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Parametric trial-by-trial prediction of pain by easily available physiological measures

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ABSTRACT

Pain is commonly assessed by subjective reports on rating scales. However, in many experimental and clinical settings, an additional, objective indicator of pain is desirable. In order to identify an objective, parametric signature of pain intensity that is predictive at the individual stimulus level across subjects, we recorded skin conductance and pupil diameter responses to heat pain stimuli of different durations and temperatures in 34 healthy subjects. The temporal profiles of trial-wise physiological responses were characterized by component scores obtained from principal component analysis. These component scores were then used as predictors in a linear regression analysis, resulting in accurate pain predictions for individual trials. Using the temporal information encoded in the principal component scores explained the data better than prediction by a single summary statistic (ie, maximum amplitude). These results indicate that perceived pain is best reflected by the temporal dynamics of autonomic responses. Application of the regression model to an independent data set of 20 subjects resulted in a very good prediction of the pain ratings demonstrating the generalizability of the identified temporal pattern. Utilizing the readily available temporal information from skin conductance and pupil diameter responses thus allows parametric prediction of pain in human subjects.

1. Introduction

Pain is a subjective experience and is therefore assessed by subjective reports, which are commonly mapped to a numerical rating scale or a visual analogue scale [29]. However, in many circumstances an objective pain assessment is important. For example, there are situations in which a patient is not able to understand the rating scales (eg, in children), or the report may be biased in other scenarios. The latter is relevant, because subjects may form expectations about the desired study outcome. This might actually be the case in most of the studies on pain, for example, when testing a drug or evaluating some behavioral intervention.

Candidates for an objective auxiliary measure of pain are autonomic nervous system responses that are related to pain perception [9,10], for example, skin conductance [10,18,22,23,34] and pupil diameter [8,10,13,16,27]. Changes in skin conductance levels correlate with pain ratings of heat pain stimuli [23], and pupil dilation amplitudes reflect electric stimulation intensity [8].

Studies investigating these measures often characterize physiological responses by a single summary statistic (eg, maximum amplitude) and relate that parameter to pain reports [8,13,16,22,23,27,34]. As autonomic responses typically entail both phasic and tonic components, this approach may neglect the information present in the full time-course. One way to use this information is principal component regression (PCR): individual trial time-courses are represented by scores of the most important principal components [15], thereby providing a more accurate representation of the time-course than a summary statistic. The main objective of the current study was therefore to investigate whether pain prediction can be improved by incorporating temporal information present in autonomic recordings.

Ideally, an objective measure of pain would be available at minimal costs, both monetary and with regard to the experimental design. Additionally, a signal that is reliable enough to work on individual trials is more helpful than a measure aggregated across trials. As the perceived intensity of painful stimuli varies considerably across studies and subjects, a parametric prediction

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of different pain intensity levels at the trial level seems desirable instead of relying on binary pain vs no-pain reports [31]. Furthermore, a prediction model would optimally be able to predict unseen data from an independent test data set without re-fitting subject specific parameters. In order to test an objective, parametric marker of pain intensity, predictive at the trial level across subjects, we recorded autonomic responses to a set of different cutaneous heat pain stimuli. The predictive performance of the PCR model utilizing detailed temporal information was then compared to a prediction based on summary statistics (ie, amplitudes) extracted from the physiological responses.

A recent study reported that pain prediction by a combination of several physiological measures outperforms prediction by single measures [34]. We therefore recorded 2 autonomic measures, skin conductance and pupil diameter, and combined these for parametric pain prediction.

2. Materials and methods

2.1. Samples

Thirty-seven healthy male subjects participated for payment in this study. All except one subject were right-handed. Subjects reported no history of neurological, psychiatric, or skin diseases and had not taken any medication during the last 48 hours prior to the experiment. One subject had to be excluded because of no evident skin conductance response. Two further subjects had to be excluded because of poor eye-tracking data quality. The final sample thus consisted of 34 subjects, aged 21-37 years (mean age: 25.8 years). In order to evaluate the generalizability of the PCR model, we used a second independent data set. This sample included 20 additional male subjects (mean age: 27.5 years; range: 22-39 years) participating in an experiment very similar to the main experiment. The Ethics committee of the Medical Chamber Hamburg approved the study and all subjects gave written informed consent.

2.2. Procedure

Subjects were individually tested in an eye-tracking laboratory with controlled equal illumination in all sessions. First, subjects were informed about the study and provided informed consent. Subjects then washed their hands with warm water, but without soap, to optimize skin conductance recording. Skin conductance recording electrodes were attached to the subject's left hand. To calibrate the pupil diameter properly, 2 epochs of 5 seconds duration were recorded with artificial pupils of 5 and 10 mm diameter. Fake pupils were fixed over the closed right eye while the subjects placed their head in the headrest of the eye tracker. Subsequently, a 9-point gaze calibration was performed with the subject's head positioned in the headrest. Pain thresholds (mean: 45.7°C, SD: 3.0°C) were then determined according to the method of limits (1°C/s slope). The main experiment consisted of 32 cutaneous heat pain trials, split into 4 blocks of 8 trials each. The thermode was moved to a different patch on the volar forearm after completion of a block to prevent sensitization. During heat pain stimulation, skin conductance and pupil diameter were recorded.

The heat pain stimulation paradigm consisted of 8 different stimuli, each repeated 4 times. Each stimulus occurred once per block. Stimulation order was pseudo-randomized across subjects such that each stimulus was equally often at the first position within a block. Stimulus temperatures were 45, 46, 47, and 47.5°C and lasted 8 or 20 seconds, resulting in 8 different combinations of temperature and duration. Stimulus duration included a ~1.5-second ramp-up and -down period and a plateau lasting 5 (short trials) or 17 seconds (long trials), respectively. Each trial (Fig. 1A) consisted of an anticipation period of 13–17 seconds, heat pain stimulation, a 5-second delay, pain rating on a visual analogue scale (VAS), and a 12-second intertrial interval. Subjects were asked to fixate a crosshair at the center of the screen and to refrain from blinking during the anticipation and stimulation periods. Pain stimulation was not cued, that is, the crosshair remained unchanged during both periods. Pain ratings were completed on a VAS anchored "no pain" and "unbearable pain." The delay between heat stimulation and rating was introduced to prevent contamination of autonomic recordings by button presses [20]. During the intertrial interval, a blank screen was presented and subjects were allowed to move their eyes freely. After each block, subjects could rest for a few minutes. The whole procedure lasted about 45 minutes.

2.3. Data acquisition

Response logging, thermode triggering, and synchronization with the physiological recordings were controlled by Presentation software (Neurobehavioral Systems, Berkeley, CA, USA). A 3 × 3 cm Peltier thermode (Pathway ATS; Medoc Advanced Medical Systems, Ramat Yishai, Israel) was used to deliver thermal stimulation on the left volar forearm. Skin conductance was recorded using a constant voltage (0.5 V) Biopac MP100 system (Biopac Systems, Inc., Goleta, CA, USA) at a sampling rate of 250 Hz. Ag/AgCl recording electrodes filled with 0.05 M NaCl electrolyte were placed on thenar and hypothenar eminences of the left hand. Pupil diameter was recorded at a sampling rate of 1000 Hz using an Eyelink 1000 system (SR Research Ltd., Mississauga, ON, Canada).

2.4. Data analysis

All data analyses were completed using MATLAB v7.12 (Mathworks, Natick, MA, USA) and SPSS 19 (IBM, Armonk, NY, USA). After preprocessing the physiological data, we predicted pain ratings using 2 different sets of predictors: (1) using summary statistics describing the physiological response of each trial (ie, amplitude) and (2) utilizing the temporal information of the physiological responses for prediction. The former will be referred to as summary statistic regression and the latter will be referred to as PCR [15]. According to a recent study [34], simultaneous use of multiple autonomic measures differentiates best between pain stimulus levels. Hence, we predicted pain simultaneously by skin conductance and pupil measures. Results are summarized in Table 1. For completeness, we report results on separate regression models (ie, only skin conductance or pupil dilation plus intercept) in Table 2.

The effect of stimulus duration and temperature on pain ratings was tested using a 2 × 4 repeated-measure analysis of variance.

2.4.1. Skin conductance

Skin conductance traces were down-sampled to 25 Hz, low-pass filtered at a cutoff frequency of 1 Hz, and epochs from 3 seconds before to 5 seconds after stimulus presentation were selected for further analyses. Trials with recording artifacts were removed from further analyses ($n = 22$; 2%). To quantify the skin conductance response with a summary statistic, we extracted 3 different parameters. The skin conductance response (SCR) amplitude was calculated by subtracting the local minimum at the onset of the first SCR from the first peak. The SCR onset was required to occur between 1 and 5 seconds after stimulus onset. We chose this interval because the thermode needs 1–2 seconds to reach its target temperature. SCR amplitudes below 0.02 μS were set to zero. Skin conductance level (SCL) was computed by averaging the skin conductance trace from stimulus onset until 5 seconds after stimulus