EJP
European Journal of Pain

ORIGINAL ARTICLE

Pain hypersensitivity in congenital blindness is associated with faster central processing of C-fibre input

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Funding sources
The work was supported by the Lundbeck, Harland Sanders and Elsass Foundations.

Conflicts of interest
None declared.

Accepted for publication
28 February 2016

doi:10.1002/ejp.876

Abstract

Background: We have recently shown that visual deprivation from birth exacerbates responses to painful thermal stimuli. However, the mechanisms underlying pain hypersensitivity in congenital blindness are unclear.

Methods: To study the contribution of Aδ- and C-fibres in pain perception, we measured thresholds and response times to selective C- and Aδ-fibre activation in congenitally blind, late blind and normally sighted participants. Ultrafast constant-temperature heat pulses were delivered to the hand with a CO2 laser using an interleaved adaptive double staircase procedure. Participants were instructed to respond as quickly as possible when detecting a laser-induced sensation. We used a 650 ms cut-off criterion to distinguish fast Aδ- from slow C-fibre–mediated sensations.

Results: Congenitally blind participants showed significantly faster reaction times to C- but not to Aδ-fibre–mediated sensations. In contrast, thresholds for Aδ- and C-fibre stimulation did not differ between groups. Late blind individuals did not differ from sighted controls in any aspect. A follow-up experiment using only suprathreshold stimuli for Aδ- and C-fibre activation confirmed these findings and further showed that congenitally blind individuals detected significantly more C-fibre–mediated stimuli than sighted controls. A decomposition of the reaction times analysis indicated that the faster response times in the congenitally blind are due to more efficient central processing of C-fibre–mediated sensations.

Conclusion: The increased sensitivity to painful thermal stimulation in congenital blindness may be due to more efficient central processing of C-fibre–mediated input, which may help to avoid impending dangerous encounters with stimuli that threaten the bodily integrity.

What does this study add?:

- Hypersensitivity to heat pain in congenital blindness is associated with faster responses to C-fibre activation, likely caused by more efficient central processing of C-fibre -mediated input.

1. Introduction

Vision is important for the detection, identification and localization of threats that may imperil the bodily integrity (Combe and Fujii, 2011). Similarly, the key biological function of acute pain is to trigger escape and protective behaviours to avoid physical

CE: Malarvizhi | PE: Sudhakar S
Dispatch: 12.3.16 | No. of pages: 11
WILEY
EJP | 876 | Manuscript No.
Journal Code

harm. Several studies have shown that the lack of informative vision exacerbates the experience of pain (Zubek et al., 1964; Longo et al., 2009; Master et al., 2009; Mancini et al., 2011; Haggard et al., 2013; Valentini et al., 2015), suggesting an interaction between vision and pain processing (Torta et al., 2015). We recently showed that congenitally blind, but not late blind, individuals have lower heat pain and cold pain thresholds and respond more strongly to suprathreshold noxious heat stimuli (Slimani et al., 2013, 2014). However, the mechanisms underlying this hypersensitivity to pain remain unclear. One hypothesis that has been put forward is that this hypersensitivity is caused by a generally increased selective attention to threatening stimuli (Mancini, 2013; Slimani et al., 2013, 2014). Indeed, congenitally blind individuals are more attentive to painful encounters in daily life (Slimani et al., 2013, 2014), have augmented responses to auditory signalling of threats (Klinge et al., 2010) and are better at identifying odours of negative emotional valence, such as fear and disgust (Iversen et al., 2015).

In order to probe into the physiological mechanisms underlying the increased pain hypersensitivity in congenital blindness, we studied central processing of Aδ- and C-fibre–mediated inputs by measuring reaction times (RTs) and detection frequency to brief nociceptive radiant heat stimuli. We reasoned that if pain hypersensitivity is due to increased vigilance towards stimuli that threaten the bodily integrity, congenitally blind subjects should be faster in responding to and detect more stimuli within the nociceptive range. In sharp contrast, we did not expect that late blind subjects would differ in their response times since we have shown that their response pattern to painful stimuli is not different from that of sighted individuals (Slimani et al., 2014). To test this hypothesis, we used a CO_2 laser to present brief heat stimuli to the skin, thereby taking advantage of the anatomo-physiological organization of the nociceptive system to disentangle the respective contributions of the thinly myelinated Aδ-fibres and the unmyelinated C-fibres. Due to the difference in conduction velocity of these two sets of fibres, pain is often referred to as a double alarm system, in which the first and second alarm are mediated by the fast conducting Aδ-fibres and the slow conducting C-fibres, respectively (Lewis and Pochin, 1937; Plaghki et al., 2010). Consequently, RTs to ultrafast, highly synchronized nociceptive radiant heat are distributed in a bimodal manner, whereby the first part of the distribution with relatively short RTs represent responses to the activation of the Aδ-fibres, whereas the second part of the distribution is caused by responses to the slower conducting C-fibres (Churyukanov et al., 2012).

2. Methods

2.1 Participants

We recruited 14 congenitally blind (5F; mean age: 38.6 ± 13.2 years, range: 20–61), 8 late blind (5F; mean age: 46.9 ± 12.8 years, range: 25–64) and 14 normally sighted (4F; mean age: 40.1 ± 15.4 years, range: 20–65) participants. All participants were in good health and without known neurological or psychiatric disorders. All blind participants suffered from blindness of peripheral origin, starting in the first year of life for congenitally blind subjects, or after 6 years for late blind individuals (Table 1). The ethics committee for the city of Copenhagen and Frederiksberg had approved the experimental procedures and all participants gave informed consent.

2.2 Stimuli

Thermal stimuli were delivered to the dorsum of the nondominant hand using a CO_2 laser stimulator device with a spot diameter of 6 mm (LSD; SIFEC, Ferrières, Belgium). Prior to testing, blind subjects were allowed to explore the equipment by touch and were given a detailed verbal description of it. A closed-loop control of laser power with online monitoring of target skin temperature was used to generate heat stimuli. This allowed highly accurate and contactless cutaneous stimulation of Aδ- and C-fibres without co-activation of Aβ-fibres (Churyukanov et al., 2012). An integrated contactless skin temperature measurement unit, built-in in the stimulator head, allowed skin temperature measurement at a sampling rate of 0.5 kHz and stimulus adjustment in real time, resulting in highly controlled stimuli.

2.3 Procedures

2.3.1 Aδ- and C-fibre detection thresholds

Each trial started by the measurement of the baseline skin temperature (T_0) during 1 s prior to stimulation. The skin was then preheated at a conditioning temperature (T_1) to examine whether the skin temperature immediately preceding the stimulus has an influence on Aδ- and C-fibre thresholds (LaMotte and Campbell, 1978; Darian-Smith et al., 1979a,b; Johnson et al., 1979; Hallin et al., 1982; Peng et al.,

Table 1 Demographics of the blind participants.

			Blindness		
ID	Age	Gender	Onset	Aetiology	Residual vision
CB1	50	M	0	Retinopathy of prematurity	–
CB2	24	F	0	Retinopathy of prematurity	–
CB3	26	M	0	Retinopathy of prematurity	–
CB4	61	F	0	Retinopathy of prematurity	–
CB5	49	M	0	Retinopathy of prematurity	–
CB6	28	F	0	Retinopathy of prematurity	–
CB7	39	M	0	Retinopathy of prematurity	Bright light
CB8	59	F	0	Retinopathy of prematurity	–
CB9	21	M	0	Leber's amaurosis	–
CB10	37	M	0	Retinopathy of prematurity	–
CB11	42	F	0	Retinopathy of prematurity	Bright light, shapes
CB12	43	M	0	Retinopathy of prematurity	–
CB13	20	M	0	Retinopathy of prematurity	–
CB14	42	M	1	Meningitis	Bright light, shapes
LB1	43	F	6	Retinopathy of prematurity	–
LB2	36	F	8	Glaucoma	–
LB3	44	M	9	Retinitis pigmentosa	Bright light
LB4	56	M	10	Optic nerves sectioned by a bullet	–
LB5	25	F	19	Taxoplasmosis	–
LB6	59	F	22	Iris infection	–
LB7	48	F	32	Retinopathy of prematurity	Bright light
LB8	64	M	46	Retinitis pigmentosa	–

NS, normally sighted; CB, congenitally blind; LB, late blind.

2003; Plaghki et al., 2010; Churyukanov et al., 2012). The skin temperature was raised to either 32 or 35 °C using a 1-s heating ramp and maintained steady for 2 s. Thereafter, an additional heat pulse was delivered to bring the skin to target temperature (T_2), using a steep heat ramp of 10 ms; target temperature was maintained (Lacouture and Cousineau, 2008) for 90 ms. Participants were instructed to press as quickly as possible upon detecting T_2 (Fig. 1A). The T_2 temperatures ranged between 36 and 60 °C following an adaptive up/down staircase algorithm based on RTs. This is justified by the fact that the nerve conduction velocity of unmyelinated C-fibres is much slower than that of myelinated Aδ-fibres (±1 m/s vs. ±10 m/s) (Bromm and Treede, 1983; Bjerring and Arendt-Nielsen, 1988; Mouraux et al., 2003; Mouraux and Plaghki, 2007). Opsommer et al. (Opsommer et al., 1999) showed that the time interval between the two peaks of the bimodal distribution of reaction times increases with peripheral distance. We chose a criterion of 650 ms to discriminate between C- and Aδ-fibre responses which was based on (1) the peripheral conduction distance of afferent input originating from the hand and (2) the distribution of reaction times to laser stimuli after blockade of the myelinated fibres (Bromm et al., 1983; Nahra and Plaghki, 2003). The C-fibre staircase algorithm was therefore based on a detection/no detection criterion, whereas the Aδ-fibre staircase was based on RTs (Churyukanov et al., 2012).

We always assessed the C-fibre detection threshold first to prevent that the lower intensity stimuli might be masked by the higher intensity stimuli. To reduce skin habituation, a 10-s interstimulus interval was used and successive stimuli were delivered 2 cm apart from each other, following a 5 × 5 matrix. To avoid response bias by anticipation, staircases corresponding to the two conditioning temperatures were interleaved. Threshold values were then obtained by averaging the target stimulus temperatures T_2 at which the six staircase reversals had occurred within a range of 2 °C (Fig. 1B). We also calculated RT frequency distributions.

2.3.2 Reaction times

Since the procedure for threshold assessments described above only requires a relatively low number of trials (on average 44 ± 13 trials per subject), we performed a second series of experiments with a much high number of trials in order to obtain more robust estimates of RT frequency distributions. Thereto, we recruited five congenitally blind (2 F; mean age: 41.6 ± 10.2 years, range: 30–54) and five normally sighted (2 F; mean age: 42.2 ± 11.1 years, range: 26–54) participants. We only used one T_1 temperature (35 °C) since the results of the first experiment showed that baseline temperature has no effect on thresholds. We delivered 300 T_2 stimuli, half of them at 44 °C and the other half at 52 °C. Preliminary tests indicated that the 44 °C stimulus is a clear supraliminal stimulus for C-fibre nociceptor activation with a minimal contamination by Aδ-related responses. In a similar fashion, we chose the

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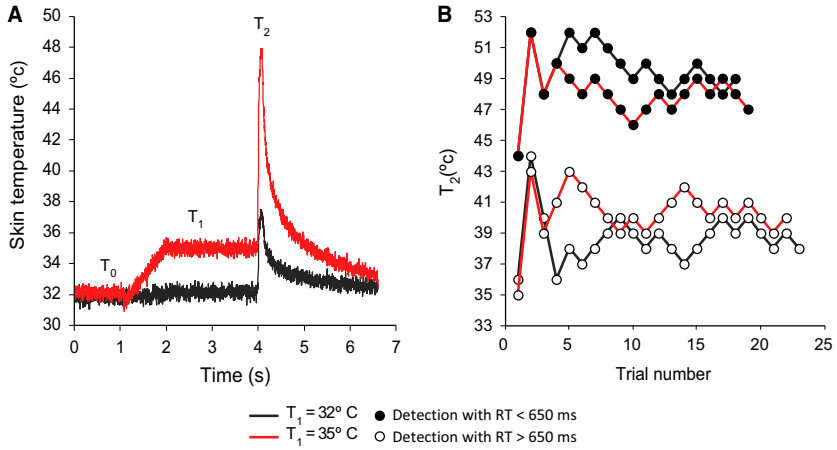

Figure 1 Experimental paradigm. (A) Thermal stimulation profiles. Thermal stimuli were applied to the dorsum of the nondominant hand using a CO_2 laser (beam diameter: 6 mm). The red and blue lines illustrate the real-time recordings of the skin temperature in two trials. After measuring the baseline skin temperature (T_0) for 1 s, the skin was raised to either the 32 or 35 °C skin-conditioning temperatures (T_1) using a 1-s heating ramp and was maintained for 2 s. Thereafter, a 100-ms pulse (10-ms heating ramp and 90-ms plateau) was delivered (T_2). (B) Staircase algorithm. T_2 consisted of varying temperatures that followed an adaptive up/down staircase algorithm. Subjects had to press a response button as quickly as possible when T_2 was perceived. Reaction times (RTs) were used to discriminate between C-fibre–related detections (detections with RTs > 650 ms) and Aδ-fibre–related detections (detections with RTs ≤ 650 ms). C-fibre thresholds were assessed first to avoid effects of habituation and/or sensitization effects that could be induced by high-intensity stimulations. Conditioning temperature staircases were presented in an interleaved fashion to prevent expectation bias. Staircases were stopped after the first six consecutive inversions within a 2 °C range. Thresholds were determined by averaging the temperature values of these six reversals.

52 °C stimuli to obtain clear supraliminal Aδ-fibre–related responses. To reduce the effect of habituation and receptor fatigue or sensitization, we started with the low-intensity stimuli first and moved the laser beam after each trial by 2 cm, following a 5 × 5 matrix, using a 4-s interstimulus interval. Every 25 trials, we introduced a short break to assure maximal attention from the participants.

2.4 Statistical analysis

To assess group differences in Aδ- and C-fibre thresholds and to examine the effect of differences in baseline temperature, we performed a three-way ANOVA using SPSS with 'nociceptor type' (Aδ- or C-fibres) and 'T_1' (32 or 35 °C) as the within-subject factors and 'group' (NS, CB and LB) as the between-subject factor. The analysis of RTs was performed for each subject separately without any *a priori* on the distribution of responses. A kernel smoothing density algorithm was applied to the empirical distribution, followed by a nonlinear regression procedure that fitted a two-term finite mixture of ex-Gaussian probability density functions. This model was chosen over a double Gaussian distribution because it takes into account the asymmetry of the response frequency distributions that is inherent to RT-based experiments (Luce and Green, 1972; Lacouture and Cousineau, 2008; Churyukanov et al., 2012). Furthermore, the model allowed us to decompose RT data into the parameters τ, μ and σ for the two fibre classes, as well as pAδ (Fig. 2). The latter determines the proportion of Aδ-fibre–related responses, whereas the parameter '(1-pAδ)' refers to the proportion of C-fibre–related responses in the distribution. The other parameters fall into the categories central decisional processing and residual latencies (Luce, 1984). The central processing latency, expressed by the parameter 'τ', is defined as the time necessary to compute the sensation and to initiate a motor response (Matzke and Wagenmakers, 2009). It is generally assumed that the central processes constitute the exponential component of the frequency distribution and account for the asymmetry of the RT data (Ratcliff and Van Dongen, 2011). Finally, the residual latencies are expressed by the parameters 'μ' and 'σ' that constitute the average and standard deviation of the Gaussian components of the RT distribution, respectively (Matzke and Wagenmakers, 2009). These residual latencies include (1) the transmission of heat from the cutaneous surface to the transducers, (2) the transduction and action potential generation, (3) the transit time, (4) the conduction and synaptic transmission in the CNS and (5) the initiation of the motor response (Luce, 1984). Assuming that processes 1–4 are similar

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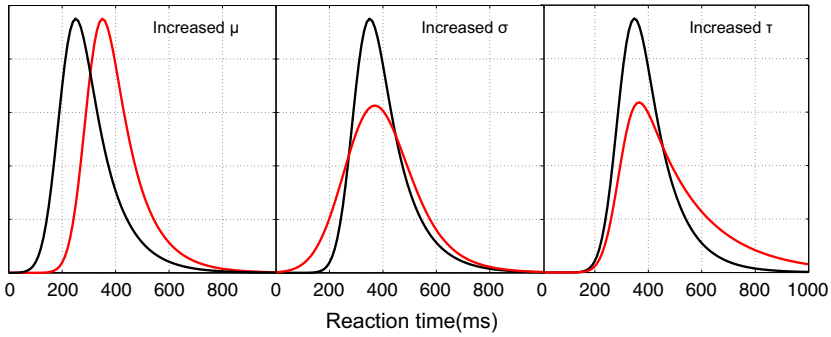

Figure 2 Parameters of the ex-Gaussian probability density function. The parameters 'μ' and 'σ' account for the mean and standard deviation of the function's Gaussian component. The exponential parameter 'τ' is responsible for the skewedness of the function and pertains to the central processing time.

in blind and sighted individuals, between-group differences in μ would translate to a difference in processing the motor response. Importantly, the bimodal ex-Gaussian model avoids the use of an arbitrary separator for the two distributions.

Standard error and confidence intervals of the mean difference between groups in Aδ- and C-fibre–mediated RT peak values of the RT distributions were computed by a nonparametric bootstrap procedure (1000 resamplings with replacement). Groups were considered to have a significant difference in peak values if the 95% bootstrap confidence interval for the difference did not include the value 0. All computations were performed with Matlab Statistical toolbox (Mathworks: http://www.mathworks.com).

3 Results

3.1 Aδ- and C-fibre detection thresholds

Table 2 shows the thresholds of Aδ- (RT ≤ 650 ms) and C-fibre–mediated responses (RT > 650 ms) of the three groups (NS, CB and LB) and for the two skin-conditioning temperatures (T_1 = 32 or 35 °C). The repeated measures ANOVA indicated that there were no significant group differences in Aδ- or C-fibre thresholds ($F = 0.168$, $p = 0.846$). The skin-conditioning temperature T_1 had also no influence on the thresholds ($F = 0.518$, $p = 0.477$). As expected, the ANOVA analysis showed a highly significant main effect of the factor 'nociceptor type' ($F = 434.155$, $p \leq 0.001$), indicating that the Aδ-fibre–mediated threshold (48.8 ± 3.3 °C) was markedly higher than the C-fibre–mediated one (40.0 ± 2.4 °C). No further significant interactions were found. Since T_1 had no influence on the thresholds, we pooled the Aδ- and C-fibre–related responses of the two skin-conditioning temperatures. The average thresholds of the pooled C-fibre–mediated responses were T_2: NS = 40.3 ± 2.1 °C, CB = 39.7 ± 2.4 °C and LB = 40.0 ± 3.2 °C and the thresholds of the pooled Aδ-fibre–mediated responses were T_2: NS = 48.9 ± 3.4 °C, CB = 49.2 ± 3.1 °C and LB = 47.8 ± 3.9 °C.

Table 2 Thresholds of C- and Aδ-fibre–mediated detections using 32 and 35 °C skin-conditioning temperatures (T_1).

	T_1 = 32 °C		T_1 = 35 °C	
Subjects	C-fibre (°C)	Aδ-fibre (°C)	C-fibre (°C)	Aδ-fibre (°C)
NS	40.3 ± 2.2	49.2 ± 3.4	40.3 ± 2.0	48.7 ± 3.5
CB	39.7 ± 2.4	49.3 ± 3.4	39.7 ± 2.5	49.1 ± 2.8
LB	39.9 ± 3.6	47.9 ± 4.0	40.2 ± 3.0	47.7 ± 3.9

NS, normally sighted; CB, congenitally blind; LB, late blind.

3.2 Reaction times

Fig. 3A shows the contour plots of the RT distributions of the first experiment as a function of stimulus strength (T_2). As illustrated, the RTs have a clear bimodal distribution. The first peak corresponds to higher target skin temperatures that triggered short-latency detections compatible with the peripheral conduction velocity of myelinated Aδ-fibres, whereas the second peak corresponds to lower target skin temperatures that triggered long-latency detections compatible with the peripheral conduction velocity of unmyelinated C-fibres (Campbell and LaMotte, 1983; Plaghki et al., 2010; Churyukanov et al., 2012). In comparison with the sighted and the late blind groups, the long-latency RTs of the congenitally blind appear to be globally shifted to the left on the time axis. This is confirmed by the RT distributions to C-fibre–mediated sensations in Fig. 3B. As illustrated, congenitally blind participants responded

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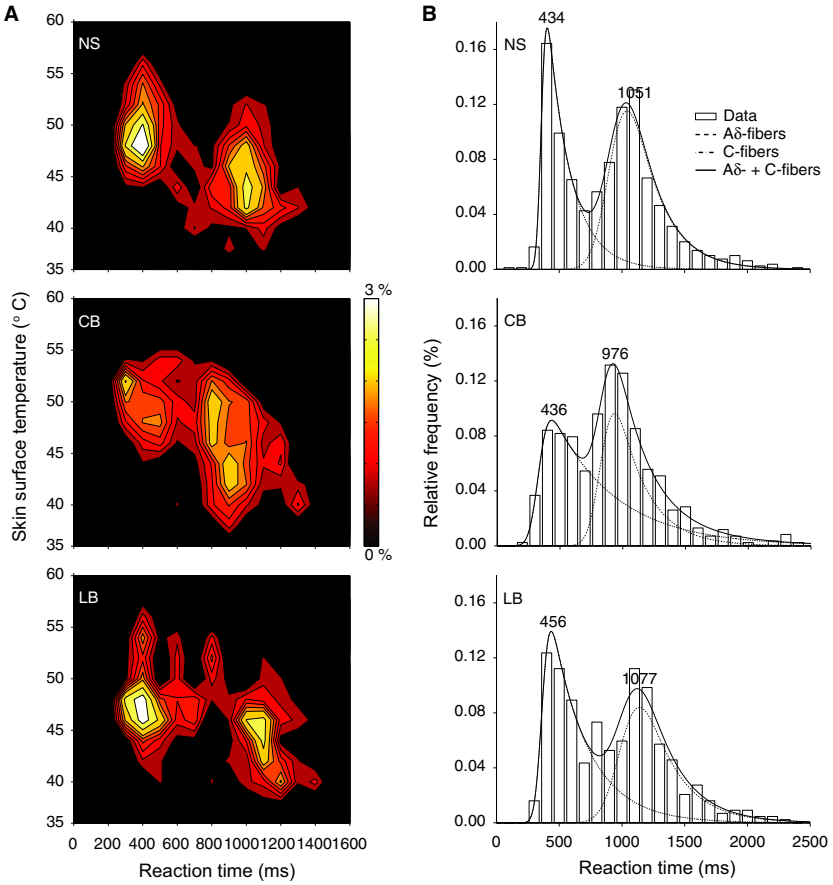

Figure 3 Reaction times frequency distributions to brief heat pulses. (A) Contour plots illustrating the frequency distribution of reaction times (RTs) paired to the temperature of the stimulus. The first (fast responses, high temperatures) and second (slow responses, low temperatures) peaks correspond to Aδ- and C-fibre distributions, respectively. CB's C-fibre peak reaction time is shifted leftwards compared to NS and LB. (B) Ex-Gaussian fitting on the RT data. The bimodal frequency distribution histograms were obtained with the pooled RTs of each group regardless to the target skin temperature (T_2) and reflect the Aδ- and C-fibres difference in conduction velocity. In each group, the black continuous line corresponds to the two-term finite mixture model with ex-Gaussian probability density functions. The dashed and dotted/dashed lines represent the contribution of the Aδ- and C-fibre–related RTs, respectively. Compared to NS and LB, CB had a faster C-fibre peak reaction time ($p < 0.001$). NS, normally sighted; CB, congenitally blind; LB, late blind.

faster to C-fibre (peak frequency of RTs in CB = 958, LB = 1076 and NS = 1051 ms) but not to Aδ-fibre stimulation compared to the two other groups (peak frequency of RTs in CB = 433, LB = 434 and NS = 427 ms). This was confirmed by computing the distributions of mean differences in RT peaks between groups by means of a nonparametric bootstrapping procedure (Table 3). This result was also corroborated by the second series of experiments that allowed a more robust estimate of the RT frequency distributions because of the much higher number of trials. Results are reported in Fig. 3. Congenitally blind participants responded significantly faster to the 44 °C stimuli than their sighted peers (peak values CB = 792 ± 72 ms, NS = 961 ± 84 ms; $p < 0.01$). Further investigation of the C-fibre RT distribution revealed that congenitally blind individuals had a faster τC and μC than their sighted peers (Table 4). It is noteworthy that the RT distribution of the C-fibre–mediated sensations was four times more skewed than that of the Aδ-fibres. Overall, these results indicate that visual deprivation from birth leads to a facilitated detection and faster RTs to C-fibre–mediated sensations, probably due to a more efficient central processing of these nociceptive signals. Importantly, blind participants also had a significantly higher detection rate (CB = 93 ± 5%, NS = 77 ± 9%; $p < 0.05$) of C-fibre stimuli. In contrast, for the more intense stimuli of 52 °C (Fig. 3B), there were no group differences in Aδ-fibre peak RTs (NS = 210 ± 21 ms and CB = 234 ± 54 ms; $p > 0.05$) or in the detection rates (95 ± 9% and

Table 3 Mean difference of peak frequencies in RT distributions.

	Aδ-fibre–mediated			C-fibre–mediated		
	NS−CB	NS−LB	LB−CB	NS−CB	NS−LB	LB−CB
Mean	7	−22	29	93	−25	118
+95% CI	51	24	86	168	64	203
−95% CI	−37	−68	−27	17	−114	43
t-statistic	0.298	0.936	1.035	2.411	0.558	2.729
p	0.383	0.175	0.150	**0.008**	0.286	**0.003**

NS, normally sighted; CB, congenitally blind; LB, late blind.

Table 4 Decomposition of the ex-Gaussian probability density function parameters (mean ± SD) from 44 °C nociceptive heat stimuli.

	μC	σC	τC
NS	752 ± 12	206 ± 20	250 ± 21
CB	702 ± 9	73 ± 7	193 ± 33
p	<0.001	<0.001	<0.001

NS, normally sighted; CB, congenitally blind.

95 ± 6%, respectively; $p > 0.05$). Overall, these results indicate that visual deprivation from birth leads to a facilitated detection and faster RTs to C-fibre–mediated sensations.

4 Discussion

The aim of this study was to test the role of Aδ- and C-fibres in hypersensitivity to heat pain in congenitally blind individuals (Slimani et al., 2013, 2014). We addressed this question through the investigation of Aδ- and C-fibre response times and detection frequencies to brief nociceptive radiant heat stimuli. Results indicated that compared to late blind and sighted participants, congenitally blind subjects reacted faster to C-fibre–mediated sensations. In addition, these subjects also detected significantly more C-fibre–mediated heat stimuli. These data provide a possible physiological basis for the earlier reported hypersensitivity to heat in congenital blindness.

4.1 Faster response times to C-fibre–mediated sensations

We previously showed that congenitally blind individuals are hypersensitive to noxious thermal stimulation (Slimani et al., 2013, 2014). In these studies, we measured pain thresholds using the method of limits. It has been argued that this method is prone to anticipatory responses, particularly when using a slow stimulus ramp rate, because anxiety may buildup and participants may respond before the stimulus becomes painful, leading to an underestimation of the true pain threshold (Kunz and Lautenbacher, 2014). In this study, we circumvented this problem by making two important changes to our testing paradigm. First, we minimized response bias by anticipation by interleaving two adaptive up/down staircase algorithms. As a result, participants in the first experiment were unable to predict the relationship between their response and the relative temperature of the upcoming stimulus (higher or lower than the last presented one). Second, by using very fast ramped and short laser pulses, 10 and 90 ms, respectively, we avoided the 'reaction time artefact' generated by threshold assessment procedures that involve RTs (Yarnitsky and Ochoa, 1991). This artefact is particularly consequential when estimating sensory modalities with longer RTs like those mediated by unmyelinated C-nociceptors. Also, anxiety buildup, caused by slowly increasing stimuli, may contribute to this reaction time artefact. Using this new method, we found that compared to sighted and late blind participants, congenitally blind subjects responded significantly faster to C-fibre–mediated sensations. This result was confirmed in the second experiment that employed a much higher number of stimuli, allowing a more precise estimation of RTs. Since we recently showed that congenitally blind individuals outperform the sighted in a nonpainful heat discrimination task (Slimani et al., 2015), one could argue that the shorter RTs to C-fibre–mediated sensations are due to a faster processing of innocuous warmth stimuli through low threshold C-warm receptors. However, this seems rather unlikely since low threshold C-warm responses represent <10% of the responses in the first experiment (Fig. 3A). We therefore explain our results by the activation of C-fibre polymodal nociceptors. This is in line with results reported in primates, showing that rapidly adapting C-fibre polymodal nociceptors already respond to heat of ~40.8 °C (Wooten et al., 2014). The results obtained in the second experiment further support our con-

jecture since the temperature that was used (44 °C) is well in the range for C-nociceptor activation and far above that for activating C-warm receptors. Together, these data indicate a faster accumulation rate of sensory evidence in congenitally blind subjects for C-fibre–mediated input. This conjecture was supported by a decomposition analysis of the RTs of the second experiment showing that congenitally blind individuals had a faster τC – which provides an estimate of the decisional component of response times – than their sighted peers, indicating a more efficient central processing of C-fibre–mediated nociceptive signals.

Both congenitally blind and sighted controls responded faster in the second experiment in which we only used suprathreshold stimuli for C-fibre nociceptor activation. However, the gain in response time in the second experiment was double in the congenitally blind compared to the sighted controls. This means that when the stimulus is more salient, the gain in central processing time becomes even larger for the congenitally blind subjects. In addition, the results of the second experiment indicate that congenitally blind subjects also had a higher detection rate of C-fibre–mediated heat responses. This finding further supports our hypothesis that increased responses to painful stimulation in congenital blindness are due to a hypervigilance to threatening stimulation.

We did not find a significant difference for Aδ-mediated responses between the three groups. This result may be explained by a ceiling effect. Response times are already so fast in the control subjects, around 200 ms when using supra-threshold stimuli, that a further gain in reaction time in the congenitally blind group is not possible. This interpretation could be tested in future studies whereby responses are recorded to Aδ-mediated responses that are only slightly above threshold and that are applied to more distal areas such as the lower leg or the dorsum of the foot. Indeed, augmenting the peripheral distance allows a better separation of the bimodal distribution of RTs of the C- and Aδ-fibre–mediated responses. An alternative interpretation for the lack of a group difference for the Aδ-mediated responses is that the Aδ-fibres, because of their higher threshold, play a lesser important role than C-fibres in approach behaviour towards stimuli that may cause skin injury. For example, shorter RTs to C-fibre–mediated responses around threshold will assure that a blind person will get too close to a hot stove, hence protecting him from skin injury. However, for higher stimulus intensities that activate Aδ-fibres, tissue injury has already taken place and default RTs are already so fast that increasing vigilance adds little in terms of protection from injury. This suggests a more automatic processing of the Aδ-fibre input that is less dependent on top-down modulatory influences than C-fibre–mediated responses. This conjecture is supported by the observation that the RT distribution to C-fibre–mediated sensations was four times more skewed than that to Aδ-fibre–mediated sensations, indicating that it is a less reliable channel (Fig. 4). Here, reliability refers to the precision, or the inverse variance of the probability density function of sensory responses, with larger variances indicating less reliable response rates. The inverse variance can be interpreted as a measure of the noisiness in a sensory channel (Green and Swets, 1988). This may result from the fact that Aδ-fibre inputs are more salient than C-fibre inputs (Nahra and Plaghki, 2003; Vierck et al., 2004; Churyukanov et al., 2012), leading to a faster central accumulation of sensory information and ultimately to a faster decision making (Ratcliff and Van Dongen, 2011). This, together with the already very short response latencies to Aδ-fibre stimulation, makes it unlikely that congenitally blind individuals would show faster reaction times to this type of input. The C-fibre channel, however, is more open for improvement through other central processes such as multimodal integration and top-down attentional modulation. In line with our previous finding that congenitally blind individuals are more attentive to signs of threat (Slimani et al., 2013, 2014), this provides a possible mechanism for faster responses to C-fibre–mediated input.

4.2 Aδ- and C-fibre–mediated detection thresholds

We chose a cut-off of 650 ms to discriminate between Aδ- and C-fibre–mediated responses. This criterion was based on the peripheral conduction distance of afferent input originating from the hand, and on the distribution of reaction times to laser stimuli after blockade of the myelinated fibres (Bromm et al., 1983; Nahra and Plaghki, 2003). The RT analysis that was performed without any *a priori* on the distribution of the responses, confirmed the validity of our criterion in the adaptive staircase algorithm. In contrast with the RT data, there were no group differences in Aδ- and C-fibre–mediated detection thresholds. Although this finding may seem surprising at first sight, it does not contradict our earlier finding of lower heat pain thresholds in

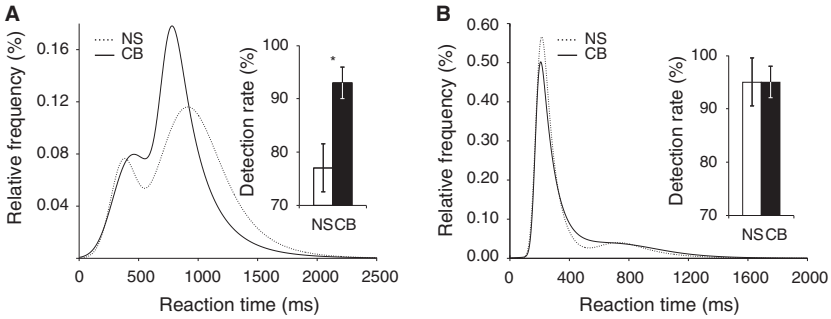

Figure 4 Reaction times frequency distributions to suprathreshold C- and Aδ-fibre heat pulses. (A) Stimuli given at 44 °C. CB had a higher detection rate ($p < 0.05$) and a faster C-fibre peak RT ($p < 0.01$) than NS. (B) Stimuli given at 52 °C. NS and CB had a similar detection rate ($p > 0.05$) and Aδ-fibre peak RT ($p > 0.05$). NS, normally sighted; CB, congenitally blind; LB, late blind.

congenitally blind individuals (Slimani et al., 2013, 2014). Indeed, in this study, we asked participants to respond whenever they felt a stimulus, irrespective of whether it was painful or not. Although the stimulation intensities we used mainly activated C-fibre nociceptors, the induced sensation was not always painful. This finding can be explained by the fact that we stimulated a very small surface area and that stimulus duration was very short (100 ms). Indeed, the induction of pain perception is critically dependent on the magnitude of spatial summation by applying a single stimulus with an increasing area (Machet-Pietropaoli and Chery-Croze, 1979; Kojo and Pertovaara, 1987; Defrin and Urca, 1996; Defrin et al., 2003), or on temporal summation by C-fibre wind up (Torebjörk and Hallin, 1974).

4.3 Hypervigilance to threat

The hypersensitivity to threat hypothesis takes into account that attention provides top-down modulation that, with development, shapes bottom-up signals by strengthening synaptic connections. Therefore, the increased use of nonvisual senses can lead to an enhanced selective attention for nonvisual types of stimuli that would ultimately lead to neuroplastic changes in the visually deprived brain (Kupers and Ptito, 2014). Indeed, blind individuals employ different strategies, including other detection criteria for tactile exploration and object localization than the sighted (Sterr et al., 2003; Pietrini et al., 2009; Beaulieu-Lefebvre et al., 2011). This may explain why congenitally blind individuals score higher for odour awareness (Beaulieu-Lefebvre et al., 2011), pay more attention to painful encounters in daily life (Slimani et al., 2013, 2014), have augmented responses to auditory threats (Klinge et al., 2010) and are better at identifying odours with negative emotional valence (Iversen et al., 2015). We therefore suggest that congenitally blind individuals use such mechanisms for attention orienting towards potentially harmful stimuli in order to quickly identify and react to dangerous events. Indeed, not only do congenitally blind subjects react faster to C-fibre–mediated sensations but they also have a higher accuracy of detection of C-fibre–mediated heat at suprathreshold levels.

4.4 Late blind individuals

Unlike congenitally blind subjects, late blind subjects did not differ from sighted controls. This observation indicates that the lack of visual experience, rather than blindness *per se,* is responsible for the hyperresponsiveness to nociceptive stimuli. This is in line with our previous results showing that late blind participants do not have an enhanced sensitivity to pain or a heightened vigilance towards painful stimuli (Slimani et al., 2014). More broadly, this finding also fits with studies indicating that these individuals are less susceptible to compensatory plasticity (Grant et al., 2000; Alary et al., 2008; Collignon et al., 2009; Wan et al., 2010). In fact, many animal and human studies have shown that structural and functional brain changes following blindness are less likely to occur later in life (Desgent and Ptito, 2012; Kupers and Ptito, 2014). In contrast, it is well established that early visual deprivation causes cross-modal plastic changes that lead to the recruitment of the visual cortex in nonvisual tasks (Kupers and Ptito, 2014).

5 Conclusion

In conclusion, using a new method allowing for a psychophysically unbiased measurement of Aδ- and C-fibre–mediated thresholds, we showed that hypersensitivity to heat pain in congenital blindness is

associated with a more efficient central processing of C-fibre–mediated input. This may help these subjects to avoid impending dangerous encounters with stimuli that may threaten their bodily integrity. As a corollary, the present results also reveal how the use of reaction times to selective Aδ- and C-fibre input may be a helpful tool to probe into mechanisms of pain perception.

Author contributions

HS, LP, MP and RK conceived and designed the experiments. RK and MP contributed with experimental equipment. LP contributed with the data analysis tools. HS performed the experiments. HS and LP performed the data analysis. HS, LP, MP and RK wrote and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors are grateful to Nina Reislev, Elisabeth Spénard and Johan Stender for helping with various administrative and practical aspects of the study.

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