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Investigation of threshold and magnitude criteria of the nociceptive blink reflex ☆

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ABSTRACT

Objective: The nociceptive blink reflex is a trigeminofacial brain-stem reflex which is used in pain research to evaluate the modulation of pain processing. To standardize the analysis of the reflex we investigated which electromyographic parameters show the best correlation with subjective pain ratings and should therefore be used for scoring blink reflex magnitude. Furthermore we investigated which parameters show the highest accuracy and reliability to define the blink reflex threshold.

Methods: Forty-six subjects each received 54 electrical stimuli to the supraorbital nerve at nine different stimulus intensities, which corresponded to pain ratings between 0 and 70 (scale 0–100). Multilevel modeling was performed to determine which electromyographic blink reflex parameter showed the best correlation with subjective pain ratings. To define the blink reflex threshold ROC analyses were performed, comparing different electromyographic blink reflex parameters with the judgment of expert raters for 2500 blink reflex recordings from this study and 1400 from another.

Results: The baseline-adjusted area under the curve showed the best correlation with subjective pain ratings. Seventy-six percent of the residual variance of the pain ratings could be explained by this parameter. The peak *z* score showed the highest accuracy in defining the blink reflex threshold and also the highest cut-point stability.

Conclusions: We recommend the baseline-adjusted area under the curve for scoring the magnitude of the nociceptive blink reflex and the peak *z* score to define the nociceptive blink reflex threshold.

Significance: The here defined standardized criteria to score blink reflex magnitude and threshold improve the comparability and validity of blink reflex studies.

1. Introduction

The blink reflex, as a trigeminofacial brain-stem reflex, is a non-invasive tool to study trigeminal transmission in humans. It is elicited by stimulation of the supraorbital nerve and assessed by an electromyogram of the orbicularis occuli muscles. To increase the nociceptive specificity of the reflex a special concentric planar electrode is used for stimulation which produces a high current density in superficial skin layers already at low current intensities, therefore predominately exciting superficial A delta fibers (Kaube et al., 2000).

The nociceptive blink reflex paradigm is used in experimental pain research as a tool to evaluate the modulation of pain perception by pharmacological or physiological influences as well as alterations in pain processing in patients with pain disorders (Ayzenberg et al., 2006; Giffin et al., 2003; Katsarava et al., 2003; Koh and Drummond, 2006; Kowacs et al., 2003; Magis et al., 2007; Obermann et al., 2007; Williams and Rhudy, 2009).

Like other pain specific reflexes as tools for the investigation of pain perception the blink reflex can be used in two ways: the blink reflex threshold can be used as an objective surrogate measure of the nociceptive threshold and changes in the magnitude of the blink reflex following constant suprathreshold stimuli can be used to assess changes in the nociceptive responding.

However, up to now no investigation has been performed to determine the optimal electromyographic parameters to score blink reflex magnitude. Since blink reflex magnitude is used as a surrogate for nociceptive perception, we decided a priori to define the quality of a magnitude parameter according to its correlation with the subjective pain ratings. Apart from scoring blink reflex magnitude, also no investigation has yet been performed to define standardized scoring criteria for the blink reflex threshold. Analyses of both scoring criteria for magnitude and threshold have already been performed for other nociceptive reflexes as the nociceptive flexion reflex (Rhudy and France, 2007; Rhudy et al.,

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2008). However, the results of these studies cannot be applied for the blink reflex without difficulty, since the shapes of the reflexes in the EMG differ considerably.

Therefore the goals of the present study were first to determine the electromyographic parameters of the nociceptive blink reflex which show the best correlation with the subjective pain ratings and second to determine the parameters with the highest accuracy and reliability to define the nociceptive blink reflex threshold.

2. Methods

2.1. Subjects and setting

After approval of the Local Ethics Committee (Berlin, Germany) and written informed consent the investigation of blink reflex magnitude and threshold criteria was performed in 25 male and 25 female volunteers, ranging in age from 21 to 44 years. The experimental sessions were all carried out during the same time of the day (9–12 AM) to reduce variability due to circadian changes. During the course of the study the subjects were comfortably rested in reclining chairs and were instructed to keep their eyes closed. Before the data acquisition for the study commenced, the subjects were introduced and accustomed to the method by the application of electrical stimuli at different intensities. Prior to testing, all subjects were instructed to refrain from caffeine, nicotine, alcohol and strenuous exercise for at least 24 h and from analgesic medication for 48 h. To rule out states of extreme anxiety Spielberger's State/Trait Anxiety Inventory (STAI-) scores were determined before the experimental procedure was started (French et al., 2005; Spielberger, 1983).

2.2. Recording procedure of the nociceptive specific blink reflex

To elicit the nociceptive blink reflex electrocutaneous stimulation was applied via a planar concentric electrode assembly of a central metal cathode, an isolation insert and external anode ring (Kaube et al., 2000). The concentric electrode was placed for every subject on the left forehead, approximately 10 mm above the supraorbital foramen to stimulate the supraorbital nerve. Stimuli were applied as trains consisting of three pulses of 0.5 ms duration each with an interpulse interval of 5 ms, to further increase nociceptive specificity (Giffin et al., 2004). Repeated stimulation was applied at randomized intervals between 18 s and 22 s to minimize the likelihood of stimulus predictability.

To record the reflex responses to the stimuli, surface electrodes were placed infraorbitally and at the root of the nose. The recorded signals were amplified and band-pass filtered between 2 Hz and 1 kHz (g.Bsamp, gTech, Graz, Austria), digitized at 2 kHz (Micro1401, CED, Cambridge, UK) rectified and analyzed using Signal 3.10 software (CED, Cambridge, UK).

To investigate the R2 component of the blink reflex the post-stimulus interval of 27–87 ms was used (Ellrich et al., 1998).

2.3. Pain scoring

The pain evoked by each stimulus was subjectively rated on a combined verbal-numerical rating scale (NRS) between 0 and 100. Several anchors are attached to the scale ranging from 0 (no sensation), 5 (no pain sensation), 10 (faint pain sensation) up to 95 (extremely intense pain) (Gendreau et al., 2003). The subjects were instructed to open the eyes for a short moment after the application of each stimulus and rate the pain according to the scale.

2.4. Experimental design for the investigation of blink reflex magnitude and threshold criteria

After the setup of the stimulation and recording electrodes, the subjects were introduced and accustomed to the method by the application of 10 electrical stimuli at different intensities up to a NRS pain score of 70. After a break of 5 min, increasing stimuli in steps of 2 mA were applied up to a NRS pain score of 70.

To record the blink reflex recruitment curves, after another break of 5 min three blocks of 18 stimuli were applied with breaks of 5 min in between. In each block, stimuli were applied at nine different stimulus intensities that were evenly spaced between 0 mA and the stimulus intensity which was identified before to elicit a NRS pain score of 70. The order of the stimuli within each block was randomized.

After another break of more than 5 min, the blink reflex threshold was estimated by the application of an up–down staircase method. For this up-down staircase method stimulation intensity was increased in 0.4 mA increments until a reflex was detected, then was decreased in 0.4 mA decrements until the signal was indistinguishable from the baseline again. Continuing from this intensity, the procedure was then repeated using 0.2 mA increments and decrements until a total number of 18 stimuli have been applied. Decisions whether a reflex occurred or not were made visually and subjectively by an experienced rater, dependent on whether a sizeable peak occurred in the blink reflex interval or not. The rater was identical for all experiments in this study to rule out inter-rater variability. The reflex threshold in mA was finally calculated as the point of a 50% chance of reflex occurrence according to a logistic regression of the applied stimuli. The pain threshold in mA was calculated as the point at which the NRS rating exceeded the value of 5, which according to the anchored pain scale corresponds to "no pain sensation".

To increase the number of data traces around the blink reflex threshold to 50 per individual for a receiver operating characteristic analysis, after another break of 5 min, the blink reflex was stimulated at intensities around the blink reflex threshold by using a computer based algorithm. This algorithm follows an up–down

Table 1
Criterion variable definitions.

Criterion variable	Definition
Blink Interval Peak	Peak voltage in the blink reflex interval
Blink Interval Mean	Mean voltage in the blink reflex interval
Blink Interval AUC	Blink reflex interval area under the curve
Baseline adjusted Blink Interval Peak	Blink interval peak − baseline mean
Baseline adjusted Blink Interval Mean	Blink interval mean − baseline mean
Baseline adjusted Blink Interval AUC	Blink interval AUC − baseline AUC
Blink Interval Peak *z* score	(Blink interval peak − baseline mean)/baseline SD
Blink Interval Mean *z* score	(Blink interval mean − baseline mean)/baseline SD
Blink Interval AUC multiples	Blink interval AUC/baseline AUC
Blink Interval Cohen's *d*	(Blink interval mean − baseline mean)/(pooled SD of Blink interval and baseline)