Research report

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

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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...
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 CO2 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 Aδ- and unmyelinated C-fibers were activated without co-activation of the large myelinated Aβ 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 blinded 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 procedure. 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.

2.4. 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 CO2 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, 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 α = 0.05, using a Bonferroni correction for
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