Pain rather than induced emotions and ICU sound increases skin conductance variability in healthy volunteers

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Background: Assessing pain in critically ill patients is difficult. Skin conductance variability (SCV), induced by the sympathetic response to pain, has been suggested as a method to identify pain in poorly communicating patients. However, SCV, a derivative of conventional skin conductance, could potentially also be sensitive to emotional stress. The purpose of the study was to investigate if pain and emotional stress can be distinguished with SCV.

Methods: In a series of twelve 1-min sessions with SCV recording, 18 healthy volunteers were exposed to standardized electric pain stimulation during blocks of positive, negative, or neutral emotion, induced with pictures from the International Affective Picture System (IAPS). Additionally, authentic intensive care unit (ICU) sound was included in half of the sessions. All possible combinations of pain and sound occurred in each block of emotion, and blocks were presented in randomized order.

Results: Pain stimulation resulted in increases in the number of skin conductance fluctuations (NSCF) in all but one participant. During pain-free baseline sessions, the median NSCF was 0.068 (interquartile range 0.013–0.089) and during pain stimulation median NSCF increased to 0.225 (interquartile range 0.146–0.3175). Only small increases in NSCF were found during negative emotions. Pain, assessed with the numeric rating scale, during the sessions with pain stimulation was not altered significantly by other ongoing sensory input.

Conclusion: In healthy volunteers, NSCF appears to reflect ongoing autonomous reactions mainly to pain and to a lesser extent, reactions to emotion induced with IAPS pictures or ICU sound.

Editorial comment: what this article tells us
Variation in skin conductance is influenced by pain, emotions, and sound. The authors performed a volunteer study to evaluate if variability in skin conductance to pain can be used as an analgesia trigger. This method appears to identify mainly pain and responds less to emotions and ICU sound. Trends rather than a single absolute number seem to better identify if the subject was in pain.
Critically ill patients experience significant levels of pain and discomfort while in the ICU. During the ICU stay, patients may be exposed to disease-related pain, as well as therapy-induced pain. Unrelieved acute pain may lead to negative physiological and psychological consequences.\(^1\) Evaluation and treatment of pain in ICU patients has shown to be associated with shorter duration of mechanical ventilation and ICU stay, as well as reduced adverse events.\(^2\)–\(^4\) Assessing pain in ICU patients may, however, be difficult as many ICU patients are not able to communicate or self-rate their experience. So far, the only method to assess pain in non-com- municative patients has been by observing behavioral indicators of pain.\(^5,6\)

There has recently been growing interest in palmar skin conductance variability (SCV) and it has been suggested for detecting autonomous responses to nociceptive stimulation.\(^7,9\)

Skin conductance variability is derived from traditional skin conductance measurement used for monitoring autonomic nervous system activation in basic psychology research, and also in research on populations with problems such as phobias and post-traumatic stress.\(^10,11\) In short, distress increases sympathetic activation of palmar and plantar sweat glands, leading to increased electrical conductivity (i.e., skin conductance). Traditional skin conductance monitoring measures the change in absolute skin conductance in response to a stimulus. In contrast, SCV is an online method that identifies fluctuations of skin conductance caused by ongoing palmar sweat release and reabsorption.\(^7,8\) Thus, SCV is less sensitive to individual baseline skin conductance or body temperature than absolute measures of skin conductance and mirrors current sympathetic neuronal activity.\(^12,13\)

Skin conductance variability has shown to be a valid method for pain assessment in post-operative patients.\(^14\) Results from a recent study in ICU patients indicated that pain induced SCV changes in these patients.\(^15\) However, SCV increased not only due to painful stimulation but also appeared to increase due to emotional stress as assessed with the Motor and Activity Assessment Scale.\(^15\)

Our aim was to, with an experimental design in healthy subjects, investigate if SCV could distinguish between pain and emotional stress. Moreover, we hypothesized that pain would be perceived more intensely during simultaneous potentially stressful exposures, namely negative visual stimuli and ICU sound.

**Methods**

After approval from the regional ethics committee in Stockholm, Sweden, we conducted the experiment at the Psychology Laboratory, at the Department of Psychology, Mid-Sweden University, Östersund, Sweden.

**Participants**

Twenty healthy volunteers (mainly psychology students) were invited to the study and 18 participated (seven men and 11 women with a median age of 25 years, ranging from 20 to 53 years) in the study. One participant revealed afterwards that he had scored pain levels falsely high in the pain titration part of the experiment and was therefore excluded. One participant did not come for the experiment as planned. Reasons for exclusion were pregnancy, chronic pain, heart problems including pacemakers, or the use of psychotropic drugs. All participants signed an informed consent.
**Procedure**

Participants were seated in a chair in a quiet lab room in front of a computer and were given headphones. Electrodes for measuring skin conductance were placed on the palmar side of the left hand. A pain stimulator was placed on the index finger of the right hand. Participants could not see the investigators but were monitored by a remote camera.

Each participant was exposed to twelve experimental conditions (sessions), each lasting 60 s. Between each session, there was a 1-min resting period. The 12 sessions consisted of all possible combinations of two pain states (pain/no pain), three different emotion-inducing picture batteries (positive, negative, or neutral), and two sound states (sound/no sound). After each session, a message on the screen instructed participants to relax until they heard a sound, indicating the start of the next session.

**Materials, apparatus and exposures**

E-prime (Psychology Software Tools Inc, Sharpsburg, PA, USA) was used to program the experiment with triggers for electrical stimulation, pictures, and sound playback, as well as data collection from online self-reports.

**Standardized electrical pain stimulation**

Pain was induced with the Coulbourn Transcutaneous Aversive Finger Stimulator (Coulbourn Instruments, Whitehall, PA, USA), with remote triggering via Biopack Systems MP150 (BIOPACK Systems INC, Goleta, CA, USA). The electrical stimulus was delivered to the distal phalanges of the index and middle finger in 1 ms spikes set to 100 ms duration. To standardize the stimulation, pain was titrated individually to a modified visual analog scale (VAS) of 5 prior to the 30-min experiment. VAS 5 was chosen as a pain level encountered in ICU patients, indicating clear need for analgesia. Participants could change the position of the VAS scale indicator, rating pain from ‘no pain’, which was the first rating for all participants prior to electrical stimulation, to ‘worst imaginable pain’. The back of the scale contained a numbered scale, range 0–10, visible to the conductor of the trial. The Coulbourn device was set at a starting point of 0.6 mA, after which the mA was increased in increments of 0.3 mA until 2.3 mA and thereafter a final increase to 4 mA. When the individual rated pain as more than VAS 4 but less than VAS 6, this level was used during the exposure session.

Participants received this standardized pain stimulation during half of the 12 sessions. Electrical stimulation was given at random intervals, with a total of 24 electrical stimulations over the 1-min-long session (0.4/s). The order of the two pain sessions was randomized over the four sessions within each emotion block (described below).

**Emotion-inducing pictures**

In order to induce three different emotions (positive, neutral, or negative), a total of 36 emotionally charged pictures from the International Affective Picture System (IAPS) were used (12 for each emotion).

International affective picture system is based on large set of pictures used for standardizing emotional stimulation. They are calibrated for affective response and characterized primarily by normative ratings of valence and arousal. Valence refers to the attractiveness (high valence) or aversiveness (low valence) of an object (or event/situation). Arousal refers to how excited (high arousal) or calm the subjects feel in response to an object/event/situation. Both measures range from 1 to 9. Pictures were selected to gain a variety of content and three levels of emotional valence: 12 positive, 12 neutral, and 12 negative pictures (Table 1). The pictures were presented in a 1024 × 768 resolution, giving them a measurement of 22 × 18.7 cm on the computer screen.

The positive picture series portrayed for example, smiling people and beautiful sceneries (IAPS pictures: 2091, 2224, 4612, 4622, 4698, 5470, 5480, 5626, 5833, 7325, 7472, 7492). The neutral picture series included innate objects, such as a chair or a spoon (IAPS pictures: 7000, 7002, 7004, 7006, 7010, 7012, 7025, 7052, 7183, 7185, 7186, 7705). The negative picture series contained images of death, threat, mutilation, and suffering people and were chosen in order to resemble unpleasant persecutory hallucinations and fears.
described by patients after their ICU stay (IAPS pictures: 2811, 3063, 3068, 3150, 3168, 6230, 6250, 6830, 9000, 9301, 9490, 9599). According to IAPS policy, pictures from the database cannot be published. IAPS-like images, from pixabay.com (copyright-free), are included as similar examples (Fig. 1).

In each 1-min session, the 12 pictures from the same emotion category were shown twice (n = 24), for 2.5 s each time. Each emotion-inducing picture battery was shown in four consecutive sessions (emotion block). The order of the three emotion blocks was randomized for each participant (Table 2).

**ICU sound**

To simulate the background sound of an ICU environment, an authentic daytime sound recording from a fully occupied three-bed room at the General ICU, Karolinska University Hospital Solna, Sweden was used. The recording included background sounds (from ventilators and other machines), doctors and nurses talking, and monitor alarms. The sound presentation lasted for 60 s, with volume peaks at 80 dB. The order of sound/no sound in the four sessions within each ‘emotion block’ was randomized (Table 2).

**Outcome assessment**

**Skin conductance variability measured with NSCF**

The Med-Storm Stress Detector device (MED-STORM Innovation AS, Oslo, Norway) was used to measure SCV. In this measurement application, used in most recent studies as well as our study, SCV is reported as the number of skin conductance fluctuations/second (NSCF).

The criterion for the registration of a skin conductance fluctuation was an amplitude between skin conductance trough and peak of > 0.02 microsiemens (µS), as in previous studies. The fluctuations registered with this method correlate with bursts of sympathetic neuronal stimulation of the palmar sweat glands. Before the start of the session, three disposable Ag/AgCl electrodes were attached to the palmar surface of the participants hand: thenar eminence (current electrode), hypothenar eminence (measurement electrode), and just below the second and third digits (reference electrode), respectively. NSCF was measured during the

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**Table 1** Mean and standard deviation (SD) for valence and arousal of the three series of emotionally charged pictures from international affective picture system (IAPS). Data from IAPS standardized values of each picture ranging from 1 to 9.

<table>
<thead>
<tr>
<th></th>
<th>Positive pictures (n 12)</th>
<th>Neutral pictures (n 12)</th>
<th>Negative pictures (n 12)</th>
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<tbody>
<tr>
<td></td>
<td>Valence</td>
<td>Arousal</td>
<td>Valence</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.2 (1.6)</td>
<td>5.1 (2.2)</td>
<td>5.0 (1.1)</td>
</tr>
</tbody>
</table>

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![Fig. 1. International affective picture system-like pictures with the purpose to induce emotions. Examples of positive, neutral, and negative emotion-inducing pictures. These pictures were not used in the study. Source: Pixabay.com (Free pictures).](image-url)
entire experiment. Mean NSCF values over each minute of exposure were used in the analysis.

**Pain rating**

After each 1-min session, participants were instructed to rate pain on the screen in front. To rate pain during the session, a modified numeric rating scale consisting of 11 unnumbered horizontal boxes on the computer screen was used. Pain was rated from ‘no pain’ to ‘worst pain imaginable’ by ticking a box. For analysis, boxes were later assigned values from 0 to 10 (in concordance with the VAS). The self-ratings were followed by a 1-min resting phase.

Number of skin conductance fluctuations was measured on the 18 participants across the 12 sessions, resulting in a total of 216 observations (12 × 18 = 216) (Table 2). Each participant rated pain six times, for a total of 108 self-reports of pain. In all subjects, VAS was rated as zero prior to the experiment sessions. These values were included in the random-effect linear regression model.

### Statistical analysis

Power calculation was made for within-subjects analysis with anticipated mean NSCF of 0.07 (Standard Deviation, SD 0.15) in non-painful exposures and mean NSCF of 0.21 (SD 0.15) during painful stimulation. With a sample size of 20, with the alpha error < 0.05, power was 97%.

A within-subjects (2 × 3 × 2) analysis for dependent measures was used. The dependent variables NSCF and self-perceived pain (NRS) were analyzed in two separate random-effect linear regression models. The participants’ random effects were included to take into account the potential correlation between the repeated measures in each subject. In each model, the predictors of interest were type of pain stimulation (no pain/pain), emotion (positive, neutral, or negative), and sound (no sound/sound).

For regression analysis, we used the NSCF from the session with neutral pictures, no electrical stimulation, and no ICU sound as the baseline. The same combination was also treated as the NRS 0 baseline condition in the regression analysis of NRS. Based on the results of the regression models, NSCF and NRS reactivity were estimated for the different sessions. The intra-individual correlation was also estimated with Spearman’s rho. Rho indicates the correlation within individuals compared to the group correlation. Rho 0.5 = substantial intra-individual correlation, Rho 0 = all individuals have the same values across sessions. Rho can also be translated to the percentage of inter-individual difference. Thus, a rho value of 0.55 equals an inter-individual difference of 55%, (a substantial difference, indicating that the variability within the group is large).

Results with P-values of < 0.05 were considered statistically significant.

### Results

Data for the mean, standard deviation, median, interquartile range (IQR p25–p75), and full range of NSCF for the 12 exposures sessions are presented in Table 3.

#### NSCF and NRS during pain stimulation

The 18 individuals’ baseline session measurement (neutral pictures, no electrical stimulation, and no sound) rendered a median NSCF value of 0.068 peaks/s (IQR p25–p75: 0.013–0.089 peaks/s, respectively). In the 108 measurements with pain stimulation, median NSCF was 0.225 peaks/s (IQR p25–p75: 0.146–0.318 peaks/s), respectively. The median NRS during pain stimulation (all pain sessions) was
All but one subject demonstrated an elevation in NSCF during pain stimulation (Fig. 2). Pain stimulation increased NSCF significantly, 0.13 peaks/s from baseline, after adjusting for picture-induced emotion and ICU sound ($P < 0.001$) (Table 3, Fig. 3). Negative emotion also increased NSCF significantly, 0.03 peaks/s, after adjusting for the effect of ICU sound and pain, ($P < 0.05$). Positive emotion and ICU sounds did not impact NSCF significantly. The intra-individual correlation rho 0.58 indicates that 58% of the variability was due to inter-individual differences.

**NSCF in relation to combined pain stimulation, pictures, and sound**

Pain stimulation increased NSCF significantly, 0.13 peaks/s from baseline, after adjusting for picture-induced emotion and ICU sound ($P < 0.001$) (Table 3, Fig. 3). Negative emotion also increased NSCF significantly, 0.03 peaks/s, after adjusting for the effect of ICU sound and pain, ($P < 0.05$). Positive emotion and ICU sounds did not impact NSCF significantly. The intra-individual correlation rho 0.58 indicates that 58% of the variability was due to inter-individual differences.

**NRS in relation to electrical stimulation, pictures, and sound**

As hypothesized, pain rating was increased, with NRS 3.95 during pain stimulation.
(P < 0.001) (Tables 3 and 4, Fig. 4). Negative emotion also increased VAS significantly but to a much lesser extent, by 0.36 units (P < 0.05). Positive pictures and ICU sound did not affect NRS significantly. The intra-individual correlation rho 0.35 indicates that 35% of the variability was due to inter-individual differences.

The random-effect linear regression coefficients for NSCF as a NRS-dependent variable implied that a 1-unit increase in NRS was associated with a NSCF increase by 0.073 peaks/s (P < 0.001). The intra-individual correlation rho 0.25 indicates that 25% of the variability was due to inter-individual differences.

**Discussion**

In our study, pain stimulation titrated to VAS 5 prior to the sessions, led to a distinct increase in skin conductance variability, while emotions induced by IAPS pictures and authentic ICU sound had limited effects on NSCF.

Our interpretation is that in a controlled environment, NSCF is more specific to pain than to emotion. In a previous study of NSCF in critically ill ICU patients, many patients were unable to self-report ongoing adverse perceptions. While non-painful adverse perceptions, such as intense fear, hallucinations, or delusions may lead to agitation, untreated pain itself may also lead to agitation. The results of the
present study suggest that agitation noted in some of these poorly communicating, intubated patients may have represented an expression of pain. Poorly treated pain has in fact been associated with agitated delirium.22

Pain, titrated to an individual VAS 5 in each participant prior to the experiment, led to a median NSCF of 0.27. This is similar to the findings from skin conductance variability studies in post-operative and ICU patients. In these studies, moderate pain, equivalent of VAS 4–5 was associated with NSCF of approximately 0.25.14,15

The rho value for NSCF of 0.58, however, indicates that there are substantial inter-individual differences. This is depicted with the raw data presented in Fig. 1 and Table 3. Thus, in the clinical setting, NSCF changes in the individual patient, in combination with clinical assessment may be more relevant to follow than to use a strict NSCF threshold value as an analgesia trigger.

Currently, the most objective measures of pain in poorly communicating ICU patients are composite observer’s scales.5,24 These scales are better than arbitrary assessment, in that inter-rater variability may be reduced. Nonetheless, some parameters common for the Clinical Pain Observation Tool (CPOT)5 and Behavioral Pain Scale (BPS),24 such as poor ventilator compliance or facial grimacing, might be observed for other reasons than pain. Considering that pain was the main determinant in NSCF increases and findings from a previous study in ICU patients,15 our interpretation is that NSCF may potentially be considered as a complementary pain assessment method in poorly communicating patients. The potential benefits, however, need large-scale evaluation. Further study of SCV monitoring in critically ill patients deemed in pain and receiving analgesics may be of value to confirm its role and validity in this specific population.

Compared with the effect of pain, there were only minor NSCF and NRS differences between the different picture series, with negative pictures increasing NSCF and NRS marginally (Table 3). Affective modulation of autonomic reactions to noxious stimulation has been stated in earlier studies in which different emotion-inducing picture series were presented during nociceptive stimulation.25–27 In our study, the reference values of valence and arousal of the chosen IAPS pictures used in the three IAPS picture series were sufficiently different to have induced the proposed emotions according to the IAPS paradigm which should further support the finding of pain as the main determinant for SCV increases.

We evoked pain intermittently with electrical stimulation in otherwise healthy and drug-free volunteers, in order to reduce the heterogeneity in exposures and potential drug effects found in critically ill ICU patients. One major difference between our experimental setting and the real ICU scenario is that the stimulations and interpretation of these, as well as the autonomic response in the two settings may be vastly different. The pain exposure in our study may resemble procedural pain in relatively stable and otherwise pain-free patients. Many ICU patients, however, may suffer from ongoing nociceptive inflammatory and in some cases neuropathic pain. In parallel, they may be aware of their life-threatening situation or be in delusional fear (e.g., of staff trying to kill them). Such fear may be more emotionally distressing and perhaps lead to greater autonomous responses than what can be mimicked in a study in healthy volunteers. The same applies to the connotation of ICU sound. For some ICU patients, the alarms from a ventilator or monitor are very intimidating, as this may indicate a problem with life-supporting devices or vital functions.28 Thus, while our study assessed standardized stimuli in subjects able to self-report, a significant limitation may be that these volunteers are likely not as vulnerable and sensitive to adverse stimuli as are critically ill patients in the ICU. Additionally, it is unclear whether some drugs, such as beta-blockers or

Fig. 4. Mean numeric rating scale values and 95% confidence intervals for the six sessions with pain stimulation from the random-effects model.
alpha-2-agonists, or severe critical illness might interfere with sympathetic tone and responses to stimulation. A future study in ICU survivors, recently exposed to intensive care, could evaluate if there are potentially larger SCV increases to non-painful, adverse stimuli and as stated, studies of critically ill patients with validated pain assessment tools during stimulation and analgesia are warranted.

In summary, skin conductance variability increased mainly in response to pain and only marginally in response to induced emotion or ICU sound in healthy volunteers. Individual trends rather than absolute thresholds appeared to be relevant. In conclusion, skin conductance variability, as defined in our study, reacts more to pain (rated as VAS > 4 and < 6) than strongly negative emotionally charged pictures in healthy volunteers. There is a substantial degree of inter-individual differences in skin conductance variability reactions. Skin conductance variability can potentially be a supplement in assessing pain in the critically ill, poorly communicating patient but needs evaluation as a complement in the ICU setting. Studies of skin conductance variability as an adjunct to observational scales in the assessment and treatment of pain in poorly communicating ICU patients are warranted.

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