	73.0	29/30	blood sampling procedure	1x 5s	44 AUs	fr /in	no-stimulation	5% occurrence during pain & pain>baseline (p<0.05)	1,4,7,17,45	4,17
Hampton et al. [16]	healthy	142	20.8	96/46	temp. (heat) 10x 26s	10x 8s	41 AUs	fr /in	non-painful stimulation	5% occurrence during pain	1,2,4,6,7,9,10,12, 14,17,23,24,25, 26,43,45	
Karmann et al. [19]	healthy	126	39.9	63/63	temp. (heat) 10x 5s	10x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,12 , 14,17,18, 23, 25_26_27	4,6_7,9_10,18, 25_26_27
Karmann et al. [18]	healthy	49	22.2	24/25	temp. (heat) 10x 7s	10x 7s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,12 , 14,17,25_26_27	4,6_7,9_10
Karmann et al. [20]	healthy	35	25.6	20/15	temp. (heat) 3x >10s pressure 4x 5s	3x 12s 4x 7s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	temp.: 1_2,4,6_7, 9_10,12,14,17,24, 25_26_27,28,43 pressure: 1_2,4, 6_7,9_10,12,14, 25_26_27,43	temp.: 1_2,4,6_7, 9_10 pressure: 4,6_7, 9_10,25_26_27,4 3
Kunz et al. [30]	healthy	40	24.0	20/20	pressure 20x 5s electric. 10x 1ms	20x 5s 10x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (p<0.05)	pressure: 1_2,4, 6_7,9_10,12,17, 25_26_27,45 electrical: 1_2,4, 6_7,9_10,12,14,17	pressure: 4,6_7, 9_10,12 electrical: 1_2,6_7,9_10,12,

											,25_26_27,45	25_26_27,45
Kunz et al. [28]	healthy	40	24.8	20/20	temp. (heat) 3x 10min	3x 10min	6 AUs (Prkachin 1992)	in / duration	non-painful stimulation	pain>baseline (p <.05)		4,6_7
Kunz et al. [36]	patients: dementia	42	76.7	22/20	pressure 20x 5s	20x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,17, 25_26_27,45	1_2,4,6_7,9_10,17, 25_26_27
Kunz et al. [25]	healthy	44	21.8	22/22	temp. (heat) 8x 5s	8x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,12, 14,25_26_27,43,45	4,6_7,9_10,12, 25_26_27,43
Kunz et al. [31]	healthy	61	72.3	48/13	pressure 20x 5s electric. 10x 1ms	20 x 5s 10x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	pressure:1_2,4, 6_7,9_10,25_26_27,45 electrical: 1_2,4, 6_7,9_10,12,14,17 ,25_26_27,45	pressure: 4, 6_7,9_10 electrical: 6_7, 9_10,45
Kunz et al. [29]	patients: dementia	35	75.7	17/18	electric. 12x 1ms	12x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,17, 25_26_27,45	6_7,9_10,45
Kunz et al. [32]	patients: mild cognitive impairment	42	74.2	28/14	electric. 12x 1ms	12x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10,17, 25_26_27,45	6_7,9_10,45
Kunz et al. [26]	healthy	34	23.4	18/16	temp. (heat) 8x 5s	8x 7s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	4,6_7,9_10,14, 25_26_27,43,45	4,6_7,9_10,14, 25_26_27,43
Kunz et al. [27]	healthy	42	28.9	22/20	temp. (heat) 4x 6min	4x 6min	44 AUs	in / duration	none	1% duration during pain	1_2,4,6_7,12,14, 25_26_27,43	
	congenitally blind	21	31.5	11/10							1_2,4,6_7,12, 25_26_27,43	
Kunz et al. [33]	healthy	60	22.9	30/30	temp. (heat) 10x 5s	10x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10, 12,14,25_26_27	4,6_7,9_10, 25_26_27
Kunz et al. [22]	healthy	127	36.3	60/67	temp. (heat) 10x 5s	10x 5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10, 14,17,18,24, 25_26_27,45	4,6_7,9_10,12, 25_26_27
LaChapelle et al. [38]	intellectual disabilities	40	49.6	11_29	injection	1x 10s	44 AUs	fr /in	no-stimulation	5% occurrence during pain & pain>baseline (p<0.05)	2,4,6_7,8,12,17, 25_26_27,45	4,17

Lautenbacher et al. [41]	healthy	23	33.8	12/11	temp. (heat) 8x 5s	8x 5sec	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain & pain>baseline (d≥0.5)	1_2,4,6_7,9_10, 14,17,18,23, 25_26_27	4,6_7,9_10,23, 25_26_27
	patients: depression	23									1_2,4,6_7,9_10, 12,14,17,18,24, 25_26_27,43	4,6_7,9_10,17,18, 25_26_27
Limbrecht-Ecklundt et al. [44]	healthy	87	41.0	43/44	temp. (heat) 80x 4s	4x 5.5s	44 AUs	fr /in	non-painful stimulation	5% occurrence during pain, pain>baseline (p<0.05)	4,10,25,26,43,45	4,10,25,26
Lints-Martindale et al. [45]	patients: dementia (and healthy controls)	63	appro x. 78.0	?/?	pressure 15 x 5s electric 15x 5s	2x 15s	44 AUs	fr /in	no-stimulation	25% occurrence & pain>baseline	pressure: 4,7,25, 26,43,45 electrical: 4,7,26, 43,45	pressure: 4,7,25, 26,43 electrical: 4,7,26, 43,45
Patrick et al. [47]	healthy	30	28.0	30/0	electric. 15x 0.05s	15x 3s	44 AUs	fr	non-painful stimulation	10% occurrence during pain & pain>baseline (p<0.05)		4,6,10,45
Priebe et al. [48]	healthy	23	68.2	3/ 20	temp (heat) 3x 20s /1x 5s	3x 20s /1x 5s	44 AUs	in/ duration	none	10% occurrence during pain	1_2,4, 6_7, 9_10,14,17,18, 25_26_27	
	patients: Parkinson	23	67.1	3/ 20							4,6_7, 9_10,14, 25_26_27,43	
Prkachin [49]	healthy	60	23.1	30/30	electric. 12 x 3s	12x 6s	44 AUs	fr /in	non-painful stimulation	1% occurrence during pain & pain>baseline (p<0.05)	1,2,4,5, 6_7, 9_10,12,14,17,18, 20,23,24, 25_26_27, 41/42/43	4, 6_7, 9_10, 12, 25_26_27, 41/42/43
Prkachin [51]	healthy	41	20.3	21_20	electric 1x: 3s, pressure 1x ≤3 min, temp (cold) 1x ≤3 min, ischemia1x ≤15 min	4x 6-10s	44 AUs	duration /in	no-stimulation	1% occurrence during pain & pain>baseline (p<0.05)	across all types of pain: 1,2,4,6,7,9,10,12,14,17,24,25,26,38,41,43,45	electrical: 4,6_7, 9_10,12 pressure: 6_7,9_10 temp: 6_7, 9_10 ischemia: 6_7

temp = temperature stimulation; elec = electrical stimulation; fr = coding AU frequency; in = coding AU intensity

Table 3: Pain-related facial responses

Overview of how often an AU was found to be pain-related across the included studies based on **criterion (a)** its "frequency of occurrence" during pain and **criterion (b)** whether it occurred more frequently/intensely during pain compared to a baseline condition, using a statistical threshold criterion like effect size or T-tests. The values indicate the percentage of studies in which an AU proved pain-related. In case a study included different samples and/or different types of pain, the results are reported separately, and thus, this study is counted more than once.

(a) criterion: <u>frequency of occurence</u>

Action Units		**overall** (all samples & all types of pain)	**type of pain**						**cognitive status**	
			clinical pain	**experimental pain**	**experimental pain**				**unimpaired**	**impaired**
					heat	pressure	electrical	others#		
AU	**name**	N=39	N=4	N=35	N=16	N=8	N=7	N=4	N=31	N=7
1_2	Inner/outer brow raise	82%	75%	83%	81%	88%	86%	75%	84%	71%
4	Brow lower	100%	100%	100%	100%	100%	100%	100%	100%	100%
5	Upper lid raise	5%	0%	6%	0%	0%	14%	25%	7%	0%
6_7	Cheek raise/lid tighten	97%	100%	97%	94%	100%	100%	100%	97%	100%
9_10	Nose wrinkle/ upper lip raise	82%	75%	83%	88%	88%	86%	50%	90%	57%
12	Lip corner pull	56%	75%	54%	63%	38%	57%	50%	68%	0%
14	Dimpler	56%	25%	60%	88%	25%	57%	25%	71%	0%
17	Chin raise	62%	75%	60%	56%	38%	86%	75%	65%	43%
18	Lip pucker	21%	50%	17%	25%	0%	14%	25%	26%	0%
20	Lip stretch	13%	75%	6%	0%	0%	14%	25%	16%	0%
23	Lip tightener	10%	0%	11%	19%	0%	14%	0%	13%	0%
24	Lip press	28%	50%	26%	31%	13%	29%	25%	36%	0%
25_26_27	Opening of the mouth	97%	100%	97%	100%	100%	100%	75%	100%	86%
43	Eyes close	51%	100%	46%	50%	38%	43%	50%	58%	29%
45*	Blink	100%	100%	100%	100%	100%	100%	100%	100%	100%

(b) criterion: pain > baseline

Action Units		Overall (all samples & all types of pain)	type of pain						cognitive status	
			clinical pain	experimental pain	experimental pain				unimpaired	impaired
AU	name	N=37[a,b] /42	N=6 [a,b]/ 10	N=32 [b]/ 33	heat N=12[b]/ 13	pressure N=8	electrical N=8	others# N=3	N=28 [a,b] /32	N=9
1_2	Inner/outer brow raise	14%	33%	10%	8%	13%	13%	0%	14%	13%
4	Brow lower	79%	90%	75%	85%	88%	50%	67%	81%	67%
5	Upper lid raise	0%	0%	0%	0%	0%	0%	0%	0%	0%
6_7	Cheek raise/lid tighten	86%	70%	91%	92%	100%	100%	33%	88%	89%
9_10	Nose wrinkle/ upper lip raise	74%	60%	78%	92%	75%	88%	0%	81%	56%
12	Lip corner pull	23%	25%	23%	25%	13%	38%	0%	30%	0%
14	Dimpler	3%	0%	3%	8%	0%	0%	0%	4%	0%
17	Chin raise	16%	33%	13%	8%	13%	0%	47%	11%	25%
18	Lip pucker	5%	0%	7%	17%	0%	0%	0%	7%	0%
20	Lip stretch	3%	13%	0%	0%	0%	0%	0%	3%	0%
23	Lip tightener	3%	0%	3%	8%	0%	0%	0%	4%	0%
24	Lip press	5%	13%	0%	0%	0%	0%	0%	3%	0%
25_26_27	Opening of the mouth	59%	88%	52%	75%	50%	38%	0%	63%	50%
43	Eyes close	29%	50%	22%	23%	25%	25%	0%	31%	22%
45*	Blink	22%	17%	23%	8%	0%	75%	0%	18%	38%

Grey shaded fields indicate that this Action Unit fulfilled the criteria in ≥50% of the studies.

[a]AU 1_2, AU5, AU14, AU17, AU18, AU23, AU45 were NOT coded in 2 studies [50,52]

[b]AU 1_2, AU5, AU12, AU14, AU17, AU18, AU20, AU23, AU24, AU45 were NOT coded in 2 study [9,28]

* specifications about whether AU 45 was coded or not are not always clear, thus values for AU45 are an approximation

the experimental pain category "others" refers to procedures like venipuncture and injection