Modulation of spinal nociceptive excitability by nociceptive-visual interaction

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Conflict of interest

The authors declare no conflict of interest.

Abstract

Background. The existence of multisensory interactions between nociception and vision has recently been demonstrated, by showing that near visual stimuli can influence nociceptive perception. However, although such interactions have been hypothesized to serve a motor function, their effects on nociception-related motor responses have not been investigated yet. The aim of the present study was, therefore, to investigate whether spinal nociceptive excitability, measured with the nociceptive withdrawal reflex (NWR), can be modulated by the presence of dynamic visual stimuli, and whether this would be specifically the case for visual stimuli presented near the stimulated lower limb. **Methods.** NWRs were elicited by applying transcutaneous electrical stimuli at the sole of the foot of healthy participants. The electrical stimulus was either preceded by a visual stimulus rapidly approaching a location near the stimulated foot, a visual stimulus approaching a location further away from the stimulated foot, or applied without any visual stimulus (baseline). Measures of interest were NWR amplitude, latency and perceived intensity of the electrical stimuli. **Results.** Results show that NWR amplitude was significantly increased (change from baseline ~30%) by the presence of a visual stimulus, but no significant difference between near vs. far visual stimuli. There were furthermore no significant effects on NWR latency and perceived intensity. **Conclusions.** This suggests that spinal nociceptive excitability can be modulated by the presence of external visual stimuli that have no explicit emotional or task-related valence. Whether the proximity of the visual stimuli might play a role in such interactions needs to be further investigated.

1. Introduction

There is increasing evidence in recent years that pain and other nociceptive responses do not only depend on how noxious stimuli are coded, transmitted and processed in the nociceptive system, but also on interactions with other sensory modalities. The majority of those studies focused on the perceptual effects of such multisensory interactions, and demonstrated for example that the presence of visual stimuli can influence the detection, the perceived intensity and temporal perception of experimental nociceptive stimuli (e.g. De Paepe et al., 2014; Filbrich et al., 2019; Pomper et al., 2013). These interactions have furthermore been shown to be mutual, since the presentation of acute nociceptive stimuli can also affect how visual stimuli surrounding the body are perceived (e.g. Filbrich, Alamia, Blandiaux, et al., 2017). Importantly, such multisensory effects might also be of relevance in the context of certain chronic pain disorders, as it has for example been shown that the perception of the visual space surrounding the painful limb can be affected in complex regional pain syndrome (Bultitude et al., 2017; Filbrich, Alamia, Verfaille, et al., 2017). While the existence of nociceptive-visual interaction effects on perception seems now established, their effects on nociception-related motor responses have not been investigated. It is generally assumed that such interactions would rely on the existence of a multisensory cortical system that gives processing priority to stimuli that are the most meaningful for homeostasis, with the ultimate aim to prompt adaptive behavior (Legrain et al., 2011). In the context of pain, it can accordingly be hypothesized that one of those adaptive behaviors would be to optimize defensive reactions against threatening stimuli. The present study therefore aimed at testing the potential influence of visual stimulation on nociception-related motor processes, by more specifically investigating whether spinal nociceptive excitability, as measured with the spinal lower-limb nociceptive withdrawal reflex (NWR), can be affected by the presence of external visual stimuli. This reflex, which is observed in response to noxious stimuli and induces the involuntary reaction of withdrawing the limb, can be considered as a prototype of defensive motor reactions (Sandrini et al., 2005). Previous research has repeatedly demonstrated that the

NWR, although being a spinal phenomenon, can be modulated by various cognitive and emotional factors and states (e.g. Henrich et al., 2022; Rhudy et al., 2005), showing that it is under supraspinal and even cortical descending influence, which also makes it a potential target for multisensory interaction effects. We therefore hypothesized that the presence of visual stimuli would affect the NWR induced by an electrical noxious stimulus, by modulating its magnitude and/or latency. We furthermore hypothesized that this would be specifically the case for visual stimuli presented near the stimulated lower limb, as compared to visual stimuli presented further away, as previously shown in the context of the perceptual effects of multisensory interactions between nociception and vision (e.g. De Paepe et al., 2014; Filbrich, Alamia, Blandiaux, et al., 2017). Potential effects on the perception of the electrical stimulus were also tested.

2. Methods

2.1 Participants

Twenty-four healthy volunteers were recruited for the study. Sample size was determined in G*Power 3.1, assuming a medium Cohen's f effect-size of 0.25 (within-participant design, 4 measurements, α=0.05, r=0.5) to achieve power of 0.8. General exclusion criteria were the presence of any known neurological, severe psychiatric, cardiac or chronic pain condition, any traumatic injury of the lower limbs within the 6 months preceding the experiment, any tissue damage or dermatological disease of the lower limbs, non-corrected vision difficulties, regular use of psychotropic or analgesic drugs, as well as intake of analgesic drugs within the 12 hours preceding the experiment. Three participants were excluded from the statistical analysis, based on either an absence of reflex responses in the majority of trials due to habituation (N=1) or a hypersensitivity to the electrical stimulation which led to an excessive amount of voluntary movements potentially affecting the reflex amplitude (N=2). The mean age of the remaining twenty-one participants (9 women) was 27.28 years (SD= 5.30, range 20-41 years). The experimental procedure was

approved by the local ethics committee (The North Jutland Region, Denmark Committee on Health Research Ethics; N-20180047) in agreement with the declaration of Helsinki. Participants signed an informed consent form prior to the testing session and received financial compensation.

2.2 Stimuli and apparatus

EMG recordings. Surface EMG responses of the tibialis anterior (TA) muscle of the right leg were recorded using a double differential configuration (Frahm et al., 2012). Three recording electrodes were placed in parallel on the belly of the muscle and a common reference electrode on the ipsilateral tibia (Neuroline 720, Ambu A/S, Denmark). EMG data was collected for 3 s on each trial, starting 200 ms before the first trigger. The raw EMG signals were amplified (gain 2k), online band-pass filtered (5-500 Hz), sampled at 2 kHz and stored for offline analysis.

Electrical stimulation. NWRs were elicited by transcutaneous electrical stimulation of the sole of the right foot, with a cathode electrode placed on the medial part of the arch of the foot (Neuroline 700, Ambu A/S, Denmark; diameter reduced to 6 mm (Henrich et al., 2020)) and an anode electrode placed on the dorsum of the foot (Pals 7.5 x10 cm, Axelgaard Ltd., Fallbrook, California, USA). Stimuli were delivered by means of a computer-controlled electrical stimulator (Noxitest IES 230, Aalborg University, Denmark) and consisted of a train of five 1-ms pulses delivered at 200 Hz. Stimulation intensity was set to 140% of the pain threshold (PTh) or the NWR threshold (NWRTh), taking the one with the highest value. In case this intensity was reported as too unpleasant/painful by the participant during the familiarization phase (see Procedure), stimulation intensity was changed to 120% of the PTh or the NWRTh. Both NWRTh and PTh to a single stimulus were determined using an automated staircase procedure (Jensen et al., 2015). For the NWRTh the staircase started with an intensity of 1mA and increased in steps of 2mA until a NWR was detected. The intensity then decreased in steps of 1mA until a NWR was no longer detected. Steps of 0.5 mA were used for the subsequent increases/decreases. The procedure stopped after three ascending and

three descending staircases were reached and the NWRTh was defined as the average intensity between the last two peaks and two troughs. The detection of a NWR was based on the automatic calculation of an interval peak z-score (IPZ) calculated as the difference between the peak amplitude in the NWR quantification interval (80 to 150 ms, post-stimulus window) and the baseline mean amplitude (70 ms pre-stimulus window), divided by the standard deviation of the baseline EMG (Rhudy & France, 2007). An IPZ exceeding a predefined threshold of 12 defined the presence of a NWR (France et al., 2009). The same staircase procedure was used to define the PTh, with the exception that the criterion to increase/decrease stimulation intensity was based on the verbal reports by the participants whether the stimulus was perceived as non-painful/painful.

Visual stimulation. Dynamic visual stimuli were presented by means of a 1 m strip of LEDs (NeoPixel Digital RGB LED strip, Adafruit, NY, US; controlled by an Arduino Uno). The strip was horizontally fixed on a panel placed in front of the participants' legs, with the left end of the strip placed next to the participant's right foot (see Fig. 1a). Only part of the strip was used during the experiment, with a distance of ~75 cm between the LED at the left end and the LED on the right end of the used part. The strip was configured in a way that the illumination of the LEDs always started at the LED located in the middle of the used part of the strip (yellow color, corresponding to the fixation point) before switching to a green color for the next LED and continuing towards the left (near the foot) or right end of the strip, depending on the condition (see Experimental procedure). The duration of the sequential illumination of the LEDs, from the first green illuminated LED after fixation to the last illuminated LED, was 150 ms. This sequential illumination created the illusion of movement of one single green LED moving from starting to end point.

2.3 Experimental procedure

Participants were comfortably lying on a bed in supine position with a 120° back support. After the electrode placement, the individual thresholds (see above) were assessed in counterbalanced order to

determine the individual stimulation intensity used during the experiment. Across participants, this stimulation intensity was 11.68 ± 3.29 mA (range 6.00-18.62 mA). Participants were then familiarized with the electrical and visual stimuli as well as the different conditions before starting the experiment.

During the experiment, the participants were presented with different conditions. A trial always started with the illumination of the fixation point in the middle of the strip of LEDs. In the *NWR-visual near* condition, a visual stimulus, starting 1200 ms after the illumination of the fixation point, moved from the fixation point towards the left end of the strip of LEDs, i.e. towards the right foot, and was followed by the application of the electrical stimulus on the right foot, inducing the reflex. In the *NWR-visual far* condition, a visual stimulus moved from the fixation point towards the right end of the strip of LEDs, i.e. in the opposite direction of the right foot, and was followed by the application of an electrical stimulus on the right foot. In the *NWR-only* condition, which was considered as baseline condition, only an electrical stimulus was applied, without presenting any visual stimulus except the fixation point. For all conditions, the electrical stimulus could either be presented 1300 ms (*early timing*) or 1450 ms (*late timing)* after the illumination of the fixation point, i.e. 100 ms or 250 ms after the potential occurrence of the visual stimulus, respectively. Since the duration of the visual stimulus from starting to end point was 150 ms, the electrical stimulus was accordingly applied when the visual stimulus was still moving or after it arrived at its endpoint, for the conditions in which a visual stimulus was presented. These two timings were determined based on a pilot experiment. The exact time course can be seen in Fig. 1b. To render the visual stimulus less predictive of the arrival of the electrical stimulus, participants were also presented with control conditions, in which only the fixation light was switched on (*fixation only*) or only a visual stimulus (near or far) without applying an electrical stimulus (*visual near only*; *visual far only*) was presented. The predictability of the electrical stimulus has indeed previously been shown to be able to modulate the amplitude of the NWR (Jure et al., 2020). Participants were instructed to keep their gaze at the fixation point as long as it was switched on, i.e. during the entire duration (1700 ms) of the trial, as well as to move

as less as possible. Once the fixation LED switched off the next trial started after a randomised inter-trial interval (ITT) of 8-15 s. After each trial, i.e. during the ITT, participants were asked to rate the intensity of the electrical stimulus by using a numerical rating scale (NRS) ranging from 0 to 10 (0= no sensation, 5= pain threshold, 10= maximum imaginable pain). They were instructed to give a rating of 0 if they did not perceive any electrical stimulus.

The experimental session was composed of 144 trials, divided into 4 blocks of 36 trials each. Every block comprised 12 trials of the *NWR-visual near* condition, 12 trials of the *NWR-visual far* condition and 6 trials of the *NWR-only* (baseline) condition, with half of the trials of each stimulus condition for each of the two timings (early vs. late) of the electrical stimulation, as well as 2 trials for each of the control conditions (*fixation only*, *visual near only*, *visual far only*). Within the same block all trials were presented randomly. To maintain the participants' vigilance throughout the experiment, they were also asked 2 to 3 times per block whether a visual stimulus was presented in the trial and in which direction it moved. These responses were not recorded. There was a break of 5 min between each block. The total duration of the experiment was approximately 90 mins.

2.4 Measures and Analyses

The NWR amplitude was obtained for each trial by calculating the root-mean-square (RMS) amplitude in the 60 to 180 ms poststimulus window of the EMG data. Furthermore, for each trial, the latency of the maximum peak in the 60 to 180 ms poststimulus window was taken as NWR latency. NRS values at each trial were used as measure of perceived intensity of the electrical stimulation. The trials of each condition of interest were averaged for each participant and each measure. Trials with technical problems of the strip of LEDs or the electrical stimulation, as well as large EMG responses on visual inspection due to voluntary movements in the pre-stimulation window, were excluded from the dataset. A total of 3.13% of

trials was excluded throughout all participants. For some analyses, we directly computed *percentage of change from baseline* (i.e. the NWR-only condition).

To test for potential NWR amplitude or latency differences between the conditions of interest, repeated measures (RM) ANOVAs with *stimulus condition* (*NWR-only vs. NWR-visual near vs. NWR-visual far*) and *timing* (*early vs. late*) as within-participant factors were performed. For the latency analysis, the height of the participants was added as a covariate in the ANOVA. To furthermore test for significant increases and/or decreases in NWR amplitude or changes in latency induced by the presence of the visual stimuli as compared to the *NWR-only* condition (baseline), *percentage of change from baseline* was compared to 0 using one-sample t-tests, for both the *NWR-visual near* and *NWR-visual far* conditions and each of the two *timing* conditions. These analyses were completed with Bayesian one-sample t-tests, by computing a Bayes factor (BF_{10}, Cauchy prior width: 0.707) to quantify the evidence for the alternative hypothesis (H1; change from baseline) as compared to the null hypothesis (H0; no change from baseline). Interpretation of the obtained evidence for the alternative hypothesis as compared to the null hypothesis was based on the classification scheme proposed by Lee and Wagenmakers (Lee & Wagenmakers, 2013; Wagenmakers et al., 2018). Potential differences in perceived intensity of the electrical stimulation between the different conditions were tested with the non-parametric Friedman test. A non-parametric tests was chosen because self-reported perception of electrical stimulation intensity can be considered as an ordinal variable (Decruynaere et al., 2007). For both the *NWR-visual near* and the *NWR-visual far* condition and for the two *timing* conditions, *percentage of change from baseline* was compared to 0 using one-sample t-tests. Analyses were also completed with Bayesian one-sample t-tests.

When necessary, Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were performed. Effect size was measured using Cohen's d for t-tests, partial Eta squared for ANOVAs or Pearson's r for the non-parametric tests. The significance level was set at $p \leq 0.05$. All the frequentist statistical analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.,

Armonk, N.Y., USA) and Bayesian statistical analyses using JASP 0.9.1 (University of Amsterdam, The Netherlands)(JASP Team, 2018).

3. Results

NWR amplitude (Figure 2a). The RM ANOVA showed a significant main effect of *stimulus condition* ($F(2,40) = 4.864$, $p = 0.013$, $\eta^2_p = 0.196$). Neither the main effect of *timing* nor the interaction between both factors reached significance (all $F \leq 2.777$, $p \geq 0.096$*).* Contrast analyses indicated a significant difference between the *NWR-only* condition (M = 17.48, SD = 18.32) and both the *NWR-visual near* (M = 18.92, SD = 18.41; $t(20) = -2.412$, $p = 0.026$, d = -0.526) and *NWR-visual far (*M= 18.63, SD = 18.55; $t(20) = -2.809$, $p = 0.011$, d = -0.613) conditions. The difference between the *NWR-visual near* and the *NWR-visual far* condition was not significant ($t(20) = -0.666$, $p = 0.513$, d = 0.264). The one sample t-tests on the *percentage of change from baseline* furthermore showed that the increase in amplitude with regard to the *NWR-only condition* was significant in both the *NWR-visual near* and the *NWR-visual far* conditions, for both *early* (*NWR-visual near:* M = 33.56, SD = 42.24, $t(20) = 3.641$, $p = 0.002$, d = 0.794, 95% CI (14.33, 52.79) ; *NWR-visual far*: M = 30.41, SD = 61.47, $t(20) = 2.267$, $p = 0.035$, d = 0.495, 95% CI (2.43, 58.39)) and *late timing* (*NWR-visual near:* M = 30.52, SD = 56.40, $t(20) = 2.480$, $p = 0.022$, d = 0.541, 95% CI (4.85, 65.20) ; *NWR-visual far*: M = 22.76, SD = 49.97, $t(20) = 2.087$, $p = 0.050$, d = 0.455, 95% CI (0.01, 45.51)) conditions. The Bayesian analysis showed strong evidence for H1 (change from baseline) for the condition *NWR-visual near* combined with *early timing* ($BF_{10} = 23.706$, error = $2.307e^{-7}$ %), but only anecdotal evidence for H1 when it was combined with late timing ($BF_{10} = 2.618$, error = $9.387e^{-7}$ %), as well as for both timings for the NWR-visual far condition (*early timing*: $BF_{10} = 1.862$, error = $1.833e^{-6}$ % ; *late timing:* $BF_{10} = 1.368$, error = 0.023%).

NWR latency (Figure 2b). The RM ANOVA showed no significant main effect or interaction, neither between *stimulus condition* and *timing*, nor between any of the two factors and the covariate *height of the participants* (all $F \leq 1.458$, $p \geq 0.245$*).* There was also no significant main effect of the covariate ($F(1,19)$

= 3.131, p = 0.093, η^2_p = 0.141). The one sample t-tests on *percentage of change from baseline* showed that the latencies in neither the *NWR-visual near*, nor the *NWR-visual far* condition and none of the *timing*s were significantly different from baseline (all $t \leq$ -1.268, $p \geq 0.219$). The Bayesian analysis indicated moderate evidence for H0 for both stimulus conditions in the *early timing* condition (*NWR-visual near:* BF_{10} = 0.273, error = 0.02%; *NWR- visual far:* BF_{10} = 0.281, error = 0.021%) and anecdotal evidence for H0 for both stimulus conditions in the *late timing* condition (*NWR-visual near:* BF_{10} = 0.376, error = 0.022%; *NWR- visual far*: BF_{10} = 0.460, error = 0.023%).

Intensity ratings (Figure 2c). The non-parametric Friedman test showed no significant differences between the conditions ($X^2(5)$ = 8.074, p = 0.152). The results of the t-tests on *percentage of change from baseline* furthermore showed that there was no significant change in intensity ratings with regard to baseline, for neither the *NWR-visual near*, nor the *NWR-visual far* condition and none of the timings (all $t \leq 2.079$, $p \geq$ 0.051). These results were mostly supported by the Bayesian analysis, which indicated anecdotal evidence for H1 for both stimulus conditions in the *early timing* condition (*NWR-visual near:* BF_{10} = 1.076, error = 0.024%; *NWR- visual far:* BF_{10} = 1.352, error = 0.023%) and moderate evidence for H0 for both stimulus conditions in the *late timing* condition (*NWR-visual near:* BF_{10} = 0.254, error = 0.02%; *NWR- visual far*: BF_{10} = 0.239, error = 0.019%).

4. Discussion

The present study investigated whether multisensory interactions between nociception and vision, which have been shown to be able to affect the perception of nociceptive and painful stimuli (e.g. De Paepe et al., 2014; Filbrich et al., 2019; Pomper et al., 2013), can also have modulatory effects on nociception-related motor responses. Although such interactions between somatic and non-somatic stimuli have been hypothesized to serve a motor function, and, specifically in the context of nociception, to optimize defensive reactions against threatening stimuli (Graziano & Cooke, 2006), this has been mainly been based on studies in non-human primates (e.g. Dong, 2024). In humans, there are previous studies (e.g. Sambo et

al., 2012; Versace et al., 2019) suggesting that visual stimuli might be able to influence defensive reflexive responses organized at subcortical level, but these studies have rarely been conducted in the context of actual nociceptive stimuli. Additionally, an unambiguous interpretation of their results in terms of interaction between somatic and non-somatic stimuli is difficult, since visual stimuli were not external to the body, as they corresponded to the hand on which the reflex-inducing somatosensory stimulus was applied and since the modulation was rather explained by the felt position of the hand than the visual information (e.g. Sambo et al., 2012). To date, the idea of a defensive purpose of visuo-nociceptive interactions has thus not clearly been demonstrated in humans.

Our protocol also tested whether modulatory effects of the visual stimulus would be mostly observed for visual stimuli approaching, i.e. presented near, the limb on which the electrical stimulus eliciting the NWR was applied, as shown in the studies investigating the perceptual effects of nociceptive-visual interactions. This hypothesis is based on the idea that multisensory interactions rely on an integrated multisensory representation of the body and its immediately adjacent space, which for example allows determining the position of possibly harming objects in near external space with regard to the body. Such a representation is conceptualized by the notion of peripersonal frame of reference (e.g. Vallar & Maravita, 2009), a reference frame coordinating the processing and integration of somatic and extra-somatic stimuli occurring near the body. The involvement of the peripersonal reference frame in multisensory interaction has been extensively studied in the context of interactions between touch and vision (Serino, 2019). That such multisensory representations would shape motor behaviour has been based, amongst others, on studies showing that visual and auditory stimuli approaching the peripersonal space of a hand can modulate the motor excitability of that hand (e.g. Finisguerra et al., 2015; Makin et al., 2009).

The present results partly confirm our hypotheses, showing that NWR amplitude was increased by the presence of a dynamic visual stimulus that shortly preceded the electrical stimulation eliciting the reflex, as compared to a condition in which only the electrical stimulation, without any dynamic visual stimulus,

was applied. This effect was specific to NWR amplitude, since neither significant effects on reflex latency, nor on the perception of the electrical stimulus were observed. We were however not able to verify our hypothesis that effects would be significantly more important for near visual stimuli, i.e., those approaching the stimulated foot, than for far visual stimuli, i.e., those receding from the stimulated foot. At first glance, it could therefore be difficult to distinguish our finding from more general attention-related effects on NWR amplitude. It has indeed been regularly shown that manipulating attention, by either instructing participants to engage in a distracting task with high cognitive demand (e.g. Bjerre et al., 2011; Deldar et al., 2021; Henrich et al., 2022; Ruscheweyh et al., 2011; Willer et al., 1979) or by specific instructions to pay attention to the electrical stimulus (e.g. Bjerre et al., 2011; Ruscheweyh et al., 2011), can modulate the NWR. One has to note, however, that our study fundamentally differs from those previous studies in that participants did not engage in any specific cognitive activity. The visual stimuli we used were furthermore not of any emotional value, which is another factor that has been shown to modulate spinal nociceptive excitability (Bartolo et al., 2013; Rhudy et al., 2005; Roy et al., 2011). Although it could be argued that participants were in a way asked to attend to the electrical stimuli, since they were instructed to rate them after each trial, this was the case for all conditions. Furthermore, the fact that we used a fixation LED in all conditions and that participants did not know whether a dynamic visual stimulus would be presented or not also reduced potential differences in the general attentional context between the conditions with and without dynamic visual stimulation. Another important difference with our results is that the attentional manipulations in the majority of previous studies lead to a significant modulation of pain or intensity ratings to the electrical stimuli (Bjerre et al., 2011; Deldar et al., 2021; Ruscheweyh et al., 2011; Willer et al., 1979), even in the studies in which modulatory effect on the NWR was not observed (e.g. Terkelsen et al., 2004). However, one also has to note that, while it has previously been proposed that there would be a linear relationship between NWR amplitude and perceived pain during its induction, this has not always been replicated (see e.g. Terkelsen et al., 2004 for a discussion). Furthermore, studies

testing for correlations between the modulatory effects of attention on pain ratings and reflex magnitude were not able to show any association between the two (e.g. Ruscheweyh et al., 2011; Terkelsen et al., 2004). Although any possible relationship might be non-linear, it is also possible that effects on perceived intensity and effects on spinal excitability rely on different mechanisms, potentially at different spinal vs. supraspinal and even cortical levels of the sensory processing.

These considerations are also of relevance for the question regarding the potential mechanisms underlying the effects of visuo-nociceptive interactions on spinal processing. The presence of visual stimuli has been shown to be able to change the perception of acute nociceptive stimuli (De Paepe et al., 2014; Filbrich et al., 2019; Pomper et al., 2013). Accordingly, it could be hypothesized that potential multisensory effects of vision on spinal motor processing are mediated by effects on the perceived intensity of the electrical stimulation. Alternatively, they could also have a more direct descending effect on spinal motor excitability, independently from effects on perceived sensation. Our finding of an effect on NWR amplitude but not on the perceived intensity of the electrical stimuli seems to support this latter possibility. This should nevertheless be taken cautiously. First of all, the fact that we have no significant effects on intensity ratings does not exclude the possibility of other perceptual effects, such as on pain or reflex thresholds. Furthermore, we also have to consider that potential differences could possibly have been masked, at least partly, by habituation, since we observed that most participants systematically rated the electrical stimuli as non-painful (NRS < 5) even though stimulation intensities were deliberately and systematically set to higher values than individually assessed pain thresholds.

Finally, regarding the absence of a significant difference between near vs. far visual stimuli, two more elements seem relevant to be discussed. Since participants were not engaged in any specific task during the elicitation of the NWR, we had less control over any potential individual cognitive or emotional strategies that they might have adopted, and which could also have influenced NWR amplitude. Previous experiments have indeed shown that healthy participants can self-regulate and gain control over the NWR

(Arsenault et al., 2013; Ruscheweyh et al., 2015). We can thus not exclude the possibility that any potential differences between our conditions of interest could have been minimized or masked by individual strategies modulating the reflex amplitude and/or perceived intensity induced by the unpleasant electrical stimuli. What should furthermore be considered for future studies is the ecological value of the visual stimuli we used. As discussed previously, interactions between nociception and vison are hypothesized to rely on a multisensory cortical representation of the body and its nearby space, which would allow optimizing defensive actions against stimuli that are the most threatening for body integrity, i.e. most often stimuli near or approaching the body. However, even though the visual stimuli that we used were dynamic, they can hardly be considered as posing a threat for participants. It is thus possible that it might have been just not relevant for participants to make a distinction between near vs. far visual stimuli. Future studies should therefore consider optimizing the potentially threatening character of visual stimuli, by increasing their ecological value and relevance for body integrity, with the use of virtual environments for example.

To conclude, we showed that the NWR elicited by electrical stimulation can be modulated by the presence of external visual stimuli that have no explicit emotional or task-related valence, without a concomitant modulation of the perceived intensity of the noxious stimulus. Future studies should clarify whether such effects can be further modulated by the potential threatening value of the visual stimuli, such as, amongst others, their distance from the stimulated body part.

Author contributions

L.F. and K.S.F. conceived and discussed the experimental design. L.F. oversaw data acquisition. L.F. and K.S.F. analyzed the data. All authors interpreted the data. L.F. wrote the manuscript. All authors critically revised and reviewed the manuscript. All authors approved the submitted version.

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Figure captions

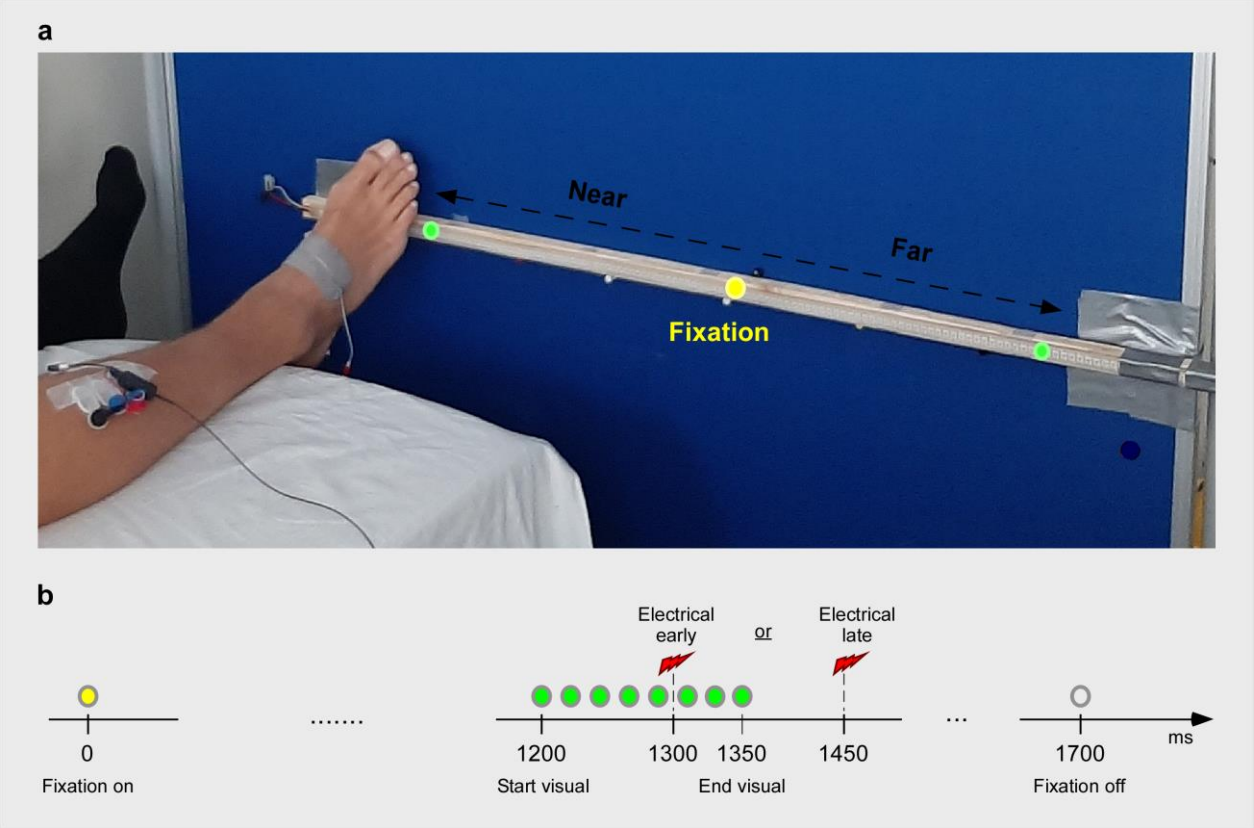

Figure 1. Experimental set-up and procedure. **(a) Visual stimuli** are presented on a strip of LEDs. The yellow dot in the middle of the strip represents the fixation LED, indicating the start of each trial. Depending on the condition, the LEDs are then illuminated sequentially, moving either from the fixation LED towards the foot (*near* condition) or in the opposite direction (*far* condition). The green dots represent the two possible endpoints of the sequential illumination (total duration of 150 ms) of the LEDs, for the near and the far condition, respectively. **(b) Time course (ms)** of a trial in which a dynamic visual stimulus (near or far) is presented in addition to the electrical stimulus eliciting a nociceptive withdrawal reflex (NWR). The electrical stimulus is either applied while the visual stimulus is still moving (*early timing* condition) or when it already arrived at its endpoint (*late timing* condition).

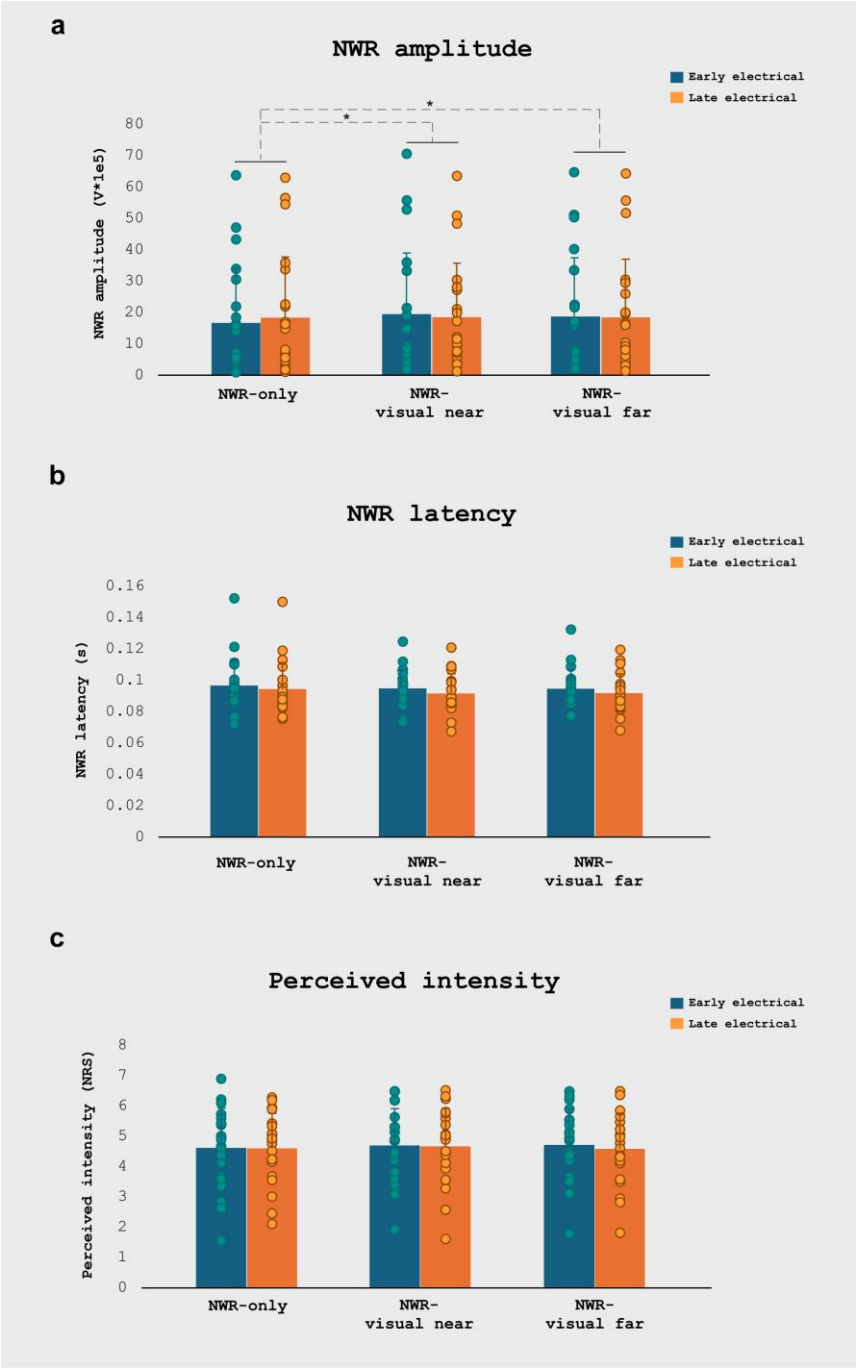

Figure 2. Results. Mean (**a**) NWR amplitude, (**b**) NWR latency and (**c**) perceived intensity of the electrical stimulus on a numerical rating scale ranging from 0 to 10 (0= no sensation, 5= pain threshold, 10= maximum imaginable pain) for the three main *stimulus conditions* and the two *timings* of the electrical stimulus**.** The dots represent the individual data of the 21 participants included in the analysis. Error bars represent standard deviations. *p ≤ 0.05.