Directional discrimination is better for noxious laser stimuli than for innocuous laser stimuli

Frahm, K.S.; Mørch, C.D.; Andersen, O.K.

Published in:
European Journal of Pain

DOI (link to publication from Publisher):
10.1002/ejp.1521

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Title: Directional discrimination is better for noxious laser stimuli than for innocuous laser stimuli.

Running head: Directional discrimination is better for noxious stimuli

Authors: K.S. Frahm[1], C.D. Mørch[1], O.K. Andersen[1]

[1] Integrative Neuroscience group, Center for Neuroplasticity and Pain (CNAP), SMI®, Dept. of Health Science & Technology, Aalborg University, 9220 Aalborg, Denmark

Corresponding author:

Ken Steffen Frahm

Center for Neuroplasticity and Pain (CNAP)

SMI®

Dept. of Health Science & Technology

Aalborg University

Fredrik Bajersvej 7D3

9220 Aalborg, Denmark

ksf@hst.aau.dk

+45 99 40 98 42

www.cnap.hst.aau.dk

Manuscript category

Original article

Funding

This study was funded the Danish National Research Foundation (DNRF121).

Conflict of interest

There are no conflicts of interest.

Significance (64 words)

This study showed that the directional discrimination of painful laser stimuli is better than that for non-painful laser stimuli. These findings supplements our current knowledge regarding the tempo-spatial discrimination in the nociceptive system, , where evidence from previous discrimination studies differs somewhat regarding difference between painful and non-painful discrimination. This, therefore, indicates that there is lacking knowledge regarding the discrimination within the nociceptive system.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/EJP.1521

Abstract

Background

The directional discrimination is lower for painful laser heat compared to non-painful mechanical stimulation. The aim of the current study was to investigate how the directional discrimination of radiant heat stimulation depends on stimulation intensity and displacement velocity.

Methods

Fifteen healthy subjects were stimulated in the right volar forearm with a CO_2 laser at intensities that were expected to be either painful (46 ^oC) or non-painful (39 ^oC). The laser beam was continuously displaced distal-proximally along the arm during the stimulation. After the stimulation, subjects indicated the perceived direction and intensity (NRS: 0: perception 3: pain 10: maximum pain). Stimulations were delivered with five lengths (20, 40, 60, 80, 100 mm) and three velocities (10, 30 and 100 mm/s). To estimate the directional discrimination threshold (DDT) the data was fitted to a sigmoidal curve.

Results

For the lower intensity (39 ^oC) the DDT was 81.8 mm for the slowest velocity, and above 100 mm for the two faster velocities. For the higher intensity (46 ^oC) the DDT was 58.8 and 69.6 mm for the slowest velocity and middle velocity, respectively, and above 100 mm for the fastest velocity. The perceived intensity increased with stimulation length, stimulation intensity and decreasing velocity (LMM, $p < 0.001$).

Conclusions

This study shows how the DDT for thermal stimuli is shorter for higher intensity and lower displacement velocities. Additionally, it was shown that for the velocity where directional discrimination is optimal for mechanical stimuli it is not possible to discriminate a thermal stimulus.

Keywords

Directional discrimination, laser stimulation, noxious intensity, innocuous intensity

Introduction

The tempo-spatial discrimination of cutaneous stimuli has only been vaguely investigated within the pain domain. The ability to discriminate the direction of a moving stimulus is lower for noxious laser stimuli compared to innocuous mechanical stimuli (Frahm et al., 2018, 2019). This finding is in line with studies showing that the 2-point discrimination threshold is poorer for noxious stimuli compared to innocuous stimuli (Frahm et al., 2018; Martikainen and Pertovaara, 2002; Mørch et al., 2010). Several studies have compared the single point localization ability of innocuous and noxious stimuli and one study found that localization is better for innocuous stimuli than noxious stimuli (Ylioja et al., 2006) while two other studies found that localization is similar between innocuous and noxious stimuli (Martikainen and Pertovaara, 2002; Schlereth et al., 2001). Most of the studies investigating 2-point discrimination or single point localization apply mechanical touch stimuli to test the discrimination of innocuous stimuli (Frahm et al., 2018; Martikainen and Pertovaara, 2002; Mørch et al., 2010; Schlereth et al., 2001; Ylioja et al., 2006) and radiant laser heat to test noxious stimuli (Frahm et al., 2018; Mørch et al., 2010; Schlereth et al., 2001; Ylioja et al., 2006). It is somewhat surprising that most studies applied different modalities (mechanical and thermal) to compare the discrimination of innocuous and noxious stimuli – because any differences between innocuous and noxious intensities may in part reflect differences between sensory modalities. One study did compare both innocuous and noxious mechanical stimuli and found that localization of noxious mechanical stimuli was better than for innocuous mechanical stimuli (Schlereth et al., 2001). However, the authors argued that this could be due to the fact that the noxious mechanical will inherently activate both nociceptive and non-nociceptive tactile receptors, thus, the improved single point localization ability may be due to synergy between the two sensory sub-systems (Schlereth et al., 2001). A similar prospect could be expected if applying noxious directional mechanical stimuli. In addition, the directional discriminative abilities for both innocuous and noxious thermal stimuli have not been investigated.

The neural background for sensing directional (orientation) information has been studied extensively for the visual cortex, demonstrating how such tuning is one the most prominent features of neurons in V1 (Mazer et al., 2002). For cutaneous mechanical stimuli, it has been shown that part of the underlying neural mechanism behind directional discrimination, may be the presence of tactile direction-sensitive neurons in the primary somatosensory cortex (Costanzo and Gardner, 1980; Essick and Whitsel, 1985a). These neurons are sensitive to stimuli being displaced at velocities of 30-350 mm/s (Costanzo and Gardner, 1980; Dreyer et al., 1978; Essick and Whitsel, 1985a, 1985b), with a maximum sensitivity around 100-200 mm/s (Costanzo and Gardner, 1980). Discrimination of noxious stimuli may depend on similar cortical mechanisms (Frahm et al., 2018), and it is conceivable that for nociceptive stimulation any directional discrimination may depend on the displacement velocity.

This study investigated whether the directional discrimination differed between innocuous and noxious laser stimuli. Besides the stimulation intensity, it was also hypothesized that the discrimination of the stimulus direction improves when the stimulus is displaced at lower velocities. Thus, the aims of this study were to investigate how directional discrimination depends on 1) the stimulation intensity and 2) the displacement velocity.

Methods

Subjects

Fifteen healthy subjects agreed to participate in this study (7 females, mean age 27.8 ± 4.1 years). The subjects were placed in a bed with inclined back rest during the experiment. The right forearm was kept horizontal and supported by a pillow. The hand was supinated during the stimulation. The forearm was stimulated with both painful and non-painful laser heat stimuli. To ensure compliance with the Declaration of Helsinki, all participants received both written and oral information about the experiment, and gave written consent prior to the experiment. The experiment was approved by the local ethical committee (N-20140093).

Laser stimulation

A 100 W CO_2 laser (Firestar ti-series, Synrad, USA) was used to deliver the laser stimuli. The beam of the laser was directed through a beam expander (5x) and then into a scanner head (GSI Lumonics General Scanning XY10A). The scanner head allowed rapid and accurate displacement of the laser beam. The beam diameter was 5 mm. Throughout the experiment, the skin temperature was monitored using an Agema 900 (FLiR, Sweden) infrared (IR) camera, at a rate of 30 frames per second. The experiment was stopped if the skin temperature exceeded 50 ^{o}C. The stimulation temperature was measured as the hottest pixel(s) during stimulation.

Two stimulation intensities were applied in this study. For the low intensity, the laser was calibrated to obtain a skin surface temperature of 39±1^{o}C and for the high intensity the laser intensity was calibrated to obtain a skin surface temperature of 46±1^{o}C. The calibration of the laser intensity was based on the IR recordings, if the measured skin temperature was below the desired range (39±1^{o}C or 46±1^{o}C) the laser intensity was increased until the desired skin temperature was reached and vice versa. During stimulation, both the investigator and subject wore protective goggles.

Experimental protocol

During the laser stimulation, the laser beam was displaced across the skin using three different displacement velocities (10, 30 and 100 mm/s). Two different stimulation directions were used, either distally towards the hand or proximally towards the elbow. Five different lengths of displacement were used (20, 40, 60, 80, and 100mm) to determine the directional discrimination threshold. All combinations of intensity, direction, displacement velocity, and stimulation length were delivered twice in randomized order.

After each stimulation, the subjects indicated the direction of the laser stimulus (proximal or distal, forced choice) and they rated the perceived intensity on a NRS scale. The NRS scale was set as 0: perception threshold, 3: pain threshold, 10: maximum pain. The subjects were allowed to use one decimal point on the scale. This scale was used since the stimuli were expected to be perceived both below and above the pain threshold. Subjects were instructed that the pain threshold was defined as when the stimulation elicited a pricking/sharp sensation.

Threshold estimations

To determine the directional discrimination threshold (DDT) for the laser line stimuli, the responses for each combination of velocity and intensity were fitted to a sigmodal curve (Matlab, Natick, MA, USA) (Mørch et al., 2010; Schlereth et al., 2001) (Eq. 1).

$$y = \frac{0.5}{1 + e^{(a(b-x))}} + 0.5 \qquad \text{Eq. 1}$$

where x is the stimulation length, b corresponds to the point where y = 0.75, and a is the slope of the curve at this point. In this equation 0.75 corresponds to the point where the subjects answer 75 % correct, i.e. half between merely guessing and absolute certainty (Mørch et al., 2010).

Modelling the temperature distribution in the skin

A finite element (FE) model was used to investigate how heating of the skin depends on stimulation intensity and displacement velocity. This model was expanded from a previously developed 2D model (Frahm et al., 2010) into a 3D model and implemented in COMSOL Multiphysics 5.3a (COMSOL A/S, Stockholm, Sweden). The model XY dimensions were 15 x 5 cm, and the model had two layers to simulate epidermis and dermis, these layers were 60 µm and 1.3 mm thick, respectively (Frahm et al., 2010; Mørch et al., 2015). The same three velocities (10, 30, and 100 mm/s) and both the low and high stimulation intensities (39 and 46 ^{0}C), which were used experimentally, were simulated in the model. The initial tissue temperature in the model was set to 35 ^{0}C, and the lower boundary was fixed at 35 ^{0}C simulating the heat sink through blood vessels in the lower dermis (Frahm et al., 2010).

$$Q(\boldsymbol{r},t) = P_{in}\mu_a e^{(-\mu_a z)}\frac{1}{\sigma\sqrt{2\pi}}e^{\left(\frac{-(x-(\frac{t}{a}+b))^2}{2\sigma^2}\right)} \quad \text{Eq. 1}$$

Where $\boldsymbol{r}$ is the spatial coordinate (consisting of the coordinates *x,y, and z*), t is time, P_{in} is the laser power, μ_a is the absorption coefficient and σ is the radius of the laser beam (2.85 mm, 1/e^2). The moving of the stimulus is expressed using the parameters a and b. For the 10 mm/s velocity, a was 100 and b was 1.5e-2, for the 30 mm/s velocity a was 33 and b was -0.0053, for the 100 mm/s velocity, a was 10 and b was -0.075.

The simulated power settings were fitted to obtain the same skin surface temperature as used experimentally. For the lower stimulation temperature the fitted power settings were 0.52, 1.0285 and 2.39 W for the 10, 30 and 100 mm/s velocities, respectively. For the higher stimulation temperature the fitted power settings were 1.425, 2.85 and 6.55 W. The model was solved for time points from 0 to 13 seconds, in steps of 0.05 seconds. The stimulation onset was set at 1 sec and lasted 10, 3.3 and 1 seconds depending on stimulation velocity (simulating a 100 mm stimulation length). The meshed model consisted of 21056 domain elements and 16328 boundary elements, with a total of 117023 degrees of freedom. After solving the model, the maximum temperatures at the skin surface and at the dermo-epidermal junction (DEJ) were extracted. The DEJ temperatures were used as estimate of the temperature which the nerve receptors were exposed to during stimulation (Frahm et al., 2010).

Statistics & data analysis

Normality was confirmed before the statistical test were applied.

The NRS for the line stimulations were analyzed in a linear mixed model (LMM). The stimulation direction, length, intensity and displacement velocity were used as factors.

A logistic regression model was used to investigate differences in correctness for the laser line responses. Factors were set as stimulation direction and whether the stimulation was perceived as painful.

p-values less than 0.05 was considered significant. The statistical tests were performed using SPSS 23 (IBM, Armonk, NY, USA). Results are reported as mean +/- standard deviation.

The thermographic data during the moving laser stimulation was extracted to find the skin surface temperature during the stimulation. This was normalized and averaged across all stimulation velocities (10 to 100 mm/s), stimulation lengths (20 to 100 mm), directions and repetitions and done so for both the 39 ^{0}C and 46 ^{0}C stimulation intensities (Fig. 1).Results

The skin temperature of the subjects never exceeded 50 ^{o}C and no subjects reported skin damages following their participation in the study.

The average stimulation temperature for the low and high intensity during the moving laser stimulation is depicted in Fig. 1. The infrared recordings show that the skin surface temperatures were within the expected ranges, i.e. 39±1^{o}C for the low intensity and 46±1^{o}C for the high intensity. Though, it can be noted that when stimulation started the laser had a brief ramp-up period before the desired intensity was reached.

[Insert Figure 1]

Directional discrimination

For the slowest displacement velocity (10 mm/s) the DDT was 81.8mm (r^2=0.98, 95% CI: 74.8-88.8 mm, Fig. 2) for the lower temperature (39 ^{o}C), for the higher temperature (46 ^{o}C) the DDT was 58.8 mm (r^2=0.93, 95% CI: 43.8-73.8 mm, Fig. 2).

For the middle velocity (30 mm/s) it was not possible to accurately fit a sigmoidal curve for the lower stimulation intensity (39 ^{o}C). However, for the higher intensity (46 ^{o}C) the DDT was 69.6 mm (r^2=0.90, 95% CI: 52.4-86.9 mm, Fig. 2).

It was also not possible to accurately fit a sigmoidal curve for the fastest displacement velocity (100 mm/s) for neither of the intensities. Evidently, the discrimination threshold is above 100 mm for the high displacement velocity.

[Insert Figure 2]

Perceived intensities

Out of the high intensity stimulations 78 % of stimuli were perceived as painful for the 10 mm/s velocity, 60 % of stimuli were perceived as painful for the 30 mm/s velocity and 43 % of stimuli were perceived as painful for the 100 mm/s velocity. The perceived intensities increased with stimulation intensity and length (LMM, $p<0.001$, Fig. 3), in contrast the perceived intensity decreased with increasing stimulation velocity (LMM, $p<0.001$, Fig. 3). But there were no differences in perceived intensity in relation to the stimulation directions (LMM $p=0.106$, Fig. 3).

[Insert Figure 3]

The logistic regression showed that the stimulation direction were more often perceived correctly when the stimulation was perceived as painful (log. reg., $p<0.001$).

Stimulation temperature at receptor level

The FE model showed that similar skin surface temperatures were obtained for different displacement velocities (Fig. 4). But despite similar temperatures at the skin surface, increasing the displacement velocity is associated with lower temperatures at the DEJ (Fig. 4) where thermoreceptors and nociceptors most likely terminate. During the temperature plateau, the average temperature at the DEJ was between 0.4 and 3.1 ^{0}C lower than the skin surface temperature.

[Insert Figure 4]

Discussion

This study, showed that the directional discrimination improves when the displacement velocity is reduced and when the stimulus intensity is painful. The perceived intensities were lower for faster displacement velocities. Our mathematical model results indicated that the perceived intensities, can partly be explained by thermal conduction mechanisms in the skin.

Directional discrimination

The directional discrimination task used in this study could potentially provide insights into the function and integration in the sensory system (Frahm et al., 2018), since this task depends on the function of higher-order neural circuits. In fact we have recently showed how the directional discrimination is altered following capsaicin sensitisation (Frahm et al., 2019). It is not known if the neural mechanism underlying directional discrimination is identical to the tactile direct-sensitive neurons demonstrated in the primary somato-sensory cortex (Costanzo and Gardner, 1980), however, directional discrimination may, similarly to saltation illusion, potentially be a method to investigate changes in cortical representation (Trojan et al., 2006). To this end, studies have shown how nociceptive and mechano-receptive sensory information appear to converge onto similar cortical areas (Iannetti et al., 2008; Mouraux et al., 2011). This is despite the sensory information following different paths in the spinal cord, where the nociceptive information is conveyed via the spinothalamic tract and the mechano-receptive information is conveyed via the dorsal lemniscal tract.

Overall the results show that directional discrimination is better for noxious stimuli and low displacement velocities (Fig. 2). In fact, the direction could not be discriminated correctly for the highest velocity (100mm/s), and no fit could be created. Additionally it should be noted that the majority of the stimuli at 100 mm/s were not perceived as painful, therefore exact conclusions regarding the underlying cause regarding the lower discrimination ability seen at this velocity cannot be drawn. This, lower discrimination ability, is surprising since this velocity (100 mm/s) is within the range of maximum sensitivity for tactile moving stimuli (Costanzo and Gardner, 1980). Thus, these findings demonstrate that sensory information from mechanical and thermal modalities may be fundamentally differently integrated in the sensory system, and it may reflect that the displacement velocity to which nociceptive direction-sensitive neurons are most sensitive, is lower than the velocities where tactile neurons are most sensitive (Essick and Whitsel, 1985a).

The better directional discrimination for noxious thermal stimuli found in this study, is highly interesting in relation to our previous study (Frahm et al., 2018) where we showed that the directional discrimination is better for innocuous mechanical stimuli compared to noxious laser heat stimuli. This indicates the importance of stimulation modality (mechanical vs. laser heat) when investigating the discriminative abilities and furthermore, these findings indicate that even for the same modality the tempo-spatial sensory information may be integrated differently. Obviously this could be due to activation of different fiber types. The low intensity (39 ^oC) will most likely activate a group of warmth sensitive C-fibers whereas the higher intensity (46 ^oC) most likely will activate nociceptive C-fibers, but, as discussed below, also nociceptive Aδ fibers and to a lesser degree warmth sensitive C-fibers (Treede et al., 1995). If Aδ fibers are activated, this would also imply that the sensory information would reach the brain earlier due to the higher conduction velocity of Aδ fibers (Kakigi et al., 1991; Treede et al., 1995). This may improve the ability to discriminate the direction of the stimulus due to less latency jitter compared to C-fiber mediated information. The results from the FE model supports this, showing that Aδ fiber activation is unlikely for the lower stimulation intensity (39 ^oC). Furthermore, Aδ activation is also unlikely for the higher intensity (46 ^oC) during the highest velocity (100 mm/s) due to a maximum temperature of less than 43 ^oC at the DEJ (Fig. 4). Regarding the DEJ temperature simulations it is important to note that this is only an estimate of receptor temperature, we choose the DEJ as we previously found evidence for the highest abundance of receptors in humans to be at this depth (Frahm et al., 2010) however, studies in primates found that heat sensitive nociceptors may be located in depths ranging from 20 to 570 µm (Tillman et al., 1995a), meaning the receptors can both be located more superficially *or* deeper than the DEJ. However, the difference in receptor temperature cannot solely explain the differences in directional discrimination. This is seen in Fig. 2, as the discrimination of the fast and high intensity stimulation (100 mm/s and 46 ^{o}C – receptor temperature approx. 43 ^{o}C, Fig. 4) is still poorer than the slow and low intensity stimulation (10 mm/s and 39 ^{o}C – receptor temperature approx. 38.5 ^{o}C, Fig. 4). Thus, since fast and high intensity stimulation (DEJ temperature 43 ^{o}C) yields worse discrimination than a low and slow stimulation (DEJ temperature 38.5 ^{o}C) – this may indicate that different discrimination abilities cannot be solely explained by differences in stimulation intensity.

Similarly, Aβ fibers have higher conduction velocities than both Aδ and C-fibers and therefore associated with even less latency jitter as a possible explanation for the better directional discrimination for tactile stimuli compared to noxious stimuli in our previous study (Frahm et al., 2018).

Costanzo & Gardner (1980) hypothesized that the neural signalling of the displacement either could be coding via the firing rate of the individual neurons or via how fast the neural activity shifts across the primary somato-sensory cortex (Costanzo and Gardner, 1980). In that case the inclusion of sensory information from Aδ fibers may affect the firing rate of the neurons in the cortex due to faster arriving sensory information. Furthermore, the information from Aδ fibers may also affect how the peak activity in the cortex moves due to higher temporal contrast in the sensory signal from the Aδ fibers. If information from both Aδ and C-fibers travels across the cortex then the information from the C-fibers will reach cortex later that of the Aδ fibers, due to different conduction velocities as discussed below. This would cause the sensory information to have different delays when it travels across the cortex, potentially reducing the directional discrimination.

Finally, the improved directional discrimination for the higher intensity may not necessarily be related to the noxious nature of the stimulus. Thus, the increase in skin temperature may be part of the reason for the improved discrimination as a study using pre-heated and pre-cooled metal probes found that tactile acuity improves if the probes are warmer or colder than normal skin temperature (Stevens, 1982). However, that study used metal stimulators that were cooled or heated in water baths to be within the noxious range (0 ^{o}C for cold, and 60 ^{o}C for warm), but authors reported that the actual temperature of the stimulators had changed to the innocuous range before they were applied to the skin (Stevens, 1982). Moreover the study incidentally used a bi-modal stimulus which most likely activated several sensory modalities improving the discrimination, as hypothesized previously (Schlereth et al., 2001). Alternatively, the improved discrimination shown in that study (Stevens, 1982) may be due to increased saliency to the stimulation (Mouraux et al., 2011), caused by the increased temperature or simply due to higher contrast in the stimulation.

Stimulation temperature

The low stimulation intensity (39 ^{o}C) was chosen to be above the warm detection threshold, which is usually 36-37 ^{o}C (Defrin et al., 2002) but below the heat threshold of C-fiber nociceptors, 40-41 ^{o}C (Churyukanov et al., 2012; Treede et al., 1995). The high stimulation intensity (46 ^{o}C) was chosen to be above heat pain threshold (HPT) but sufficiently low to avoid skin burns. The perception of heat pain relies on the activation of C and Aδ-fiber nociceptors which have activation thresholds of 40-41 ^{o}C (Churyukanov et al., 2012; Treede et al., 1995) and 44-48 ^{o}C (Treede et al., 1995), respectively. Indeed, the data from the infrared camera shows that the stimulation temperatures were within the desired ranges (Fig. 1). Most likely, the higher intensity used in this study have activated C-fiber nociceptors and may have activated Aδ fiber nociceptors. It should be noted that when determining the HPT, shorter pulses or steeper temperature ramps will typically yield higher thresholds than longer lasting stimulation e.g. it has been shown that the HPT increases with the rate of the stimulation temperature due to thermal inertia of the skin (Tillman et al., 1995b). This phenomenon is also seen when using contact thermodes, where the HPT has previously been reported to be 43-46 ^{o}C for stimulation rates of 2 ^{o}C/s (Defrin et al., 2002; Yarnitsky et al., 1995) but can exceed 50 ^{o}C for higher rates (10 ^{o}C/s) (Pertovaara et al., 1996). Similar to thermodes, CO_2 lasers only heat the most superficial part of the skin (Frahm et al., 2010), this means that the thermal energy will have to be passively conducted deeper into the skin where the nerve endings are located. For CO_2 lasers, studies have shown that shorter pulses (50 ms) yield slightly higher HPT compared to longer laser pulses (1 s) (Churyukanov et al., 2012; Treede et al., 1995). These aspects generally fit well the findings in the present study, showing that faster laser beam displacement velocities are perceived less intense, despite similar skin surface temperatures for all velocities. One major cause for the lower perceived intensity appears to be the thermal conduction mechanism in the skin. The FE model in this study showed how faster stimulation velocities caused the temperatures around the nerve receptors to be lower than during slower velocities, despite similar surface temperatures (Fig. 4). Ideally, the thermal conduction mechanisms of the skin should be taken into account during the experiment to ensure that the receptors are exposed to similar temperatures irrespective of the stimulation velocity. This is, however, not feasible as several factors will affect the achieved temperature during stimulation. Such factors mainly relate to differences in the skin both within and between subjects, e.g. skin composition, hydration, initial skin temperature etc. This is supported by the fact that it was necessary to adjust the stimulation intensity for each individual subject to achieve the desired temperature at the skin surface.

Perceived intensities

Similarly to our previous study (Frahm et al., 2018), we showed that the perceived intensity increased with stimulation length (Fig. 3), this is most likely due to combination of both spatial and temporal summation, firstly, because longer stimuli will be displaced across more receptive fields, leading to spatial summation – and secondly the longer length stimuli are associated with longer stimulus duration, leading to temporal summation (Pedersen et al., 1998; Staud et al., 2006). Similarly the reduction in reported NRS for faster velocities may firstly indicate a lower degree of temporal summation due to shorter duration of the stimulus, however, the FE model indicates that part of reason for the lower NRS is due to thermal conduction in the skin causing the nerve receptors to be exposed to a lower temperature during faster velocities (Fig. 4). Secondly, the moving stimuli will move into skin area, which surrounds the already stimulated receptive fields. This may impose a net reduction in the neural signals along the neuro-axis due to lateral inhibition (Békésy, 1962). It is likely that the amount of lateral inhibition will depend on both temporal and spatial factors which may favor the fast velocities employed in the present study, which in turn will reduce the perceived intensity (Quevedo et al., 2017).

Conclusion

The current study showed how the directional discrimination ability is better with a higher, most often painful stimulation temperature and low displacement velocities. In addition, the study showed that the neural mechanisms underlying directional discrimination of thermal stimuli may be distinctively different compared to the mechano-receptive modality. Finally, the directional discrimination task used in this study show that differences between directional discrimination of innocuous and noxious stimuli are not purely due to use of different modalities, but stimulation intensity affects the discrimination greatly.

Authors' contributions

KSF, CDM and OKA conceived and designed the study. KSF performed the experiments. KSF, CDM and OKA analysed and interpreted the data. KSF drafted the manuscript. KSF, CDM and OKA revised the manuscript. All authors have read and approved the final version of the manuscript.

References

Békésy, G.V. (1962). Lateral inhibition of heat sensations on the skin. *J Appl Physiol* 17, 1003–1008.

Churyukanov, M., Plaghki, L., Legrain, V., Mouraux, A. (2012). Thermal Detection Thresholds of Aδ- and C-Fibre Afferents Activated by Brief CO2 Laser Pulses Applied onto the Human Hairy Skin. *PLoS One* 7, 1–10.

Costanzo, R.M., Gardner, E.P. (1980). A Quantitative Analysis of Responses of Direction-Sensitive Neurons in Somatosensory Cortex of Awake Monkeys. *J Neurophysiol* 43, 1319–1341.

Defrin, R., Ohry, A., Blumen, N., Urca, G. (2002). Sensory determinants of thermal pain. *Brain* 125, 501–510.

Dreyer, D.A., Hollins, M., Whitsel, B.L. (1978). Factors influencing cutaneous directional sensitivity. *Sens Processes* 2, 71–79.

Essick, G.K., Whitsel, B.L. (1985a). Assessment of the Capacity of Human Subjects and S-I Neurons to Distinguish Opposing Directions of Stimulus Motion Across the Skin. *Brain Res Rev* 10, 187–212.

Essick, G.K., Whitsel, B.L. (1985b). Factors Influencing Cutaneous Directional Sensitivity: A Correlative Psychophysical and Neurophysiological Investigation. *Brain Res Rev* 10, 213–230.

Frahm, K.S., Andersen, O.K., Arendt-Nielsen, L., Mørch, C.D. (2010). Spatial temperature distribution in human hairy and glabrous skin after infrared CO2 laser radiation. *Biomed Eng Online* 9, 69.

Frahm, K.S., Mørch, C.D., Andersen, O.K. (2018). Tempo-spatial discrimination is lower for noxious stimuli than for innocuous stimuli. *Pain* 159, 393–401.

Frahm, K.S., Mørch, C.D., Andersen, O.K. (2019). Cutaneous nociceptive sensitization affects the directional discrimination – but not the 2-point discrimination. *Scand J Pain* 19, 605–613.

Iannetti, G.D., Hughes, N.P., Lee, M.C., Mouraux, A. (2008). Determinants of Laser-Evoked EEG Responses: Pain Perception or Stimulus Saliency? *J Neurophysiol* 100, 815–828.

Kakigi, R., Endo, C., Neshige, R., Kuroda, Y., Shibasaki, H. (1991). Estimation fo conduction velocity of Adelta fibers in humans.pdf. *Muscle Nerve* 14, 1193–1196.

Martikainen, I.K., Pertovaara, A. (2002). Spatial discrimination of one versus two test stimuli in the human skin : dissociation of mechanisms depending on the task and the modality of stimulation. *Neurosci Lett* 328, 322–324.

Mazer, J.A., Vinje, W.E., McDermott, J., Schiller, P.H., Gallant, J.L. (2002). Spatial frequency and orientation tuning dynamics in area V1. *PNAS* 99, 1645–1650.

Mørch, C.D., Andersen, O.K., Quevedo, A.S., Arendt-Nielsen, L., Coghill, R.C. (2010). Exteroceptive aspects of nociception: Insights from graphesthesia and two-point discrimination. *Pain* 151, 45–52.

Mørch, C.D., Frahm, K.S., Coghill, R.C., Arendt-Nielsen, L., Andersen, O.K. (2015). Distinct temporal filtering mechanisms are engaged during dynamic increases and decreases of noxious stimulus intensity. *Pain* 156, 1906–1912.

Mouraux, A., Diukova, A., Lee, M.C., Wise, R.G., Iannetti, G.D. (2011). A multisensory investigation of the functional significance of the “pain matrix.” *Neuroimage* 54, 2237–2249.

Pedersen, J.L., Andersen, O.K., Arendt-Nielsen, L., Kehlet, H. (1998). Hyperalgesia and temporal summation of pain after heat injury in man. *Pain* 74, 189–197.

Pertovaara, A., Kauppila, T., Hämäläinen, M.M. (1996). Influence of skin temperature on heat pain threshold in humans. *Exp Brain Res* 107, 497–503.

Quevedo, A.S., Mørch, C.D., Andersen, O.K., Coghill, R.C. (2017). Lateral Inhibition during Nociceptive Processing. *Pain* 158, 1046–1052.

Schlereth, T., Magerl, W., Treede, R. (2001). Spatial discrimination thresholds for pain and touch in human hairy skin. *Pain* 92, 187–194.

Staud, R., Price, D.D., Fillingim, R.B. (2006). Advanced Continuous-Contact Heat Pulse Design for Efficient Temporal Summation of Second Pain (Windup). *J Pain* 7, 575–582.

Stevens, J.C. (1982). Temperature can sharpen tactile acuity. *Percept Psychophys* 31, 577–580.

Tillman, D.B., Treede, R.D., Meyer, R.A., Campbell, J.N. (1995a). Response of C fibre nociceptors in the anaesthetized monkey to heat stimuli: estimates of receptor depth and threshold. *J Physiol* 485, 753–765.

Tillman, D.B., Treede, R.D., Meyer, R.A., Campbell, J.N. (1995b). Response of C fibre nociceptors in the anaesthetized monkey to heat stimuli: correlation with pain threshold in humans. *JPhysiol* 485 (Pt 3, 767–774.

Treede, R.D., Meyer, R.A., Raja, S.N., Campbell, J.N. (1995). Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. *J Physiol* 483, 747–758.

Trojan, J., Stolle, A.M., Kleinbo, D., Mørch, C.D., Arendt-Nielsen, L., Hölzl, R. (2006). The saltation illusion demonstrates integrative processing of spatiotemporal information in thermoceptive and nociceptive networks. *Exp Brain Res* 170, 88–96.

Yarnitsky, D., Ruth Zaslansley, S., HemJi, J.A. (1995). Heat pain thresholds: normative data and repeatability. *Pain* 60, 329–332.

Ylioja, S., Ve Carlson, S., Raij, T.T., Pertovaara, A. (2006). Localization of touch versus heat pain in the human hand: A dissociative effect of temporal parameters on discriminative capacity and decision strategy. *Pain* 121, 6–13.

Figure legends

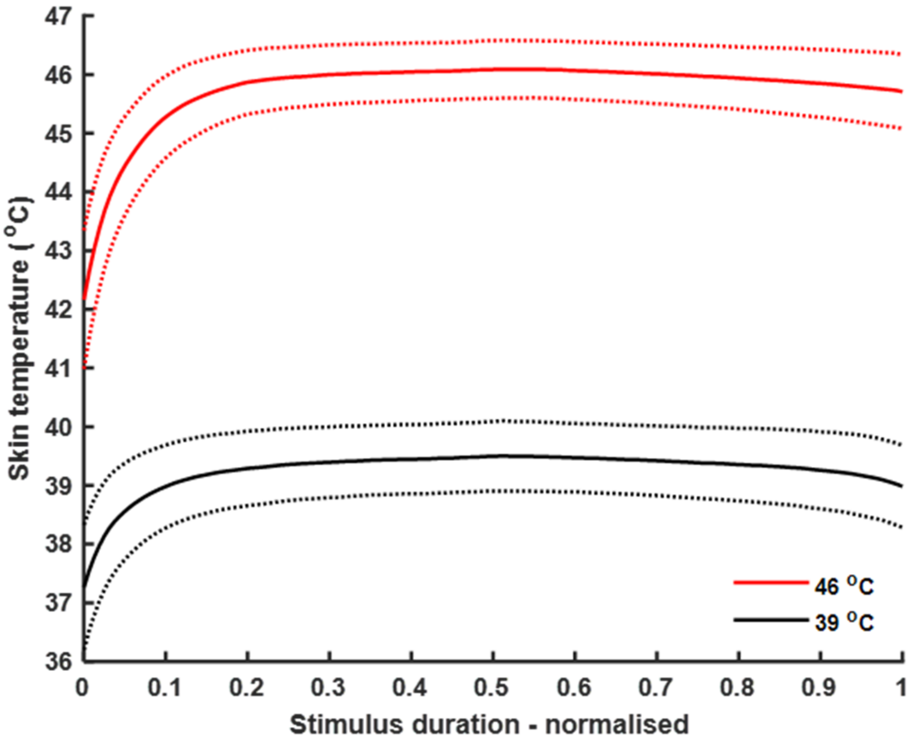
Fig. 1 – Grand average of the maximum skin temperatures during the moving laser stimulation across subjects, stimulation length and direction for both low intensity (39^{o}C) and high intensity (46 ^{o}C). The data from the infrared camera was extracted for each stimulation and resampled so data could be averaged for various stimulation lengths. The profiles were normalized across the duration (s) of the stimulation, which depended on path length and displacement velocity (i.e. shortest lasting stimuli were 20 mm at 100 m/s, meaning a duration of 0.2 s, and longest lasting stimuli was 100 mm at 10 mm/s, meaning a duration of 10 s). Full line: grand average for all subjects, dashed line: standard deviation of the grand average. Note that the initial temperature rise was truncated due to different stimulation length/durations.

Fig. 2 – Directional discrimination for three different displacement velocities (top: 10mm/s, middle: 30mm/s, bottom: 100 mm/s) and two different intensities (black: 39^{o}C, red: 46^{o}C). Circles indicate average responses across subjects and the full line a sigmoidal fit to determine the directional discrimination threshold. The dashed lines indicate the 95% CI of the fit. The DDT for the slower velocity (10mm/s, top pane) was 81.8 mm for the lower intensity and 58.8mm for the higher intensity. For the middle velocity (30 mm/s, middle pane) the DDT was 69.6mm for the higher intensity, but for the lower intensity no fit could be created (DDT > 100 mm). For the fastest velocity (100 mm/s, bottom pane), no fit could be created for neither intensity (DDT > 100 mm). Note: y-axis are differently truncated for each intensity for better visualization.

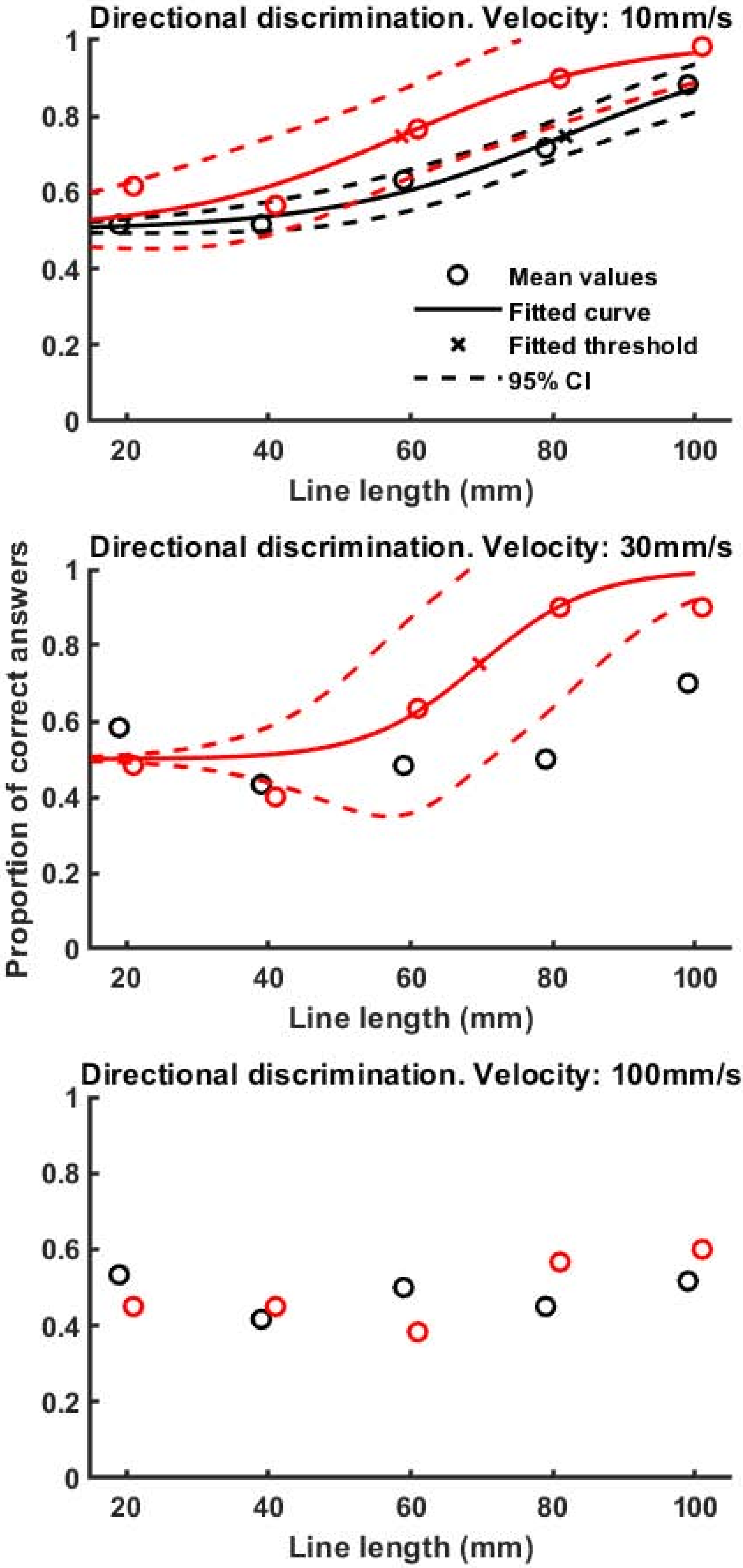
Fig. 3 – Perceived intensities for the stimulations. The perceived intensity was significantly higher for slower velocities, longer stimulation lengths and high intensity (LMM, $p<0.001$). Horizontal line in NRS=3 indicates pain threshold. The triangles indicate stimulus direction, upwards: proximal direction –

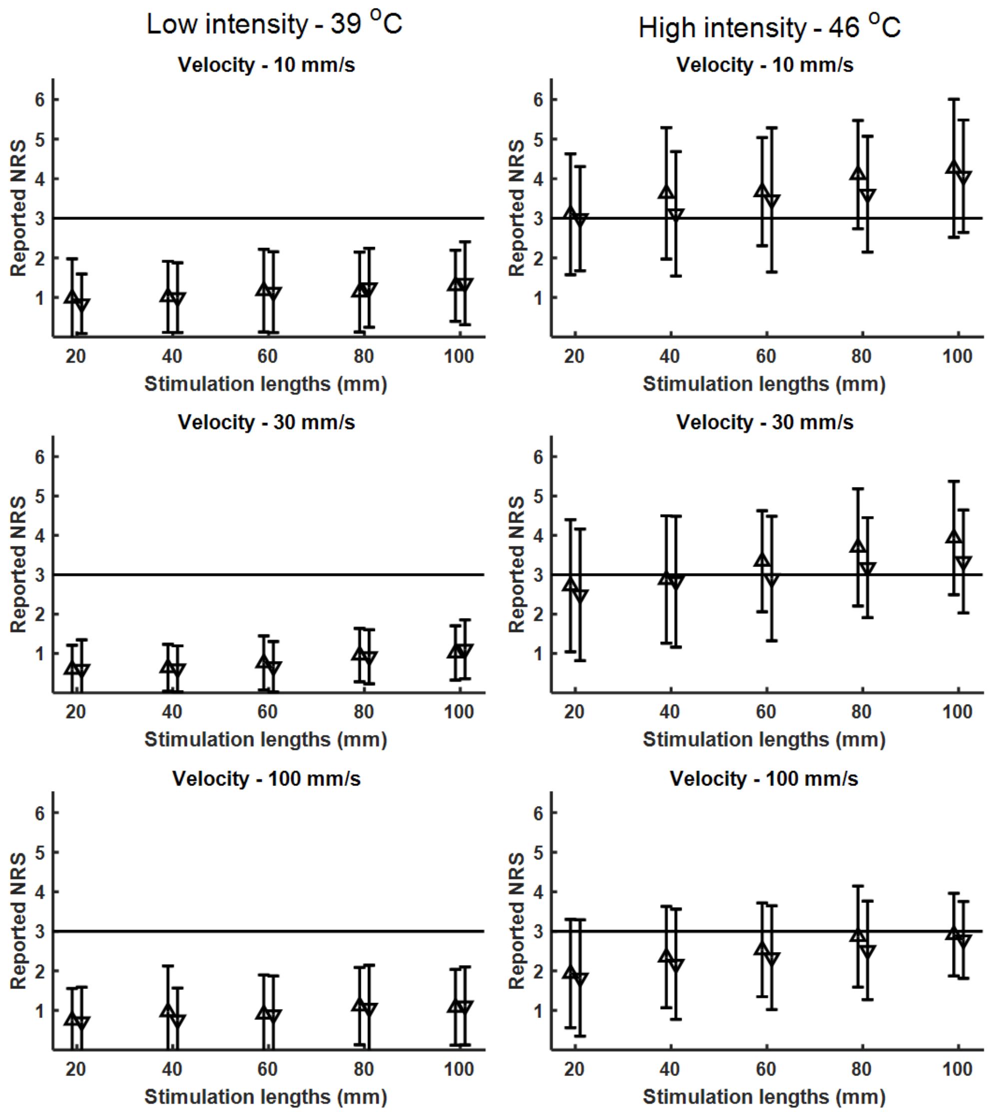
downwards: distal direction. Note: y-axis are differently truncated for each intensity for better visualization.

Fig. 4 – Simulated tissue temperatures during stimulation. The figure depicts the temperature profiles in different depth at the stimulus location during the moving stimulus. Left: simulation of the lower stimulation temperature (39 ^{o}C). Right: simulation of the higher stimulation temperature (46 ^{o}C). The model demonstrates how the temperatures at different depths are decreased for increasing displacement velocities. The top row depicts the 10mm/s stimulation velocity, the middle row depicts the 30mm/s stimulation velocity, and the bottom row depicts the 100mm/s stimulation velocity. Note: the stimulation durations were normalised.

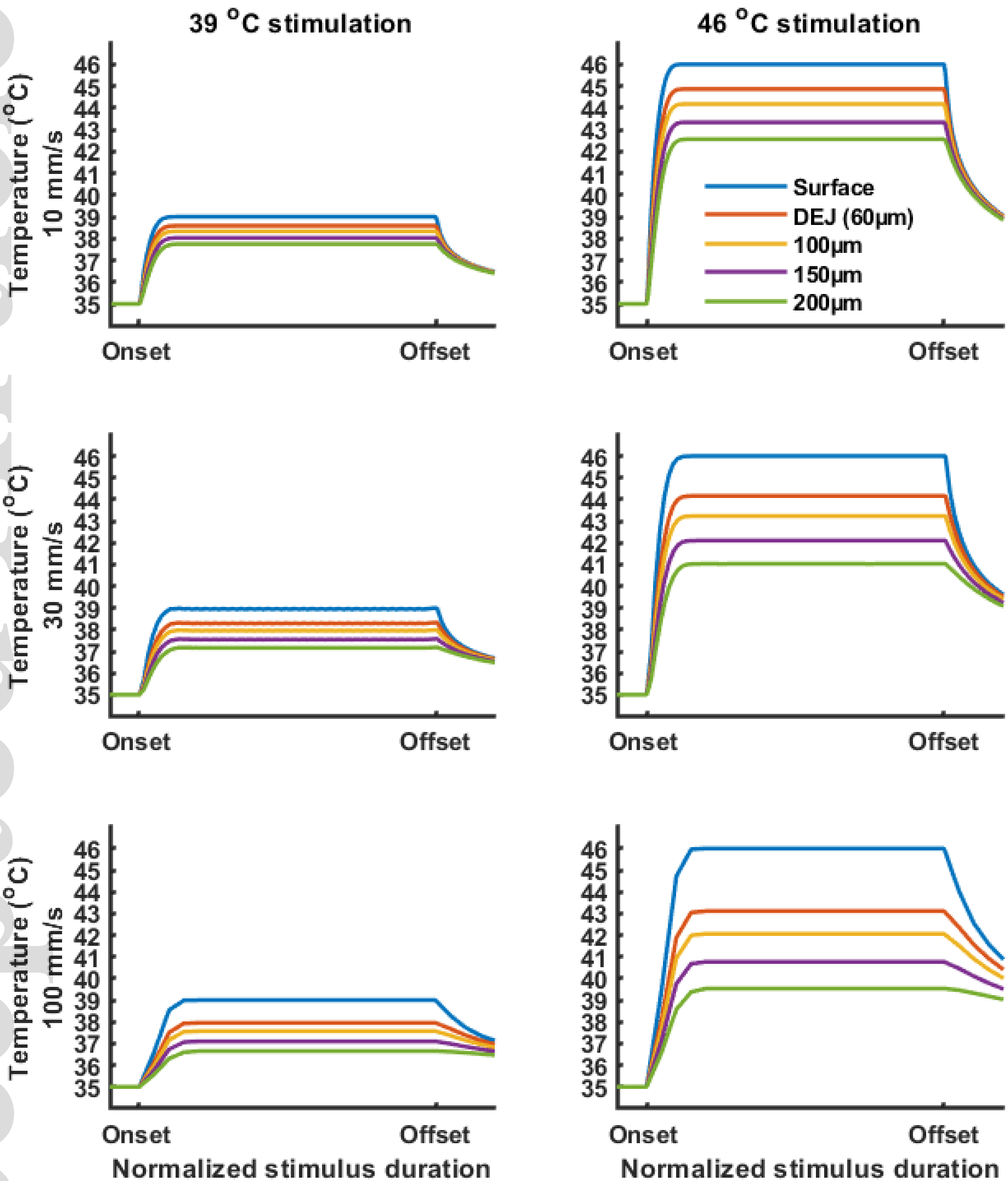


ejp_1521_f1.tif


Directional discrimination. Velocity: 10mm/s
Mean values
Fitted curve
Fitted threshold
95% CI
Directional discrimination. Velocity: 30mm/s
Directional discrimination. Velocity: 100mm/s
Proportion of correct answers
Line length (mm)
0
0.2
0.4
0.6
0.8
1
20
40
60
80
100



ejp_1521_f3.tif



ejp_1521_f4.tif