

Multisensory impact of visual stimuli on detection thresholds of thermo-nociceptive inputs conveyed by A δ and C fibers.

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Abstract

Nociception is seen as an alarm system that allows detecting and reacting to potential physical threats. It is hypothesized that such alarming function is optimized through interactions with other sensory systems such as vision that allows identifying surrounding objects that might have an immediate impact on the body. Here, we test the hypothesis according to which visual stimuli could modulate the response threshold to heat stimuli. Using an adaptive psychophysical procedure allowing, among other things, to take into account differences in conduction distance and velocity within visual and thermo-nociceptive pathways, laser-induced thermal stimuli of different temperatures were applied on one hand dorsum, and detection thresholds of thermal sensations conveyed by C- and A δ -fibers were measured, respectively. Measures were taken while visual stimuli were presented either near the stimulated hand, near the opposite hand or at a neutral position in front of the participant. Results showed that the detection threshold of A δ fibers was decreased when the visual stimuli occurred near the stimulated hand as compared to when they occurred near the opposite hand. Such modulation of nociceptive thresholds by non-somatic stimuli, at least that of A δ fibers, could reflect a defensive mechanism to facilitate detection and response to external threats. Conversely, due to their slow conduction velocity, sensory inputs conveyed through C fibers could be less sensitive to multisensory interactions because they would be less involved in immediate defensive reactions and more involved in monitoring the general state of the body.

1. Introduction

Pain generally arises from the activation of the nociceptive system, a physiological system specifically involved in coding, transmitting, and processing information about noxious events [31]. At the peripheral level, this system consists of free nerve endings associated with two main types of fibers, thinly myelinated A δ fibers and unmyelinated C fibers. These fibers are distinguished, among other things, by their conduction speed, with the conduction of A δ fibers being faster than that of C fibers, as well as their activation threshold, with the threshold of A δ fibers being generally higher than that of C fibers. The activation of these fibers generally gives rise to sensations of brief and intense pricking for A δ fibers and diffuse heat for C fibers. After relay at the spinal level, the nociceptive inputs are conveyed to the subcortical and cortical centers via the anterolateral tracks. Pain is described as a percept resulting from the central nervous system's interpretation of a pattern of neural activity arising from the different nerve fibers [9,35,46]. It is also acknowledged that nociceptive inputs transmitted to the brain activate a cortical network that prioritizes processing and integration of any sensory stimulus meaningful for body integrity [35]. Exploration of the physiological mechanisms underlying the integration of sensory inputs leading to and influencing pain has focused on the convergence of somatosensory inputs at spinal level [e.g., 29,30,47]. Nevertheless, crossmodal interactions between nociceptive inputs and non-somatic inputs at cortical level have been explored in several recent experiments [see 34]. For example, it was shown that seeing the limb on which nociceptive stimuli are applied or changing its posture can influence the responses to those nociceptive stimuli [e.g., 23,40,42,68,70]. In addition, the integration between somatic and non-somatic inputs could optimize pain localization mechanisms to

identify which part of the body is injured and what is the cause of this injury in its surrounding space [25,37]. Based on data showing close interactions between nociception and vision, more particularly for visual stimuli occurring near the body [10-13,17-20,45,69], it was suggested that spatial information about nociceptive inputs are indeed integrated into a multisensory representation of the body space slightly extending to its immediate surrounding in external space. This space, referred to as the peripersonal space [11,17,20,33,37], is considered to represent a buffer zone protecting the body against physical threats [24,34].

These visuo-nociceptive interactions have been almost exclusively investigated through experimental procedures evaluating the ability to localize the position and determine the time of occurrence of sensory stimuli. Whether visual stimuli may modulate the sensitivity to nociceptive stimuli has generally been overlooked. A recent electrophysiological study has shown that approaching visual stimuli toward the monkey body increases firing of thermo-nociceptive neurons in the inferior parietal lobe and facilitates defense behaviors [14]. In humans, only one study showed that presenting a visual stimulus near the hand onto which nociceptive stimuli are applied at intensities corresponding to their absolute detection threshold increases the probability of reporting the nociceptive stimuli as consciously perceived [19]. The aim of the present study was to measure the influence of visual stimuli and their location relative to the stimulated body part on the ability to detect near-threshold nociceptive stimuli. Most importantly, we separately assessed the influence of visual stimuli on the ability to detect nociceptive input conveyed by A δ - and C-fibers [3], to investigate whether visual stimuli interact in the same way with nociceptive inputs conveyed by these two sub-systems.

2. Methods

For each participant, detection thresholds were assessed separately for C fibers and A δ fibers in different sessions. Given that conduction distances and conduction velocities from sensory receptors to the brain differ between nociception [27,31,54-56] and vision [43,44,49,74], the simultaneous application of transient nociceptive and visual stimuli can be expected to result in an important lag between their respective times of arrival. To maximize visuo-nociceptive interactions, we therefore introduced asynchrony between the onsets of nociceptive and visual stimuli for them to be perceived simultaneously. For each session, the necessary asynchrony was estimated individually during a first phase using a temporal order judgment (TOJ) task on visual and thermo-nociceptive stimuli, and was therefore measured separately for nociceptive responses mediated by A δ fibers vs. C fibers [43,44]. Individual estimates of the time at which visual and nociceptive stimuli are perceived as occurring simultaneously were then used to delay the presentation of the visual stimulus relative to the onset of the nociceptive stimulus during the assessment of nociceptive detection thresholds. During the second phase of each session, detection thresholds were assessed using the *psi marginal* method [58,59]. As compared to other adaptive psychophysical procedures, this method allows us to determine, additionally to the threshold, the slope of the psychometric function, which provides information about the noisiness of the sensory system during input processing [7].

2.1. Participants

Twenty-seven volunteers participated in the study. The sample size was determined based on previous studies having investigated interactions between visual stimuli and near-threshold nociceptive stimuli [17-20,43-45,69]. Exclusion criteria were non-corrected vision

difficulties, any neurological, cardiac, psychiatric and chronic pain disorder, trauma of the upper limbs within the last 6 months preceding the experiment, tissue damage or dermatological disease of the hands, regular use of psychotropic drugs, intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 hours before the experiment, and having participated in our previous experiments [43,44]. The data of 7 participants were discarded from further analyses due to either technical issues or unreliable assessments during one of the experimental conditions (see Analyses section). The mean age of the remaining 20 participants (17 women, 3 men) was 23.35 years ($SD = \pm 3.48$, range 19-32 y.). According to the Flinders Handedness Survey (Flanders) [53], 19 participants were right-handed and one was left-handed. The local ethic committee approved the experimental procedure in agreement with the Declaration of Helsinki. Participants signed an informed consent prior to the experiment and received financial compensation for their participation.

2.2. Stimuli and apparatus

Thermo-nociceptive stimuli consisted of radiant heat stimuli applied to one of the two hand dorsa using a temperature-controlled CO₂ laser stimulator (10.6 μm wavelength, Laser Stimulation Device, SIFEC, Ferrières, Belgium). The laser beam was conveyed through a 7-m optical fiber ending with a head containing the optics used to collimate the laser beam to 6-mm diameter at the target site. The laser head was held above the participant's hand by means of an articulated arm attached to a camera tripod system (Manfrotto, Cassola, Italy). It was fixed into a clamp attached to a 3-way head, allowing displacements of the laser target perpendicularly to the hand's dorsum, by means of several sliders in all directions. The laser beam target was displaced after each stimulus to avoid overheating the skin. Laser stimuli lasted 100 ms with a 10-ms heating ramp to reach the target temperature, followed by a 90-

ms plateau; heating was then stopped. Laser energy was controlled using temperature measured at the skin target site by means of a radiometer in the laser head. The laser output power was adapted to the online measurement of the skin temperature at the site of stimulation to reach the specified temperature.

Visual stimuli were flashes of light delivered using a white light-emitting diode (LED) (21.5-1m luminous flux, a 7.20-cd luminous intensity, and a 120° diffusion angle; BROADCOM ASMW-FWG0-NHKH6). Visual stimulus duration was 5 ms during the nociceptive-visual TOJ task (phase 1), and 100 ms during nociceptive detection threshold task (phase 2).

The LEDs were positioned at three landmarks pasted on the table (Figure 1). A fixation cross was drawn on the table, in alignment with the participant's midsagittal plane, at 30 cm from his/her trunk. The first landmark was pasted on the midsagittal line, 15 cm distally from the fixation cross. The two other landmarks were pasted along the line perpendicular to participants' midsagittal plane, crossing the fixation cross. One landmark was left-sided, the other right-sided, each 15 cm from the fixation cross. Participants were seated in front of the table and were asked to place their hand palms down on the table, with the metacarpophalangeal joint between the index and the thumb fingers of the left and right hands located 1 cm from the left and right lateral landmarks, respectively.

To record the participants' responses, two metal plates (2*4 cm) were placed under each index finger. The plates were attached to a small plastic base and stuck on the table using double-sided tape. Participants were requested to respond by lifting the left or right index finger. Loss of contact of the finger with the plate was detected using a high resistance switch triggered by the change in impedance occurring between the metal plate and an electrode (NEO NAT Ambu ECG) attached to the skin of the forearm. During the experiment, participants

were asked to lift as fast as possible the two index fingers. Impedance was measured by an Arduino which triggered a TTL signal upon finger lift. The TTL trigger was recorded using a data acquisition card (NI USB 6343, National Instruments, USA) which also recorded the onsets of the visual and laser stimuli. Differences between stimulus onsets and response latencies measured at each plate were computed and the smaller difference was used as measure of reaction time.

2.3. Procedure

The experiment was performed in two sessions separated by one week and scheduled at the same moment of the day for each participant. One session was dedicated to assessing the influence of visual stimuli on C-fiber detection thresholds. The other session assessed A δ -fiber activation threshold. The order of sessions was counterbalanced across the participants. During each session, nociceptive stimuli were either applied on the right-hand dorsum or on the left-hand dorsum. When stimuli were applied on one hand in the first session, they were applied to the other hand in the second session. The choice of the stimulated hand was counterbalanced across participants. Each session was divided into two successive phases. The first assessed perceptual simultaneity between nociceptive and visual stimuli using a TOJ task. The second assessed the effect of visual stimuli on nociceptive detection thresholds.

Phase 1: assessment of visual-nociceptive perceptual simultaneity

Target temperatures used during the TOJ task were determined according to the thermal detection thresholds of C and A δ fibers estimated separately using an adaptive staircase procedure. Since C fibers have lower detection threshold but slower conduction velocity than A δ fibers, the absolute detection threshold was used to determine C-fiber detection threshold,

while reaction times (RTs) were used to determine the A δ -fiber detection threshold (with 650 ms as cutoff to dissociate C- vs. A δ -fiber mediated RTs) (see [3] for details). The procedures started with a stimulus of 39° for C fibers detection threshold and 46° for A δ fibers detection threshold, with 0.5°C as incremental/decremental step. During the session investigating C fiber detection thresholds, both thresholds were measured, and the target temperature used to selectively activate C fibers was defined as the average between the individual C-fiber and A δ -fiber threshold estimates [see 38,43,44]. During the session investigating A δ fiber detection thresholds, only the A δ -fiber threshold was estimated, and the target temperature was set 5°C above the individual A δ -fiber detection threshold.

The visual-nociceptive TOJ procedure was based on the one used in our previous studies [43,44]. Visual stimuli were delivered using the LED placed in front of the participant on the midsagittal plane (Figure 1). The TOJ task consisted of 2 blocks of 30 trials each. Before the task, two trials were administered to familiarize participants with the procedure and the sensation elicited by the activation of A δ and C fibers. Their performance was not recorded. A trial consisted in a pair of one visual stimulus and one laser stimulus delivered at the individual target temperature. Each trial started with a warning signal from the experimenter. Approximately 500 ms later, the first stimulus of the visual-nociceptive pair was delivered, followed by the second stimulus, according to different stimulus onset asynchronies (SOAs). During the C-fiber session, the nociceptive stimulus always preceded the visual stimulus, and the stimuli were separated by 16 possible SOAs (+100, +220, +270, +320, +370, +420, +460, +490, +510, +540, +580, +630, +680, +730, +780, +900 ms). During the A δ -fiber session, the nociceptive stimulus could either precede or follow the visual stimulus, and the stimuli were separated by 14 SOAs (-200, -150, -100, -80, -60, -40, -20, +20, +40, +60, +80, +100, +150 and +200 ms). The to-be-presented SOA was determined at each trial using the adaptive *psi*

method considering the participant's responses to all previous trials of the block [see 28 for further details about the psi method, and 14 for its use in TOJ tasks]. At each trial, participants judged the temporal order of the two stimuli of the pair by reporting verbally ("laser" or "visual") which of the two stimuli they perceived as having occurred first in one block, and as second in the other block. These two response modalities were used to minimize potential response biases [see 21,61,63 for details]. Once the experimenter encoded the participants' response, the next trial started 2000 ms later. Each block lasted approximately 4 minutes, and the entire TOJ task lasted around ten minutes. At the end of the TOJ task, the point of subjective simultaneity (PSS) was computed (see Measures), and its value was used to deliver perceptually synchronous nociceptive and visual stimuli in the second phase of the experimental session.

Phase 2: assessment of the effect of visual stimuli on nociceptive detection thresholds

During this second phase of each experimental session, visual stimuli were delivered using the LED placed in front of the participant, the LED placed near the hand onto which laser stimuli were delivered and the LED placed near the opposite non-stimulated hand (Figure 1). For each session, the threshold assessment consisted of 240 trials presented according to six randomly interleaved experimental conditions made of an equivalent number of 40 trials each. During three conditions, trials consisted of a laser stimulus applied on the hand dorsum using an intensity among different possible temperatures ranging from 30 to 50 °C with steps of 0.5 °C for the C-fiber threshold assessment session, and from 40 to 60 °C with steps of 0.5 °C for the A δ -fiber threshold assessment session. For each of these conditions, the applied temperature was determined at each trial using the *psi-marginal* adaptive method [59] by considering the participant's responses on all previous trials (see Measures for differences

from the classic *psi* method). During the C-fiber threshold assessment session, the temperature was adapted based on the probability of detecting the stimulus with a RT greater than 750 ms (i.e. a detection latency compatible with the conduction velocity of unmyelinated C fibers). During the A δ -fiber threshold assessment session, the temperature was adapted based on the probability of detecting the stimulus with a RT smaller than 750 ms (i.e. a latency compatible with the detection of input conveyed by thinly-myelinated Ad-fibers). The choice of 750 ms as a cut-off to dissociate responses mediated by C-fibers vs. A δ -fibers was based on a pilot experiment. The laser stimulus was combined with a visual stimulus in each of the three conditions. In the first condition, the laser stimulus was applied on the hand with a visual stimulus presented in front of the participant (*midline* condition). In the second condition, the visual stimulus presented next to the stimulated hand (*ipsilateral* condition). In the third condition, the visual stimulus was presented next to the non-stimulated hand (*contralateral* condition). The visual stimulus followed the laser stimulus by the amount of time corresponding to the individual PSS value estimated during the TOJ task. The remaining three conditions of each session consisted of catch trials to control for participants guessing the perception of the thermo-nociceptive stimulus. In these conditions, the visual stimulus was presented alone, either in front of the participant, close to the ipsilateral hand or close to the contralateral hand. Before each trial, the experimenter warned participants of the incoming stimuli by saying '*Attention*'. They were asked to maintain each index finger in contact with the corresponding metal plate of the response device. During each trial, they were requested to lift as quickly as possible both fingers at the same time if and only if they perceived a thermo-nociceptive stimulus. They were then asked to report whether they had perceived a thermal stimulus and/or a visual stimulus. For this purpose, they were instructed to respond after lifting their finger by saying either "*laser*", "*visual*", "*both*" or "*nothing*" and to report the

location of the visual stimulus (left, right or far). The responses of the participant were encoded by the experimenter, generating the start of the next trial. A five-minute break was taken every 80 trials. The entire experiment, including instructions, TOJ task and assessment of the thresholds, lasted about one hour and 30 minutes.

2.4. Measures

Intensities of the laser stimuli were measured in Celsius degrees (°C). The RTs recorded during the assessment of the thermo-nociceptive thresholds were measured in milliseconds (ms).

TOJ performance in the visual-nociceptive perceptual simultaneity task was estimated using the *psi* adaptive method. The proportion of thermo-nociceptive stimuli perceived as being presented first was computed as a function of SOA for each block. Parameters of interest were estimated by the logistic function $f(x)=1/(1+\exp(-\beta(x-\alpha)))$ at each trial [28]. Analyses were made on the last estimate of the block corresponding to the last update of the adaptive procedure. The main parameter of interest was the α parameter corresponding to the threshold of the function and characterizing the point of subjective simultaneity (PSS), that is, the SOA at which the thermo-nociceptive stimulus and the visual stimulus were perceived as occurring first equally often (in ms). Based on previous experiments [43,44], prior estimates of α were set respectively to 500 ± 200 ms for the C-fiber session and to 70 ± 20 ms for the A δ -fiber session. PSS values of the two blocks (i.e. '*which is first*' and '*which is second*') were averaged and the resulting value was used to individually set the time interval separating the thermo-nociceptive and visual stimuli during the threshold assessment (phase 2). Despite the slope value of the psychometric function (i.e. β) not being relevant for the purpose of threshold assessment, it was nevertheless analyzed to compare the precision of the

judgements between inputs conveyed by A δ vs. C fibers. Its prior estimate was set at 0.06 ± 0.6 for both fiber types.

The assessment of the thresholds to detect A δ and C fiber inputs in phase 2 was based on the *psi marginal* adaptive method [59], to measure the probability of detecting the thermo-nociceptive stimuli according to the respective criterion of each fiber type. The main parameters of interest were both the threshold (α) and the slope (β), estimated by the same logistic function as the *psi* adaptive method. The α parameter was used to characterize the activation threshold of the thermo-nociceptive fibers (in °C). For C fibers, the prior estimates were set to 40 ± 2 °C, for A δ fibers, they were set to 46 ± 2 °C [3,56]. Slope values (β) were considered for statistical analyses to estimate the noisiness of the detection process, i.e., the variability of the participants' responses. Their prior estimates were set to 0.001 ± 6 for both fiber types. Threshold and slope values were estimated separately for each experimental condition (i.e. *midline*, *ipsilateral*, and *contralateral* conditions). The particularity of the *psi marginal* adaptive method is that the lapse and guess rates are let to vary during the adaptive procedure (whereas their values are set in advance in the classic *psi* method). These parameters are usually considered as nuisance parameters because they influence the threshold and slope values without giving any information on the sensory mechanisms assessed. The lapse rate defines the probability of giving an incorrect response while the response should have been obvious (e.g., error due to distraction during one trial). The guess rate indicates the probability of giving a correct answer although the stimulus has not been detected by the sensory mechanism underlying the task (e.g., by chance). If their prior estimates are set correctly, their influence is minimized [57-59]. However, given that no previous study has investigated thresholds of thermo-nociceptive fibers according to the spatial position of a visual stimulus using an adaptive procedure, we could not make prior

assumptions about their fixed values. The *psi marginal* adaptive method therefore allowed us to set a uniform prior for each parameter.

2.5. Data analyses

Statistical analyses were conducted with IBM SPSS 25. The data of 7 participants were discarded from the analyses due to unstable adaptation of the *psi marginal* method during at least one experimental condition (as evidenced by a greater standard deviation of the α parameter at the last trial of the adaptive procedure compared to the standard deviation of the first trial administered) either during the threshold assessment of C fibers, or during that of A δ fibers.

Regarding the PSS and slope values of the TOJ task in phase 1, used to individually determine visual-nociceptive perceptual simultaneity, descriptive statistics are reported (see references [43,44] for more detailed analyses of crossmodal TOJs between visual and thermal stimuli).

Next, the respective impact of the occurrence and location of the visual stimuli on the threshold values of the thermo-nociceptive fibers measuring during phase 2 were analyzed using analyses of variance (ANOVA) for repeated measures. As a large difference between C fiber vs A δ fiber detection thresholds was expected and since the two types of fibers were tested in two separate experiments with different procedures (i.e. different adaptation criteria, different range of temperatures tested, different priors for α values, different hand tested), these analyses were performed separately for the assessment of each fiber type, with the position of visual stimuli as a within-participant factor (midline, ipsilateral or contralateral to the stimulated hand). The same analysis was performed for the slope values. When justified, contrast analyses were performed using t-tests with Holm correction for multiple

comparisons. Effect sizes were measured by means of partial Eta squared for ANOVA and Cohen's d for t tests. Significance level was set at p -value < 0.05. Data are expressed in means $\pm$ standard deviations ($M \pm SD$). Classic frequentist analyses with null result were complemented by Bayesian statistics (using Bayesian repeated measures ANOVA with JASP 0.9.2.0, University of Amsterdam, The Netherlands) performed on the threshold and on the slope values. To this aim, Bayes factors were computed to quantify the alternative hypothesis (H1) relative to the null hypothesis (H0) (BF10, Cauchy prior = 0.707). Since we had no a priori knowledge as to the effect size we could expect, the default priors implemented in JASP were used. Interpretations are based on the classification scheme established by Lee & Wagenmakers [32] and Wagenmakers et al. [71] in order to estimate the level of evidence for HA but also for H0 (since in frequentist analyses the rejection of H1 does not allow the evidence for H0 to be assessed).

3. Results

The PSS mean values of the TOJ task in phase 1 were 603 ± 107 ms (ranging from 380 ms to 840 ms) for C-fiber mediated stimuli, and 87 ± 15 ms (ranging from 65 to 120 ms) for A δ -fiber mediated stimuli (see Figure 2). These values are consistent with those observed in previous studies [43,44]. Slope values were 0.015 ± 0.006 with C-fiber mediated stimuli, and 0.089 ± 0.109 for TOJ with A δ -fiber mediated stimuli.

Illustrations of the estimated psychometric functions resulting from the mean parameters of the threshold measurement experiment in phase 2 are depicted in Figure 3. Individual threshold and slope values are reported in Figure 4. Analyses of the threshold values revealed

no significant impact of the location of the visual stimulus on the detection threshold of C-fiber inputs ($F(2,38) = 0.062$, $p = 0.940$, $\eta^2_p = 0.003$; *ipsilateral* condition: $41.0 \pm 1.9^\circ\text{C}$, *contralateral* condition: $40.9 \pm 2.5^\circ\text{C}$, *neutral* condition: $41.0 \pm 1.7^\circ\text{C}$). Regarding Bayesian analyses performed on C-fiber thresholds, moderate evidence was shown in favor of H_0 ($\text{BF}_{10} = 0.142$, error = 1.089), confirming that the location of the visual stimulus did not impact the detection threshold of C-fiber inputs. On the contrary, there was a significant effect of the location of the visual stimulus on the detection threshold of A δ -fiber inputs ($F(2,38) = 3.28$, $p = 0.048$, $\eta^2_p = 0.147$; *ipsilateral* condition: $48.8 \pm 1.9^\circ\text{C}$, *contralateral* condition: $49.3 \pm 1.9^\circ\text{C}$, *midline* condition: $49.2 \pm 2.3^\circ\text{C}$). Contrast analyses showed that the threshold value of A δ fibers was lower in the *ipsilateral* condition as compared to the *contralateral* condition ($t(19) = -2.441$, $p = 0.050$, $d = -0.25$). There was no difference between the *contralateral* and *midline* conditions ($t(19) = 0.543$, $p = 0.590$, $d = 0.06$) or between the *midline* and *ipsilateral* conditions ($t(19) = -1.898$, $p = 0.131$, $d = -0.19$). These results suggest that presenting a visual stimulus near the hand on which the laser stimulus is applied decreases the detection threshold of A δ -fiber inputs, as compared to when the visual stimulus is presented near the opposite hand. However, Bayesian analyses suggest only anecdotal evidence for H_1 ($\text{BF}_{10} = 1.338$, error = 0.85).

The analyses performed on the slope values for the detection threshold of C-fiber inputs did not reveal significant differences between the different visual conditions ($F(2,38) = 1.420$, $p = 0.254$, $\eta^2_p = 0.070$). The analyses of the slope values for the detection threshold of A δ -fiber inputs also failed to show significant difference ($F(2,38) = 2.752$, $p = 0.077$, $\eta^2_p = 0.127$). The lack of significant effect of visual stimuli location on the slope values is confirmed by Bayesian analyses for detection thresholds of C-fiber inputs ($\text{BF}_{10} = 0.403$, error = 1.03), and

the significance of the effect is negligible relatively to H_0 for A δ -fiber inputs ($BF_{10} = 1.143$, error = 0.58).

To control for possible confounding factors, supplementary analyses were performed on the catch trials and the speed of responses during the assessment of threshold of A δ -fibers-mediated stimuli. Those analyses are detailed in Supplementary Materials 1. These analyses show that the probability of false alarms, that is, of responses to visual stimuli in the absence of thermo-nociceptive stimuli, is very marginal and is not influenced by the experimental conditions. It also shows that the classification of responses to nociceptive inputs based on reaction times is not related to a motor bias.

4. General discussion

In order to generate the most complete representation of a physical danger and to plan the most efficient protective response, nociceptive stimuli must interact with stimuli from other sensory modalities. Nociceptive and visual stimuli have been shown to influence each other's perception, especially when the visual stimulus appears near the limb on which the nociceptive stimulus is applied, i.e. in the peripersonal space [10-12,17-20,34,45,69]. The present data suggests that the occurrence and the spatial location of a visual stimulus could potentially modulate the detection threshold of thermo-nociceptive stimuli. Specifically, we show that visual stimuli can decrease the detection threshold of perceptually coinciding nociceptive stimuli when the visual stimuli appear near the stimulated hand, as compared to when they appear near the opposite hand, at least for nociceptive inputs conveyed by A δ fibers.

The present results partly extend those of Filbrich et al. [19] in which intra-epidermal electrical stimuli were used to specifically activate A δ fibers with a constant intensity corresponding to their absolute detection threshold (see [50]). They showed that the probability of perceiving the nociceptive stimulus was increased when the visual stimulus was presented next to the stimulated limb, as compared to when no visual stimulus was presented or when it was presented near the opposite hand. As compared to the condition with no visual stimulus, they also showed that presenting the visual stimulus next to the non-stimulated hand decreased the probability of reporting the nociceptive stimulus as perceived. Based on that latter result, we expected that presenting visual stimuli contralaterally to the stimulated hand would have increased the detection threshold to A δ -fiber-mediated nociceptive stimuli applied on that hand. This was not the case in the present study. However, it is possible that the effects observed in the two studies rely on different mechanisms. Indeed, the visual-nociceptive crossmodal effects observed in the previous studies were suggested to be mainly based on attentional mechanisms [18,19,41]. Having randomly delivered different stimuli on and around the two hands would have increased attentional competition between them to the detriment of the less salient stimuli [16,26], namely the nociceptive stimuli applied at just their threshold level. Here, as supra-threshold stimuli were occasionally delivered, they could have been salient enough to disrupt attentional mechanisms [36]. Alternatively, it could also be hypothesized that the decreased threshold to nociceptive stimuli by the ipsilateral visual stimuli observed here could rather be due to multisensory integration, which corresponds to mechanisms binding sensory inputs from the different modalities into a single coherent percept [48,66]. This hypothesis could be supported by a recent study which shows that feeling heat stimulation on the hand hidden from view and seeing a visual stimulation moving synchronously on a fake rubber hand aligned with the body can create the illusion of

ownership of this rubber hand [6]. Further support for such integrative mechanism comes from electrophysiological studies in monkeys [14,15], which suggest that visuo-nociceptive interaction may be related to the activity of multimodal neurons, i.e., neurons responding to both thermal and visual stimuli, similar to those discovered for visuo-tactile interactions [24]. These neurons, located in the anterior part of the inferior parietal lobe close to the monkey's secondary somatosensory area, respond to thermal stimuli in a temperature range from innocuous to nociceptive, but also to visual stimuli if they appear close to the cutaneous receptive field [15]. It has also been shown that discharges induced by these neurons in response to thermal stimulation were increased in the concomitant presence of a proximal visual stimulus in comparison with responses induced by the thermal stimulus alone [14]. Similarly, the combination of a thermal stimulus at a non-nociceptive intensity (e.g. 43°C) and a nearby visual stimulus induces a response similar to that produced by a thermal stimulus alone at a nociceptive intensity and provokes similar avoidance behaviors in the animal [14]. In other words, seeing an object approach the stimulated skin area decreases the thermal response threshold of these neurons. Such neurons could contribute to the development of a multisensory and extended representation of the body in order to facilitate defense reactions against physical threats. There is a long-standing and unresolved debate on whether multisensory interactions rely on attentional or integrative mechanisms [e.g. 41,66]. Whatever the mechanisms, the present data suggest that visual information about what happens around a body limb can interact with the processes underlying the detection of nociceptive stimuli. In this sense, the observed decrease of nociceptive detection threshold could reflect a protective mechanism to promote defensive responses to external threat [14,34].

One of the findings of the present study is that visual stimuli modulated the detection of thermo-nociceptive inputs conveyed by A δ fibers, without modulating the detection of thermo-nociceptive inputs conveyed by C fibers. The results of the TOJ procedure in phase 1 of the present study and those from previous crossmodal TOJ studies show that participants seem to have much more difficulties to make temporal order judgements with thermal inputs mediated by C fibers as compared to A δ fibers, and that their PSS are much more variable (see Figure 2 & [43,44]). This could be due to the fact that conduction velocity of C fibers is markedly slower than that of A δ fiber, also indicating that transmission of sensory inputs through C fiber is much more susceptible to jitter than those transmitted through A δ fibers. Larger variability in C-afferent conduction could therefore have disrupted synchrony with visual inputs during the detection threshold measurement despite its preliminary estimation by our point of subjective simultaneity measures, preventing us to observe interactions between visual and C-fiber-mediated thermo-nociceptive stimuli. In other words, despite the preliminary phase 1, we might not have succeeded in correctly parameterizing the simultaneity between the respective arrivals of the visual inputs and the thermal inputs mediated by the C fibers. It is worth noting that for the purpose of measuring detection thresholds, stimuli of short duration were used. In everyday life, warm and heat stimuli are generally of longer duration, which allows an overlap with the sensations generated by other sensory modalities and promotes the establishment of a temporal window for multisensory interactions. It was indeed shown that multisensory interactions between different modalities are not based on a strict simultaneity of their respective inputs, but more on a critical time window during which the brain can accommodate the delay between the times of arrival of the different inputs [5,48]. Alternatively, because the transmission velocity of C fibers is so slow – as compared to other somatosensory fibers – the brain may not compensate for their

late time of arrival. Therefore, it could be proposed that the significant impact of visual stimuli on the detection of A δ -fiber stimuli and its absence for C-fiber stimuli potentially witnesses different functional roles for the two somatosensory subsystems. The nociceptive system is generally described as a system specifically developed to detect and react to stimuli having the capacity to damage the body, thus giving an alarming and protective role to pain [31,35]. However, we may question the effectiveness of alarm responses generated by a system whose signals take so long to be transmitted, such as those conveyed by unmyelinated fibers. The so-called defensive and protective role of nociception and pain is often illustrated by the description of cases of congenital insensitivity to pain [51]. Individuals who are unable to perceive and react to noxious stimuli would be unable to cope with bodily injuries, threatening consequently their survival. However, Sternbach [65] pointed out that this often mostly impacts people with very severe neuropathies affecting other somatosensory systems, and that the chances of adaptation to physical injuries generally depend on the ability of these patients to use other sensory signals as cueing the presence of a danger. In other words, the alarming and protective role of the nociceptive system will not solely depend on its functional integrity but on the ability of the brain to integrate nociceptive inputs with other sensory inputs [34,52]. Based on the present results, one could hypothesize that the A δ -fiber subsystem would be more suitable to carry such a function, which gives it a rather exteroceptive role [29], in the sense that the brain can use its signals to understand which part of the body is injured and which external stimulus is the most likely cause based on the spatial and temporal proximity between nociceptive and non-somatic (i.e. visual) inputs [34]. The lower capacity of the C-fiber system to interact with other sensory modalities would limit it to a rather interoceptive functions. C fibers in general respond to all kinds of physiological

changes in the body, which therefore gives it preferentially the role of monitoring the state of the body [8].

As a limit, it is worth noting that heat-sensitive C fibers are made of different subtypes, such as C-warm fibers, C mechano-heat (CMH) fibers and the C heat (CH, mechano-insensitive) nociceptive fibers [1,39,60,72]. Although the stimulation parameters used in our experiment could selectively dissociate responses triggered by the detection of C-fiber input vs responses triggered by the detection of A δ -fiber input, we did not specifically activate the different subtypes of C-fiber afferents, although the used parameters probably mostly targeted generated responses of C-warm fibers [3]. The question regarding the ability of C-fiber afferents to interact with visual stimuli is still open for other types of C fibers, such as CMH and CH fibers. However, despite slight differences in conduction velocity between different C-fiber subtypes [e.g. 1,72], such difference does not make other C fibers better candidates for multisensory interactions. It is important to note, however, that in monkey studies some of the visuo-thermal neurons in area 7b are neurons also responding to innocuous temperatures [14], i.e. to inputs probably mediated by C-warm fibers, which therefore does not rule out the possibility of an involvement of C fibers in multisensory interaction.

Another important limitation is the low statistical power suggesting that the interaction effects observed in the present experiments are borderline. As highlighted above, regarding C fibers, a difficulty in studying multisensory interactions with the thermo-nociceptive system is the slow conduction of its fibers. It is therefore subject to more jitter than the lemniscal system, which makes it difficult to correctly estimate the critical interaction time window with other modality inputs, despite phase 1 of the present study. Another concern is that the

stimuli used were very brief, both for visual and thermal stimulations. A possible solution for obtaining more robust results would be to use longer duration stimuli to optimize temporal overlaps in the critical interaction window [14]. Another advantage would be to use more dynamic stimuli, whereas the current visual stimuli were static. Studies have indeed shown that visuo-tactile effects are more pronounced when participants see the visual stimulus approaching the stimulated body part than when it appears briefly nearby [24]. In the aforementioned study of Dong [14], the tested monkey actually saw an object approaching the stimulated cutaneous receptive field. One study, for instance, shows that the probability of detecting vibrotactile stimuli, also delivered at near-threshold intensity, increases when participants see the device that triggers them approach the stimulated skin area compared to a distant body area [67]. Similarly, when two sustained periodic tactile stimuli are applied concomitantly to each hand respectively, seeing a visual stimulus approaching one of the hands selectively increases the cortical response to the tactile stimulation applied on the congruent hand compared to that induced by stimulation of the opposite hand [4]. Modulation of sensitivity to thermo-nociceptive stimuli could therefore be demonstrated more robustly using stimuli of longer duration and presented in a more dynamic manner.

The results did not show any significant effect on the slopes of the psychometric functions for the detection of thermo-nociceptive inputs. Slopes are estimates of the noisiness during participant's perceptual judgements [7]. As it is expected that the perception of the thermo-nociceptive stimulus is facilitated by a nearby visual stimulus, one could have expected its detection to be less noisy, i.e. the slope steeper. On the contrary, flattening of the slopes of temporal order judgments between stimuli of two different sensory modalities has previously

been taken as an index of multisensory integration [62,64,75]. This is explained by the fact that perceiving these two stimuli simultaneously in the same location facilitates their integration and increases the probability of the two inputs being perceived as a single sensory event. In contrast, the nociceptive and visual stimuli are more likely to be perceived as two distinct percepts when they are applied on different hands [2,62,73]. However, these hypotheses have been presented in crossmodal temporal order judgment tasks in which participants had to estimate the temporal order between two stimuli of different sensory modality. In other words, participants were instructed to consider the two stimuli as two distinct sensory events; their automatic integration when presented at the same location could then make their judgment as two noisier sensory events. This is not the case here, since participants were instructed to detect thermal stimuli according to their intensity. A hypothesis of a slope effect in favor of multisensory integration seems therefore unlikely here. Moreover, statistical comparisons showed no significant effect of visual stimuli on slope values during thermal threshold measurement.

In conclusion, this study adds to the existing literature showing that the detection of a nociceptive stimulus does not only rely on the functional integrity of the specific transmission system, but also on the ability of the brain to integrate its incoming signals with sensory inputs from other modalities. Such an ability confers an exteroceptive function to the nociceptive system, allowing it to fulfill its alarming and protective role. Crucially, the present data could potentially suggest that such a function might be limited to A δ -fiber afferents, restricting the C fiber to a more interoceptive function. While these results are a first step in determining

and characterizing potential effects of crossmodal interaction on nociceptive sensitivity, further steps will, however, firstly require a more robust replication of the present data.

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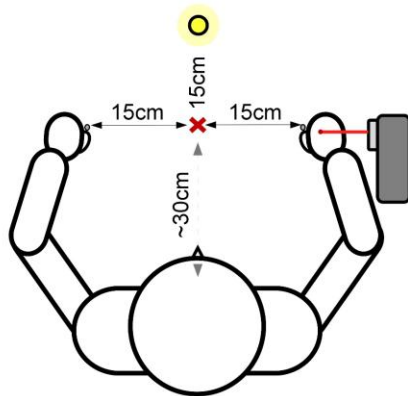
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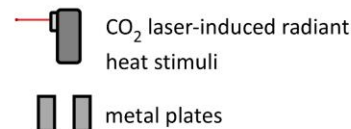
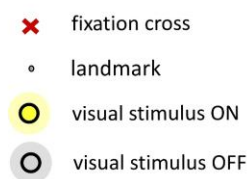
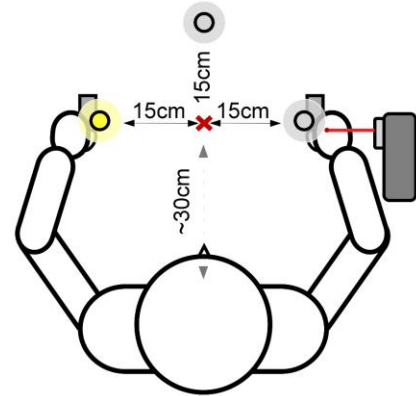
688 **Figure captions**

689

Phase 1: perceptual simultaneity assessment



Phase 2 : nociceptive threshold assessment



690 **Figure 1. Experimental setup.** The figure illustrates the stimulation and response devices used
 691 during the temporal order judgement task on the left (phase 1) and the *contralateral* condition
 692 of the detection threshold experiment (phase 2). The LED located next to the participant's left
 693 hand (illustrated by a yellow circle surrounded by a yellow halo) switched-on for 100 ms while
 694 the right-hand dorsum received a laser stimulus of 100 ms. The grey circle in front of the body
 695 midline ~45 cm from the trunk and the grey circle located next to the right hand illustrates the
 696 LEDs that were not used in this specific condition. The LED in front of the participant switched
 697 on during the *midline* condition whereas the right LED switched on during the *ipsilateral*
 698 condition. While participants responded verbally during phase 1, they responded by lifting
 699 their finger from the metal plate during phase 2.

PSS (ms)

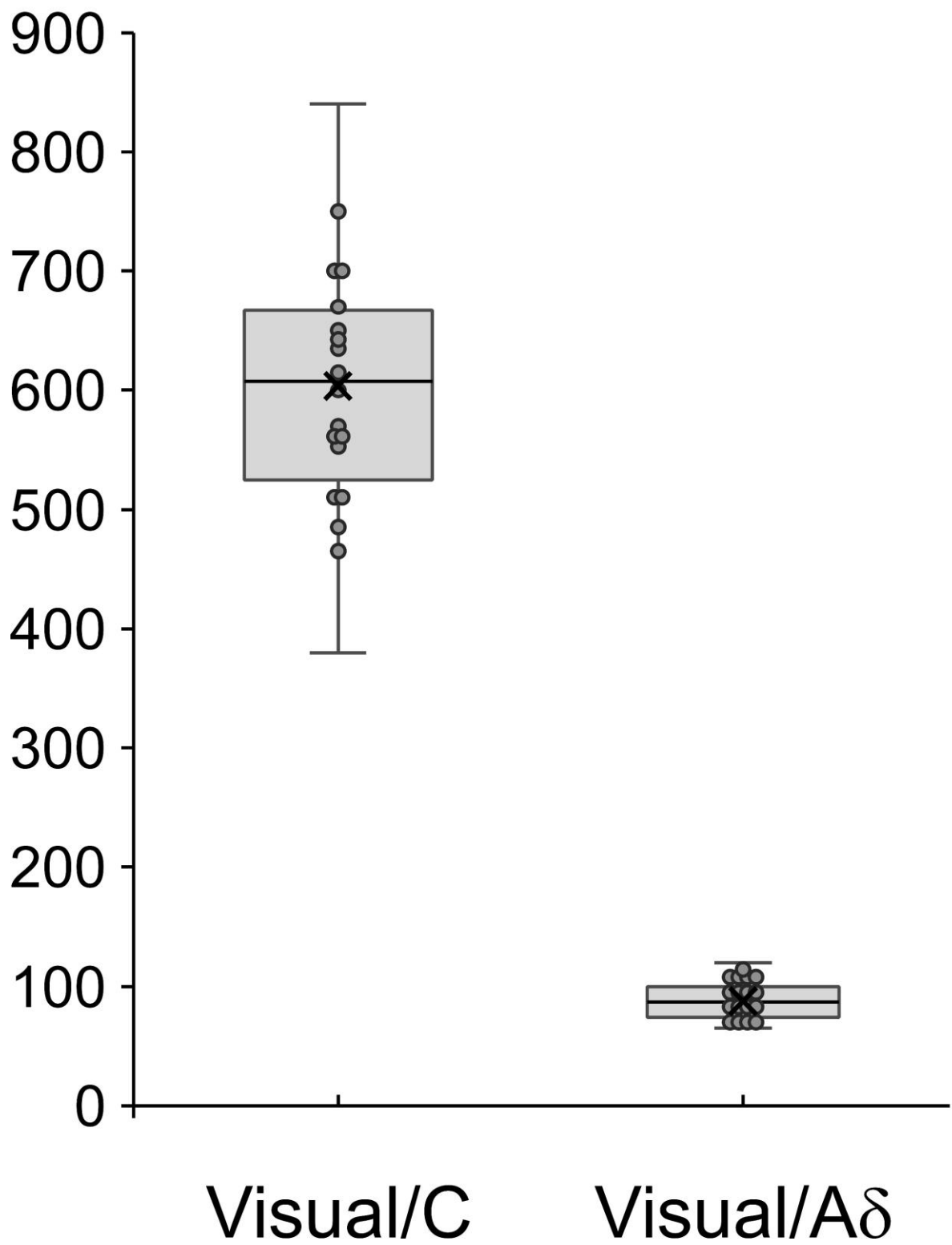


Figure 2. Points of subjective simultaneity (PSS) between visual and thermos-nociceptive stimuli. The graphs display the individual PSS values (in ms) obtained during phase 1 when participants were judging temporal order between visual stimuli and thermos-nociceptive stimuli conveyed respectively by C fibers (left) and A δ fibers (right), respectively. Individual data are superposed with boxplots mean (crosses), median (horizontal black lines), first and third quartile (box limits) and smallest and largest values (whiskers). PSS values are greater but also more variable with C-fiber stimuli than A δ -fiber stimuli. The individual PSS values were used during phase 2 to set asynchrony between visual and laser stimuli.

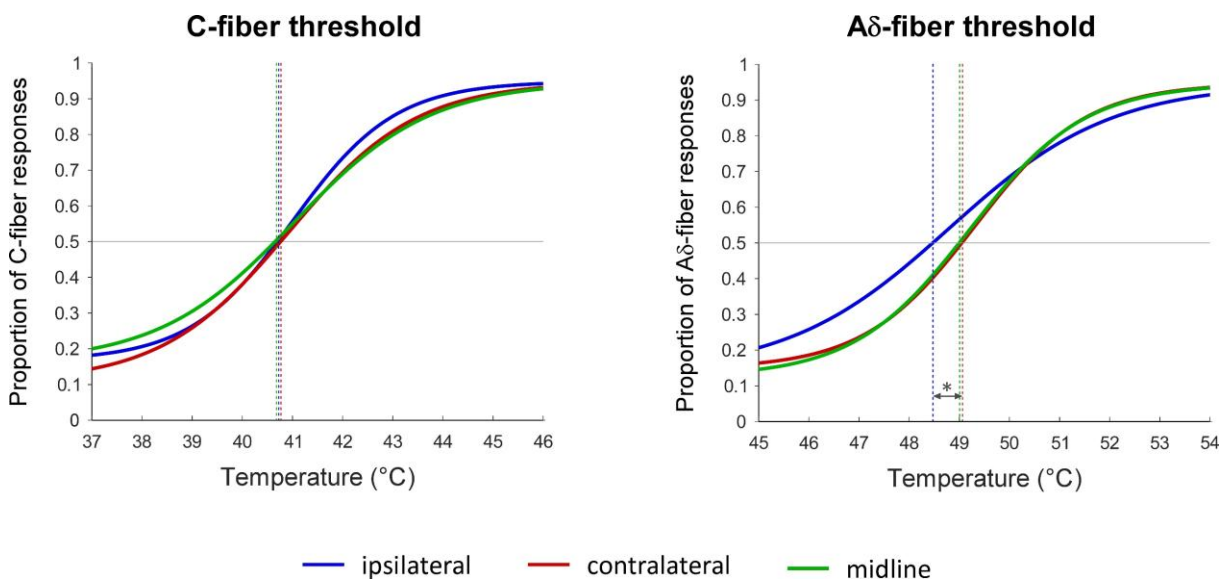
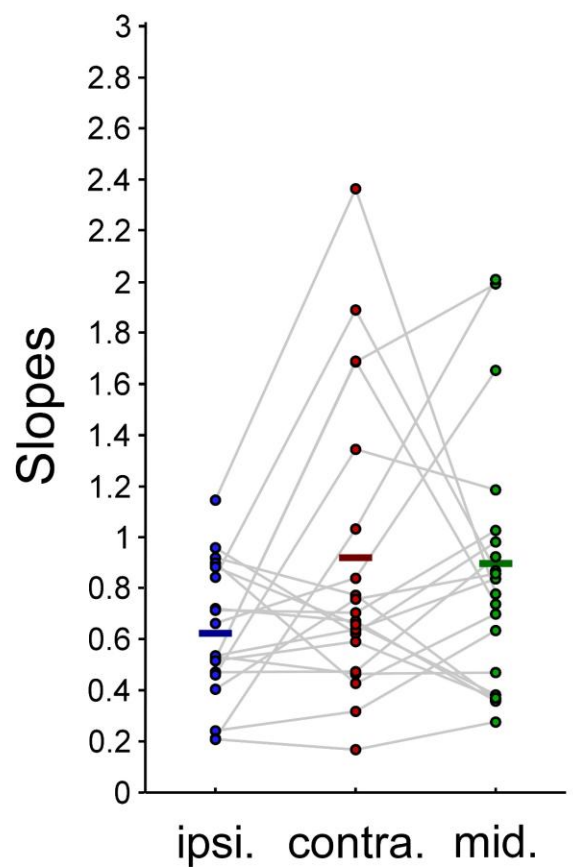
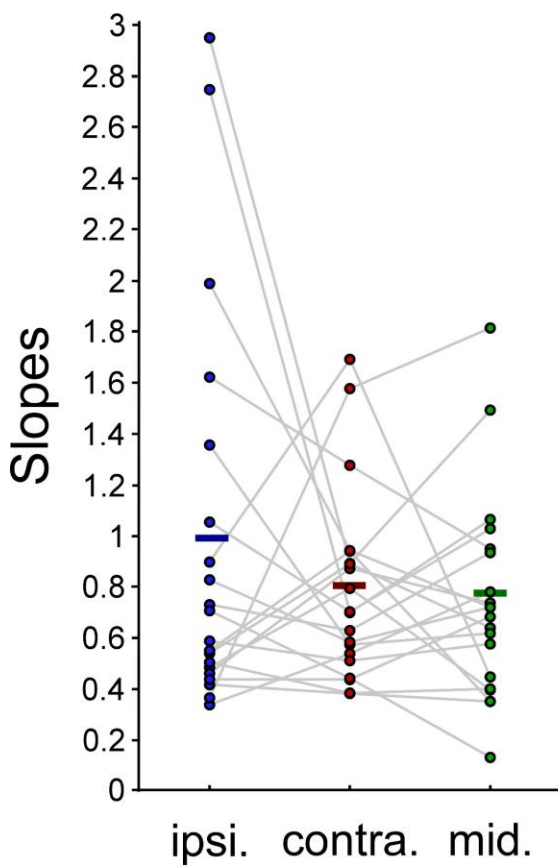
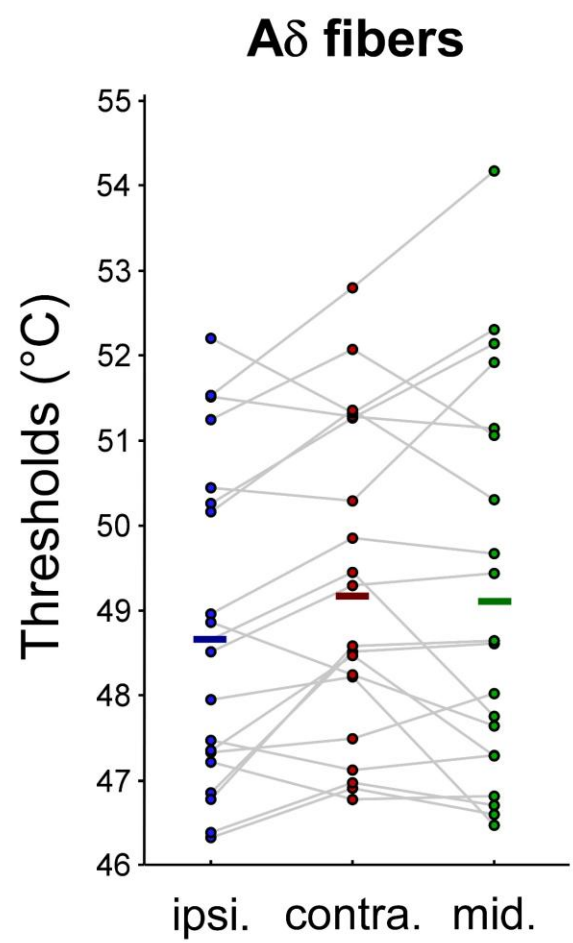
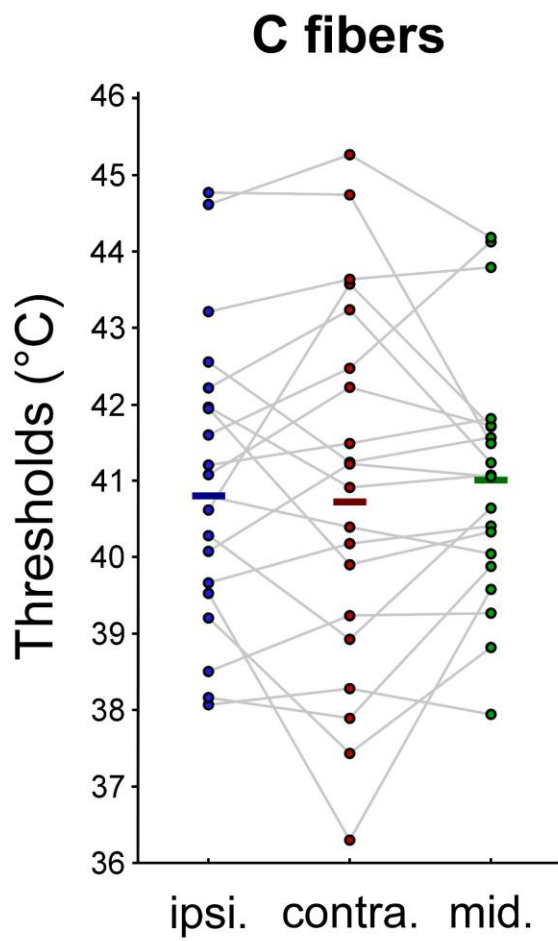


Figure 3. Psychometric curves fitting participants' responses. The figure depicts the averaged results of the 20 participants. The top graph represents the fitted logistic functions for the thermo-nociceptive thresholds of the A δ -fiber afferents. The bottom graph illustrates the fitted logistic functions for the thermo-nociceptive thresholds of the C-fiber afferents. For each graph, the x-axis represents the temperature of the stimuli and the y-axis represents the proportion of detected trials according to the adaptive criteria. The blue curves correspond to the *midline* condition, the green curves to the *ipsilateral* condition and the red curves to the

717 *contralateral* condition. The arrows indicate that the ipsilateral (green) and contralateral (red)
718 conditions are significantly different from each other. Significant differences are indicated
719 with asterisks (* $p \leq 0.05$).



721 **Figure 4. Individual threshold and slope values during detection threshold assessments.** The
722 figure shows the individual threshold (top) and slope (bottom) values of each participant
723 according to the visual conditions (*ipsilateral* [green] vs. *contralateral* [red] vs. *midline* [blue])
724 and to the stimulated fibers (C [left] vs. A δ [right]). In each graph, grey lines link the values
725 from each participant. The thick lines represent the mean value of each experimental
726 condition.