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# You can see pain in the eye: Pupillometry as an index of pain intensity under different luminance conditions

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ABSTRACT

Pupil dilation is regulated autonomically and it may be a valid measure of pain, but pupillometry for pain intensity recordings has not been evaluated under different luminance conditions. We hypothesized that the pupil response may serve as an objective indicator of pain intensity even if luminance conditions differ which is often the case in experiments with pictures.
In 20 healthy females we applied a tonic pressure pain to the fingers (20 s). During pain induction, participants looked at pictures of three different levels of luminance. Pupil dilation was recorded continuously.
Immediately after pain onset, there was a significant pupil dilation which reached its maximum about 2 s after pain onset. While this maximum pupil dilation did not differ with pressure intensity, the pupil dilation was larger for the higher pressure intensity in the period from 10 s after pressure onset to pressure offset. Even under different luminance conditions, pupillometry can serve as an objective indicator of pressure pain intensity. Thus, it seems promising to use pupillometry with complex experimental designs combining pain and pictorial stimuli.



Two opponent muscles in the iris, i.e., the sphincter pupillae and the dilator pupillae, adjust pupil size. The sphincter pupillae is innervated by cholinergic fibers of the parasympathetic system and constricts the pupil. In contrast, the dilator pupillae is controlled by adrenergic fibers of the sympathetic system and dilates the pupil. Due to the innervation and function of these opponent muscles, pupil dilation is an index of sympathetic activity (Beatty and Lucero-Wagoner, 2000). According to this, in several clinical studies investigating mental disorders or effects of psychotropic drugs, the size of the pupil is used as an indicator for autonomic nervous system reactivity (Grunberger et al., 1993).

This measure may also be useful in studies on pain. In addition to the sensory, affective, and behavioural components, autonomic arousal is part of the response to painful stimulation (Bennaroch, 2001). Painful stimulation reliably elicits pupil dilation occurring simultaneously to changes in other parameters of the autonomic nervous system (e.g., Tassorelli et al., 1995). In line with this, pupil size has been found to correlate with clinical pain (Rubin et al., 1985), and pupillometry can be used to estimate the level of analgesia in anesthetized patients (Constant et al., 2006).

Previous studies with experimentally induced pain found that the pain-evoked pupil dilation is not just an index of the presence of a painful stimulus but it may even be an index of its intensity: Chapman et al. (1999) measured pupil dilation in response to brief noxious electrical stimuli with four different intensities. They found that the peak amplitude of the pupil dilation which appeared 1 to 2 s post-stimulus was modulated by pain intensity. Ellermeier and Westphal (1995) used tonic pressure pain stimuli of varying degrees and found that the average size of the pupil in the second half of a 20 s pressure application is a significant index of the intensity of the pressure stimulus.

Despite the fact that pupil reactions are valid indices of pain intensity, reviewing the literature on pain in PubMed (accessed at http://www.ncbi.nlm.nih.gov/sites/entrez/ on 2008-06-25) and Web of Science (http://isiknowledge.com/wos 2008-06-25) reveals that heart rate appears much more frequently in the context of pain (NLM "heart rate" AND "pain" 4792 and WoS Topic=("heart rate" AND "pain") 2521 hits) than pupil size (NLM "pupil*" AND "pain" 274 and WoS Topic=("pupil*" AND "pain") 287 hits). One reason for this discrepancy may be that pain-evoked changes in pupil size are relatively small in comparison to the effects related to luminance of the surroundings which determines pupil size to a much greater extent (Beatty and Lucero-Wagoner, 2000). Furthermore, changes in pupil size (as in other physiological measures) are assumed to depend on the initial value of the measure (i.e., baseline pupil size). This dependency of initial values of physiological measures was originally explicated by Wilder (1967) in the so called law of initial value (LIV). The law states that the initial value and its corresponding change value are negatively correlated. Because of inconsistent findings in the

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literature this conceptualization has been challenged with respect to exact direction of the correlation. Jin (1992) suggested that the negative correlation between initial value and change value found by Wilder (1967) may be a result of the spurious $X(Y-X)$ effect contained in this correlation. Therefore, he recommended calculating the parameter of a structural relationship (i.e., $\beta$-value) between initial value and final value as an index for the LIV. In his reformulation of the classic LIV he stated that within a certain medium range, the organism's reactivity to stimulation increases with the height of the initial value but that a tendency to reversed responses can be seen with the initial value reaching its upper extremity.

Considering this, possible applications of pupillometry in experimental designs might be limited, especially when visual stimuli are presented which is common in studies on emotional modulation of pain (e.g., Arnold et al., 2008; de Wied and Verbaten, 2001; Kenntner-Mabiala and Pauli, 2005; Kenntner-Mabiala et al., 2007; Meagher et al., 2001). When different pictures are displayed on a screen in a dimly lit laboratory (which is usually the case when infrared pupillometry is done), picture presentation itself can change the illumination of the surroundings. Thus, the pictures' luminance might differentially influence initial pupil size. This may interfere with pain-evoked pupil dilation or it may need to be addressed in the analysis of pupillometric data.

Recently the influence of emotionally arousing pictures on pupil dilation was established (Bradley et al., 2008; Gerdes and Alpers, 2006). Both studies found that viewing arousing pictures leads to increased pupil dilation; Bradeley et al. (2008) demonstrated that pupil dilation covaries with skin conductance. Thus, it seems promising that the differential effect of pain intensity may be still observable under different levels of picture luminance.

If pupillometry proved to be an appropriate measure of autonomic pain under different luminance conditions, this may contribute to a revival of pupillometry in pain research and go hand in hand with the increasing number of modern infrared eye-tracking laboratories available in more and more laboratories (Van Gompel et al., 2007). Thus, the aim of the present study was to investigate whether pupil dilation can be used as an index of pain intensity under different screen illuminations resulting from picture luminance (low, moderate, high). We expected that, albeit measured under changing luminance conditions, different levels of pressure pain intensity would still have a distinct effect on the pupil, with higher pressure leading to greater pupil dilation compared to lower pressure.

## 1. Methods

### 1.1. Participants

Because gender differences can be observed in pupil reactions to painful stimulation (Ellermeier and Westphal, 1995; Oka et al., 2000), we only studied female participants to reduce variance. Twenty female students (between 20 and 28 years of age; $M=23.55$, SD = 2.04) without neurological or psychiatric disorder and without chronic pain participated in the experiment.

### 1.2. Visual background

In order to test the relevant range of luminance we selected three colour pictures (7150, 5740, 7491) depicting emotionally neutral objects from the International Affective Picture System (IAPS, Center for the Study of Emotion and Attention, 1995). The pictures were chosen because they differed markedly in mean luminance. The luminance values were derived from the histogram/luminance function of Adobe Photoshop™ in RGB-mode (mean luminance in RGB-mode ranges from 0 for completely black pictures to 255 for completely white pictures). Because semantic picture content was not an issue in this experiment all pictures were filtered by means of the pixelate mosaic filter of Adobe Photoshop™ so that content could not be identified. After filtering, the pictures had mean luminance values of $M=39.82$, $M=102.31$, and $M=150.21$. The edited pictures were presented with a scaling factor of .5; resulting in a size of 28.5 × 20.5 cm, i.e., a horizontal visual angle of 31.8° and a vertical visual angle of 23.2° when viewed through our eye-tracking apparatus (50 cm distance from the screen). Background colour of the screen was moderate to light grey (mean luminance in Adobe Photoshop™ RGB RGB-mode: $M=130$).

The dimly lit laboratory was illuminated by two indirect light sources on the left and the right side of the screen. Thus laboratory illumination at the site of participants' recorded (right) eye was about 37 lx excluding screen illumination.

### 1.3. Pressure pain induction

Painful stimulation was delivered with an electronically driven device built according to the model used in the study of Ellermeier and Westphal (1995). Triggered by a computer program, a lever lowered a flat-tipped stylus with a diameter of 3 mm on the middle phalanx of a finger. The site of the pressure stimulation was changed after each trial in order to prevent repetition effects by sensitization (Pauli et al., 1999). The sequence of measurement sites was held constant (ring finger, middle finger, or index finger of one, then of the other hand). The weight of the lever which is adjustable between 0 and 970 g (resulting in a constant pressure between 0 and 1339 kPa) was set at 800 g (1109.5 kPa) for the low and 950 g (1317.6 kPa) for the high intensity pain stimulus according to data reported by Ellermeier and Westphal (1995).

Pressure stimulation was applied for 20 s in each trial, again based on the Ellermeier and Westphal (1995) design.

### 1.4. Pupil size recording

Participants were seated 50 cm in front of a computer screen and pupil size was continuously recorded from the right eye with an infrared system (iView X, SensoMotoric Instruments, Teltow, Germany) with a temporal resolution of 238 Hz and a spatial resolution of approximately .5–1° (for a detailed description see Alpers, 2008; Gerdes et al., 2008). The integrated forehead and chin rest minimized head movements. Prior to the experimental task, the system was calibrated individually.

### 1.5. Experimental design and procedure

A 2 × 3 factorial design was realized with intensity of the pressure pain stimulus and luminance of the visual background as within-subject factors.

At the beginning of the experimental session, participants signed informed consent and provided demographic information. Subsequently, the algometer was calibrated to the individual finger diameter, and the experimenter marked with a felt-tip pen the positions for the pressure applications on the dorsal sides of the middle phalanges of the index, the middle, and the ring fingers of both hands. Participants were then seated in front of the screen, the head fixed at the forehead and chin rest. After participants read the instructions on the screen, the eye-tracking system was calibrated. The experiment consisted of two blocks: The low pressure weight being applied in one and the high pressure weight in the other block. Every block consisted of six trials. In each trial one of the three different pictures was presented together with a pressure stimulus of defined intensity. Three counterbalanced sequences of picture presentation (each comprising twelve picture presentations) were arranged so that, across participants, each of the three pictures was presented in counterbalanced combinations with each finger and pressure intensity. Every trial started with the presentation of a fixation cross in the centre of a grey screen. After participants fixated the cross for 1.5 s, pupil recording started and a picture was

**Table 1**
Mean baseline pupil sizes in mm with standard deviations differentiated for picture luminance

| Picture luminance | | |
|---|---|---|
| Low | Moderate | High |
| 4.90±.66 | 4.55±.56 | 3.81±.39 |

presented for a total of 45 s together with the fixation cross. Participants were instructed to gaze at the fixation cross for the whole period of picture presentation in order to control for changes in pupil size evoked by eye movements. The first 25 s of picture presentation served as an adaptation phase for the pupil and as a baseline period. Pressure stimulation started after this adaptation phase (i.e., 25 s after picture onset) and stopped with picture offset (i.e., after a total pressure duration of 20 s). Immediately after picture and pressure stimulus offset, participants rated pain intensity on a scale ranging from 0 to 10 with verbal anchors for 0 (no sensation), 4 (just noticeable pain), and 10 (the most intense pain I can imagine).

### 1.6. Data pre-processing and statistical analyses

Blinks (i.e., zero values in the data set) were removed from the pupil data by omitting the corresponding values. For each participant, a mean value for every trial was calculated, and the respective trial was subsequently screened for outliers. According to typical experimental procedures pupil values larger or smaller than $M \pm 3 * SD$ were considered artefacts caused by reflections from tear fluid or pupil occlusion and omitted from further analyses.

Continuously recorded pupil data (238 Hz sampling rate) were reduced offline by building epochs of 1 s duration and averaging the sampling points for each one of these epochs. If more than half of the data points within one epoch were missing because of blinks or artefacts, this epoch was excluded from further analyses. Thereafter, pupil size measurements were transformed from pixel to mm (based on a measurement of a dummy pupil of defined size in the same setup). Baseline pupil size was defined as the mean pupil size in the 1 s epoch right before pain onset. This baseline was subtracted from the average pupil size values of every epoch following pressure onset. The statistical evaluation was restricted to the epoch in which pupil size turned out to be maximal (2nd epoch after pressure onset; i.e., the peak) and to the time interval comprising the last 10 epochs before pain offset (i.e., the painful period). We chose the latter time interval for the painful period according to Ellermeier and Westphal (1995), who demonstrated that the sensation of pressure pain takes time to arise. We included the peak value in our analysis to test whether this measure is an index for pain intensity in a tonic pressure model and whether differential amplitudes can be observed as reported previously (Chapman et al., 1999).

Pain ratings for high and low pressure intensities were evaluated statistically using a paired *t*-test. Pain-evoked pupil responses and baseline values were statistically evaluated by repeated-measures ANOVAs with the factors pressure intensity (high, low) and picture luminance (low, moderate, high). Greenhouse–Geisser correction was applied but original degrees of freedom are reported. Significant effects were followed up by comparisons of means using the Bonferroni procedure. The significance level was set at 5% (two-tailed) for all analyses. Pupil data were tested for initial-value dependency by calculating two different parameters. First, following Wilder's (1967) conceptualization of the LIV, we calculated the correlation between baseline pupil size and pupil dilation for each participant, *z*-transformed the correlation coefficients (to account for the fact that Pearson's *r* is not normally distributed), and tested the *z*-values against zero performing a *t*-test. Second, to account for Jin's (1992) re-conceptualization of the LIV, we calculated the $\beta$-value to estimate the structural relationship between initial value and final value for each participant, and tested the resulting values against unity.

To determine the relationship between mean pain ratings and mean pupil responses, we calculated the correlation between these two variables across all participants. In addition, we computed the within-subject correlation coefficients, which were subsequently *z*-transformed and tested against zero. This method has been applied to determine the relationship of negative mood states and physiology (Alpers and Sell, 2008), pain intensity (Vendrig and Lousberg, 1997) and other self-report measures (see Alpers and Tuschen-Caffier, 2001).

## 2. Results

### 2.1. Self-reported pain ratings

The mean self-report pain ratings differed significantly for high and low pressure intensity, $t = -5.69$, $p < .001$, with higher pain ratings for high ($M = 6.97$, SD = 1.09) than for low pressure stimuli ($M = 5.68$, SD = .84).

### 2.2. Baseline values pupil size

A repeated-measures ANOVA conducted for the mean baseline pupil size revealed a significant effect for picture luminance, $F(2,38) = 117.60$, $p < .001$, but no significant effect for pressure intensity of the pain that was applied later, $F(1,19) = .72$, $p = .408$, and no significant interaction between pressure intensity and picture luminance, $F(2,38) = .28$, $p = .711$. Follow-up tests revealed that the three baseline pupil size values obtained for each luminance level (see Table 1) differed significantly from each other (all $p < .001$).

### 2.3. Pupil response to pain

Fig. 1 depicts the course of the pupil dilation response from pressure onset until pressure offset for each participant averaged across conditions. Pupil dilation was maximal 2 s after pressure onset, but substantial individual differences in the pupil dilation response can be observed.

#### 2.3.1. Peak dilation

An ANOVA conducted for the mean peak dilation revealed no effect for pressure intensity, $F(1,19) = 1.08$, $p = .311$, no effect of picture luminance, $F(2,38) = 1.39$, $p = .260$ and no significant interaction between the two factors, $F(2,38) = .28$, $p = .719$. This means that the pupil dilation maximum observed 2 s after pressure pain onset is not specific for pain intensity.

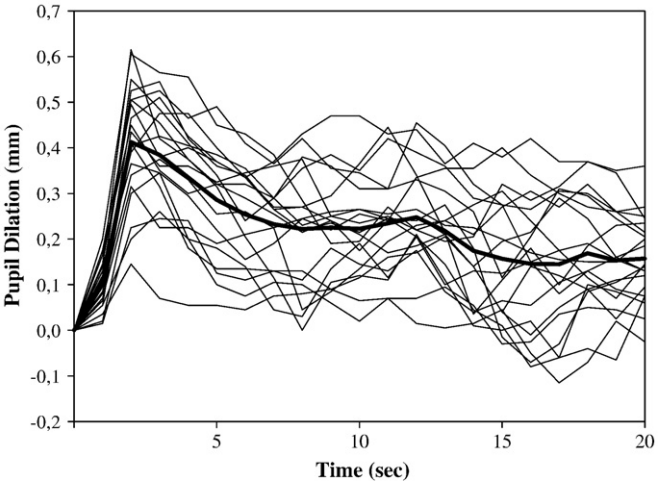


**Fig. 1.** Course of the pupil dilation response during pressure application for each participant averaged across conditions. The thickest line represents the group average.

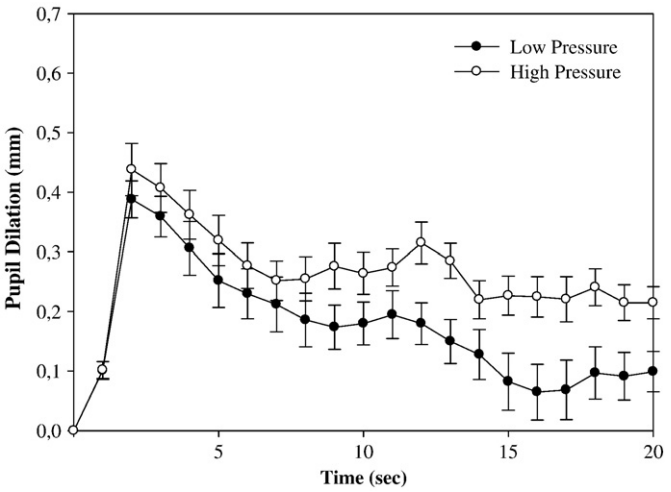


**Fig. 2.** Course of the pupil dilation response from pressure onset until pressure offset differentiated for high and low pressure pain stimuli. Each error bar indicates the range of one standard error.

*2.3.2. Painful period*

After pressure pain developed, 10 s after pressure onset pupil size differed for high and low painful stimulation with a pupil dilation of $M$=.12 mm (SD=.17 mm) for the low pressure intensity and of $M$=.24 mm (SD=.12 mm) for the high pressure intensity. The pupil response for high and low pressure intensities is displayed in Fig. 2. A repeated-measures ANOVA conducted for the mean pupil dilation values of the painful period revealed a significant effect for pressure intensity, $F(1,19)=8.03$, $p=.011$, and a small but non-significant effect for picture luminance, $F(2,38)=2.56$, $p=.093$. There was no significant interaction between pressure intensity and picture luminance, $F(2,38)=.36$, $p=.674$.

*2.4. Controlling for initial values*

Pupil data were carefully inspected for the impact of initial values on pupil dilation response (LIV). The correlation coefficients between initial value and mean dilation value during the painful period for each participant (LIV according to Wilder, 1967) did not significantly differ from zero ($t=-1.12$, $p=.277$). In contrast, the $\beta$-value in the painful period was different from unity ($\beta=1.14$, $t=2.13$, $p=.047$) indicating initial-value dependency according to Jin (1992).

In order to statistically control for the detected initial-value dependency, pupil dilation was expressed as a proportion of baseline pupil size. This procedure attenuates the proportion of dilation which is due to higher initial values and has already been used in other studies to control for initial-value dependency (e.g., van Gerven et al., 2004).

We ran the analysis for the corrected pupil size data during the painful period but the pattern of results remained the same. We found a significant effect for pressure intensity, $F(1,19)=8.06$, $p=.011$, no significant effect for picture luminance, $F(2,38)=1.05$, $p=.356$, and no significant interaction, $F(2,38)=.23$, $p=.753$.

*2.5. Correlation between pain ratings and pupil responses*

The correlation coefficient between pain ratings and pupil responses across participants was non-significant ($r=-.127$, $p=.592$). In contrast, averaging the $r$ to $z$-transformed correlation coefficients obtained for each participant revealed a mean $z$-value of $M$=.21 (SD=.48) which is a marginally significant difference compared to zero, $t=2.01$, $p=.059$, and corresponds to a mean correlation coefficient of $r=.21$.

## 3. Discussion

The aim of the present study was to investigate if pain-evoked pupil dilation may be useful as an objective index of pain intensity despite of variable luminance conditions in a typical pupillometry setup. Variations in luminance conditions resulted from the presentation of three pictures which differed in luminance. As expected, these pictures produced significantly different baseline pupil size values.

When pressure was applied with an algometer we found comparable pupil dilation under all three luminance conditions. Pupil dilation was maximal 2 s after pressure onset, but the average difference between baseline and peak amplitude of pupil dilation did not differ for the two pressure intensities. Thus, this peak dilation seems to be an unspecific response to the stimulation in our paradigm. Other pain induction methods may yield different results. For example, Chapman et al. (1999) who used brief noxious stimuli found that the peak amplitude of the initial pupil dilation varied with pain intensity. Chapman et al. (1999) used phasic noxious stimuli which result in different pain intensity immediately. Painfulness of tonic noxious pressure stimuli as the ones we presented seem to take some time to emerge (also see Ellermeier and Westphal, 1995). Peak dilation in tonic pressure pain models might thus be related to the initial sensory input (tactile stimulation) the intensity of which might not be differentiable at such an early point in time, or it may respond to other aspects such as the cognitive anticipation of impending pain (see Bitsios et al., 2004). Further research is needed to directly compare the different pain models.

In contrast to the results for peak pupil dilation, the average difference between baseline and the average pupil dilation in the painful period (20 s after pressure onset) differed significantly for the two pressure intensity levels. No initial-value dependency could be detected for the average pupil dilation in the painful period using Wilder's (1967) index for LIV. The estimated structural relation between initial and final value following Jin's (1992) considerations indicated initial-value dependency. According to Jin (1992) this may be an example of a correlation between initial value and change value which contains the spurious $X(Y-X)$ effect and therefore tends to become a negative value. Because the resulting $\beta$-values were significantly greater than unity, positive initial-value dependency can be assumed (i.e., the higher the baseline pupil size, the greater the dilation response in the painful period). To control for initial-value dependency statistically had no influence on the main effect for pressure intensity. Moreover, the non-significant findings for the factor picture luminance as well as for the interaction between the factors pressure intensity and picture luminance also remained unaffected. These data suggest that pupil dilation may serve as an autonomic index of pain in spite of varying luminance conditions. Nevertheless, care should be taken when pupillometry is used in experiments where picture stimuli are used. Pictures should be balanced for luminance and pupil dilation data should be closely inspected and, if necessary, corrected for initial-value dependency.

Our data also demonstrates that the extent of pain-evoked pupil dilation is subject to substantial individual variation, and self-report of pain is also difficult to compare across participants. Thus, we found no significant correlation between pain ratings and the pain-evoked pupil reaction across participants. However, within participants, pain-evoked pupil reaction is quite a good indicator of subjective pain.

Although most participants showed responses in the expected direction (twelve participants had correlation coefficients greater than $r=.15$, resulting in a mean correlation coefficient of $r=.49$), some had the opposite pattern (three participants with correlation coefficients smaller than $r=-.15$, resulting in a mean correlation coefficient of $r=-.36$). Five more participants showed correlation coefficients around zero. The intraindividual correlation may have been somewhat underestimated because participants were asked to only judge the sensory

component of the painful stimuli. However, the experience of pain comprises not only sensory but also affective pain components (Fernandez and Turk, 1992) and pupil dilation, like other autonomic responses (e.g., heart rate and skin conductance), is markedly influenced by the extent of emotional arousal elicited by a stimulus (Bradley et al., 2008; Gerdes and Alpers, 2006). The association between affective pain components and autonomic responses seems to be even stronger than the association between the sensory components and autonomic responses (Rainville et al., 1999; Rainville et al., 2005). In future studies, sensory as well as affective pain ratings should be collected.

In conclusion, pain-evoked pupil dilation can be measured under varying luminance conditions. Thus, pupillometry seems to be a suitable instrument to measure pain-related autonomic activation in experimental designs even when visual stimuli with varying levels of luminance are presented.

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