Behavioural Brain Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Uncertainty about the intensity of impending pain increases ensuing pain responses in congenital blindness

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ARTICLE INFO

Keywords:
Pain
Congenital blindness
Anxiety
Anticipation
Experimental pain

ABSTRACT

We have shown that congenitally blind individuals are more sensitive to painful heat compared to their sighted counterparts. This hypersensitivity might be at least partly mediated by psychological and cognitive factors, such as pain expectation and anxiety. Here we investigate whether uncertainty about the intensity of a pending painful stimulus affects pain differently in congenitally blind and sighted control subjects. We measured pain and anxiety in a group of 11 congenitally blind and 11 age- and sex-matched normal sighted control participants. Painful stimuli were delivered under two psychological conditions, whereby participants were either certain or uncertain about the intensity of a pending noxious stimuli. Although both blind and sighted participants had increased anxiety ratings in the uncertain condition, pain ratings increased only in the congenitally blind participants. Our data therefore indicate that increased anxiety levels have a stronger influence on the perceived pain intensity in blind individuals, possibly because they allocate greater attention to signals of external threat.

1. Introduction

Acute pain has an important alarm function that protects us from bodily harm by inducing escape and avoidance behavior from tissue damaging stimuli [1]. Similarly, vision is important for detecting and averting possible external threats. In line with this, there is an increasing amount of data supporting the role of vision in pain perception [55]. Indeed, long-term visual deprivation in normally sighted individuals can increase pain perception [2], while seeing the stimulated limb may reduce pain ratings [3–5].

We have previously shown that congenitally blind (CB) subjects are hypersensitive to painful stimuli and have an enhanced heat discrimination compared to their sighted peers [6]. In addition, CB also react faster to C-fibre mediated sensations, suggesting a neurobiological component to their hyperalgesia [7]. We also showed that CB are more attentive to signals of external threat, raising the possibility that cognitive and/or affective processes such as uncertainty or anxiety might also play a role in the hypersensitivity to pain in congenital blindness.

Studies in normally sighted (NS) individuals have shown that pain perception is strongly influenced by the psychological state of an individual, and that anxiety increases ratings of experimentally induced pain [8–11]. According to the hypersensitivity to threat hypothesis, the lack of informative vision increases anxiety levels in congenitally blind individuals, thereby causing an overall hypersensitivity to threatening stimuli such as pain [12,6,13]. The aim of the current study was therefore to test the hypothesis that compared to matched sighted controls, congenitally blind individuals experience more anxiety in response to a strong impeding painful stimulus, and that this will cause higher pain ratings. We used a previously validated experimental pain paradigm that induces anxiety by creating uncertain expectations regarding the intensity of a pending noxious stimuli [8,9,11,14–16]. If a heightened state of anxiety is indeed the main driver behind the hypersensitivity to pain in congenitally blind subjects, we expect that they will report increased pain and anxiety ratings compared to a matched control group of sighted individuals.

2. Method

2.1. Participants

Participants were recruited from our database of congenitally blind participants or by advertisement. In total, we included 11 congenitally

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https://doi.org/10.1016/j.bbr.2017.12.005
Received 7 July 2017; Received in revised form 4 October 2017; Accepted 5 December 2017

blind (CB: 4F; mean age 34.4 ± 6.4 years, range 23–65) and 11 age and sex-matched normal-sighted (NS: 4F; mean age 34.3 ± 6.9: range 23–61) control subjects. Sample size was based upon previous studies from our laboratory on pain and temperature perception in blindness [42–44]. Blindness of peripheral origin within the first year of life was the inclusion criteria for the congenitally blind subjects. Demographic details on the blind participants are listed in Supplementary Table 1. For all participants, inclusion criteria were being in good health with no known self-reported neurological or psychiatric disorders. All participants gave informed consent and the ethics committee of the city of Copenhagen and Frederiksberg (Denmark) approved the study protocol.

2.2. Equipment

We used a CO_2 laser stimulator device with a circular spot diameter of 6 mm (LSD, SIFEC, Ferrières, Belgium) to apply highly accurate and contactless heat stimuli to the skin. Blind participants received a detailed verbal description of the equipment and they were allowed to inspect it haptically. A contactless temperature measuring unit provided online monitoring of the target skin temperature to control laser power output in a closed-loop control system. This ensured that the skin was brought to and maintained at the correct target temperature. As the device is contactless, only the thinly myelinated A∂- and unmyelinated C-fibers were activated without co-activation of the large myelinated Aß fibers [17].

2.3. Procedure

Participants were recruited between December 2013 and May 2015 and participated in one session lasting 2–2.5 h. We applied 3-s lasting laser stimuli to the dorsal part of the dominant hand, 5 s after a verbal cue. After each stimulus, the laser beam was moved to another spot within a 3 × 5 cm matrix to avoid habituation. Each spot was placed 1 cm apart from the other and was stimulated two times during each trial and up to three times during the familiarization procedure. The interstimulus interval was approximately 15–30 s, i.e. the time it took for the participants to rate the pain, reposition the laser head and then restart the next laser pulse. Participants rated pain intensity and pain unpleasantness on an 11-point numerical rating scale, with “0” indicating no pain or not unpleasant and “10” the highest pain intensity or unpleasantness that they were willing to tolerate in the experimental setting. The standard instructions by [18] were used to explain the difference between pain intensity and pain unpleasantness [18]. Sighted participants were blindfolded during all testing but did see the laser device before the testing started. Since there is a large inter-individual variability in pain thresholds, we adjusted as follows the temperatures for both the low pain and high pain stimulus for each participant. First, participants were familiarized with the sensation evoked by the laser and trained in using the VAS rating scales. Then, each participant received four stimulations of each of the following temperatures in a randomized order: 41°, 43°, 45°, 47°, 49°, 51° and 53° C. Following each stimulus, participants rated their perceived pain intensity. For each temperature, we calculated the average pain rating. The low pain temperature chosen for each subject corresponded to his/her pain intensity rating of 3, while the high pain temperature corresponded to a pain intensity rating of around 7 on the 11-point rating scale. To avoid burn injury, no participant received a stimulus temperature above 53 °C even if they had not rated the 53 °C temperature as “7” or more.

Participants received a total of 60 stimuli, 30 in each condition; they rated pain intensity and unpleasantness directly after each stimulus. In the certain condition, participants received 30 consecutive stimuli of the same low intensity temperature; they were told that they would only receive mildly painful, low temperature stimuli. In the uncertain condition, participants were told that they would receive a range of pain stimuli, going from mildly to highly painful, and that the order and intensity of the stimuli were chosen randomly. The participants then received 30 consecutive stimuli consisting of 24 low and 6 high pain intensity stimuli. The order of the six high temperature stimuli was pseudo-randomized such that participants received one within each block of five stimuli. The order of the certain and uncertain conditions was randomized across participants.

Experienced anxiety in each condition was rated on an 11-point numerical rating scale. Here, “0” was defined as no anxiety and “10” as highest level of anxiety endurable in this setting. The anxiety ratings were done only once in each condition, after the 25th stimulus, as conscious self-assessment of both pain sensation and anxiety can lead to a hypothesis-driven bias [19].

2.4. Questionnaires

At the beginning of the session, participants filled out the STAI-Y questionnaire to measure state (STAI-1) and trait (STAI-2) anxiety [20]. Questions regarding eating and sleeping habits and physical activity levels were added to mask the focus on anxiety and thus reduce hypothesis-driven artifacts [19]. After the session, all participants filled out the Pain Anxiety Symptom Scale (PASS) [21] and the Pain Vigilance and Awareness Questionnaire (PVAQ), adapted for a non-clinical population. These questionnaires measure individual reactions to painful stimuli encountered in everyday life [22]. Specifically, the PASS consists of the subscales “Physiological Anxiety” (PASS_PA), “Cognitive Anxiety” (PASS_CA), “Fear” (PASS_F) and “Escape/Avoidance” (PASS_EA). The PVAQ consists of the subscales “Intrusion” (PVAQ_I), “Monitoring” (PVAQ_M) and “Attention to changes in pain” (PVAQ_APC). The items of the two questionnaires were all read to the blind participants by the same experimenter.

2.5. Statistical analysis

We used Levene’s and Shapiro-Wilk tests to check for equal of variances and normality of the distributions of the collected data. We applied an unpaired student *T*-test for between-group comparisons of normally distributed data, and a paired *T*-test for within-group comparisons (high vs. low anxiety). We ran Mann-Whitney or Wilcoxon tests for non-normally distributed data. We used Kendall’s tau to test for correlations on the whole sample. We also calculated Cohen’s d to estimate for the first time the magnitude of the observed effect for pain intensity measurements following stimulation by a CO_2 laser device.

The statistical analysis of the pain rating data was performed using General Linear Models (GLM) that only included dependent variables and covariates that had passed Levene’s Test. All analyses were performed using raw data and not group differences. Specifically, we ran a GLM multivariate analysis with between group factors experimental group (CB versus NS) and gender (female versus male), and within group factor psychological condition (uncertain, UC, vs. certain, CC). Dependent variables were pain intensity and pain unpleasantness ratings, while STAI-1 and age were used as covariates. Specifically, anxiety VAS ratings and state anxiety scores (STAI-2) did not pass Levene’s test Age was chosen as a covariate since it is known to correlate with perception of temperature; state anxiety is a basal condition that varies across subjects and hence we want to control for it. Here, the between condition comparison took only the values of the low pain temperature ratings into account. Thereafter, we ran a GLM univariate analysis on the high temperature ratings [between factors: group (CB vs. NS) and gender (female vs. male); dependent variable: intensity rating; covariates: STAI-1 and age].

Results of the PASS and PVAQ were explored using a Fisher linear discriminant analysis (FLDA) to search for a discrimination function that could distinguish between CB and NS. Here, variables were entered using the “all-variables together” method, and the goodness of classification analysis was tested using the leave-one-out technique. For all the analyses, we choose $\alpha = 0.05$, using a Bonferroni correction for