Disruption of working memory and contralateral delay activity by nociceptive stimuli is modulated by task demands.

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Abstract

Top-down processes allow the selection and prioritization of information by limiting attentional capture by distractors, and these mechanisms depend on task demands such as working memory (WM) load. However, bottom-up processes give salient stimuli a stronger neuronal representation and provoke attentional capture. The aim of this study was to examine the effect of salient nociceptive stimuli on WM while manipulating task demands. Twenty-one healthy participants performed a change detection task during which they had to determine whether two successive visual arrays were different or the same. Task demands were modulated by manipulating WM load (set size included 2 or 4 objects to recall) and by the correspondence between the two successive visual arrays (change versus no change). Innocuous stimuli (control) or nociceptive stimuli (distractors) were delivered during the delay period between the two visual arrays. Contralateral delay activity (CDA) and laser-evoked potentials (LEP) were recorded to examine neural markers of visual WM and nociceptive processes. Nociceptive stimuli decreased WM performance depending on task demands (all $P < .05$). Moreover, compared with control stimuli, nociceptive stimuli abolished the increase in CDA amplitude for set size 4 versus set size 2 ($P = .04$). Consistent with these results, LEP amplitude was not decreased when task demands were high ($P = .5$). These findings indicate that WM may shield cognition from nociceptive stimuli, but nociceptive stimuli disrupt WM and alter task performance when cognitive resources become insufficient to process all task-relevant information.

1. Introduction

Nociceptive stimuli may evoke pain, an unpleasant sensory and emotional experience [55]. Previous studies have shown reciprocal interactions between pain and cognition [37; 39; 62; 67; 69], which may lead to pain inhibition or altered cognitive performance depending on the relative signal strength of the competing nociceptive and task-related stimuli. Indeed, nociceptive and cognitive processes compete for shared resources [10; 37; 39; 60].

Nociceptive processes and pain can be inhibited by the execution of a cognitive task that is sufficiently demanding and that engages working memory (WM) [10-12; 37-39; 62; 71]. Allocating cognitive resources to task-relevant information leaves less resources available to process nociceptive stimuli [10-12; 37-39; 60; 62; 71]. Conversely, increased allocation of resources to process nociceptive stimuli, when pain-related goals are prioritized [52; 65], leaves less resources available for the cognitive tasks [9; 16; 67; 69; 70].

The competition between nociceptive and task-related stimuli can be viewed from the perspective of limited attentional capacity theories, which posit that conscious processing of all information would overload the cognitive system [2; 7; 15; 17; 27; 33; 34; 53; 69]. Task demands may modulate this effect [10; 37; 39]. More demanding tasks leave less resources available for nociceptive processes [25; 36; 37; 39; 56; 62]. However, a recent study indicates that pain is inhibited by WM engagement only to a certain point, after which additional WM load does not increase pain inhibition [10]. According to an alternative account, cognitive resources are allocated to stimuli that are relevant to current

goals, for instance on ongoing cognitive task [67]. Because nociceptive stimuli are relevant to general motives, they may interrupt allocation of resources to current goals, despite goal-shielding mechanisms that promote current goals [67]. This goal-shielding mechanism may be less efficient when task demands are high.

Both the limited capacity and the motivational account suggests that the interaction between nociception and cognition is modulated by task demands. When task demands are high, the allocation of cognitive resources to process salient nociceptive stimuli may alter the performance of a cognitive task, despite prioritization of the task. However, the mechanism by which this may occur remains unclear.

WM is a component of cognition that involves temporary, active maintenance of information [3; 4; 18; 19]. In addition to response time and accuracy, visual WM performance can be examined with electroencephalography (EEG) [1; 21; 23; 27; 30; 42; 64]. The contralateral delay activity (CDA) is a negative slow wave which increases with the number of objects maintained in visual WM [42; 43; 72]. This increase may be used to index the alteration of WM by nociceptive stimuli.

The aim of this study was to examine the effect of nociceptive stimuli on a visual WM task (change detection). We hypothesized that the load-dependent increase in CDA amplitude would be decreased by nociceptive stimuli. Accordingly, we also hypothesized that the allocation of cognitive resources to nociceptive stimuli would decrease visual WM performance when task demands are high.

2. Methods

2.1 Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Université du Québec à Trois-Rivières. All participants gave written informed consent acknowledging their right to withdraw from the experiment without prejudice and received a compensation of $25 for their travel expenses, time, and commitment.

2.2 Participants

Thirty participants were recruited by advertisements on the campus of the Université du Québec à Trois-Rivières. Participants were included if they were between 18 and 35 years old with normal or corrected-to-normal vision. They were excluded if they reported acute or chronic pain, acute or chronic illness, psychiatric disorders, or had taken any medication or recreational drugs during the two weeks prior to the experiment. Five participants could not complete experimental procedures: three participants showed signs of skin irritation in response to laser stimuli, one participant reported tiredness, and one reported anxiety. Four additional participants were excluded due to technical failures during the EEG recordings. The resulting sample included 21 participants (13 women and 8 men; range 20–33 years old; mean ± SD: 24 ± 2.3).

2.3 Experimental protocol

This study relied on a within-subject design. Participants completed a change detection task while receiving innocuous electrical stimuli (control) or nociceptive laser

stimuli (distractors) to examine the effects of nociceptive inputs on visual WM performance and brain activity, as recorded with EEG. Participants and experimenters wore safety glasses designed for a 1340 nm wave-length laser for the duration of the experiment. Participants sat comfortably in a chair with both arms on an armrest and their hands in a comfortable and stable pronated position. Laser pain and tactile detection thresholds were determined using stimuli applied to the right hand. The cognitive task was then explained to participants, and they performed 12 practice trials to become familiar with the task, using the left hand to press keys on a computer keyboard. Participants were instructed to avoid excessive head, body, and eye movements during EEG recordings. The task was then performed and lasted approximately 75 minutes.

2.4 Change detection task

The change detection task was adapted from a previous study [73] and consisted of 960 trials. A nociceptive or control stimulus was applied during each trial. In a randomized order, nociceptive stimuli were applied for 240 trials and control stimuli were applied for 720 trials. Trials with a nociceptive stimulus were always separated by at least one trial with a control stimulus. The task is illustrated in Figure 1. Each trial of 3.2 s began when the participant pressed the space bar. A cue arrow was presented for 200 ms to indicate to which hemifield participants should pay attention, while keeping their gaze on a central fixation cross. Left and right hemifields were equally cued. Subsequently, the memory array containing either 2 or 4 blue rectangles of varying orientations to recall (set size 2 - low WM load; set size 4 - high WM load) was presented for 100 ms (in each hemifield). Participants were instructed to remember the items in the cued hemifield while ignoring

the items in the other hemifield. The minimum distance was 1.7 ° between the objects and 2.4 ° between the objects and the fixation cross. The memory array was followed by a retention interval of 900 ms during which participants were instructed to keep their gaze on the central fixation cross and avoid blinking. The nociceptive and control stimuli were delivered at 120 and 200 ms after the retention interval onset (220 and 300 ms after the memory array onset), based on the conduction velocity of nociceptive A-δ fibers and non-nociceptive A-β fibers, respectively. This allowed for the somatosensory/nociceptive to interact with visual processes during the retention interval, around 500 ms after the memory array onset. The test array (with change or no change) was then presented for a 2000 ms period during which participants provided their answer (change or no change) as quickly and as accurately as possible by pressing a key with the left index finger to respond "change" and a key with the middle finger to respond "no change". The inter-trial interval was self-paced, allowing participants to blink, move their eyes, and take pauses as needed.

When the test array differed from the memory array, one of the rectangles had a different orientation. Processing these change trials involves additional cognitive processes and increases task demands compared with no change [29]. Although attention is directed automatically and quickly to a changed item, this initial change detection is followed by a second comparison process necessary to confirm that the change indeed occurred [29]. During this limited-capacity process, the test array is compared with the representation of the initial array in VWM and this leads to longer response time. Moreover, change trials are associated with decreased accuracy [29]. Thus, both RT and accuracy effects increase with load (set size).

2.5 Nociceptive Laser stimulation

Nociceptive stimuli were produced by laser heat pulses using an infrared neodymium yttrium aluminum perovskite laser (Nd:YAP, DEKA 1340; Electronical Engineering, Florence, Italy). The laser beam was transmitted through a 10 m fiber-optic cable. Laser pulse duration was set at 4 ms and the diameter at 5 mm (15.7 mm^2 area). Based on safety recommendations for repeated laser stimuli [44], the maximum fluence limit should be set at 20 J/cm2, which corresponds to a 3.9 J upper limit for a 5 mm laser beam diameter. The laser was triggered externally using a stimulus presentation software (E-Prime2; Psychology Software Tools, Sharpsburg, PA). The in-built helium–neon laser was used for aiming purposes. Stimuli were applied in the territory of the superficial right dorsal ulnar nerve. To avoid stimulating the same area more than once per block, tiny ink marks were drawn on the dorsum of the hand as a guide.

Laser stimulation intensity was adjusted to evoke pain perception. To determine the pain threshold, participants were instructed to focus on the pinprick sensation and to report pain intensity verbally, using a numerical rating scale ranging from 0 (no pain) to 100 (worse pain imaginable) [48-50; 54]. Energy output started at the lowest possible level (0.5 J) and increased sequentially by 0.25 J increments until pain was reported, up to the 3.9 J upper limit. The energy at which pain was first reported was repeated 3 times to obtain a reliable pain threshold. To induce a clearly painful pinprick sensation, the energy was then adjusted to 2 increments (0.5 J) over the pain threshold (mean ± SD: 1.92 J ± 0.60 J). The upper limit was not reached for any participant, and the maximum energy delivered was 2.75 J. The participant was then familiarized with the selected stimulus intensity using a sequence of 3 consecutive stimuli with an interstimulus interval of 5 seconds, and was

asked to confirm that nociceptive laser stimuli evoked pain (mean ± SD: 40.2 ± 18.2). All participants reported pain in response to nociceptive laser stimuli throughout the entirety of the experiment.

2.6 Innocuous stimuli (control)

Transcutaneous electrical stimulation was delivered with an isolated DS7A constant current stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) and was applied in the innervation territory of the right dorsal ulnar nerve using a pair of custom-made surface electrodes (1 cm^2) separated by 2 cm. The stimulation consisted of a 1 ms pulse at 1.5 times the detection threshold (mean ± SD: 1.7 mA ± 0.6 mA), which evoked a light tactile sensation. The device was triggered externally using a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA).

2.7 Electroencephalographic recordings

EEG was recorded using a 64-channel TruScan RE system (Deymed Diagnostic, Hronov, Czech Republic) with 64 electrodes mounted according to the International 10-20 system. Electrodes were nose-referenced, and the ground was set at FPz. Signals were band-pass filtered (0.1 to 100 Hz) and sampled at 1000 Hz. Eye movements and blinks were recorded using electrooculography (EOG) with electrodes placed at the suborbital ridge and lateral to the external ocular canthus. Electrode impedance was kept below 10 kΩ.

2.8 Contralateral delay activity

EEG signals were analyzed offline using EEGLAB v.13.5.4b [13]. After applying a 0.16–35 Hz finite impulse response (FIR) band-pass filter and re-referencing the signal to the common average, data were segmented into epochs extending from -200 ms to +1100 ms relative to the memory array onset. It should be noted that high-pass cut-off frequencies used in CDA studies vary from DC to 0.5 Hz [1; 21; 47]. In the present study, we used the lowest available cut-off frequency on the acquisition system (0.16 Hz), within this range of frequencies. Epochs were baseline corrected using the -200 ms to 0 ms window. Each trial was inspected visually to reject trials during which the task could not be performed, including trials with excessive eye movements (HEOG signal exceeding 50 μV or −50 μV), eye blinks, or in which the participant attended the wrong hemifield during the time window from the cue to the memory array presentation. This led to the rejection of a mean ± SD of 69.5 ± 42.6 trials out of 960 trials. An Infomax independent component analysis (ICA) was then applied using the in-built EEGLAB function Runica to identify and remove components associated with noise (e.g., eye movements and blinks, and cardiac and muscle artifacts). The CDA amplitude was calculated for trials with a correct response as the difference between the mean amplitude for the contralateral and ipsilateral cued side activity from the PO7 and PO8 electrodes in a 500-800 ms time window following the onset of the memory array, similarly to previous studies [5; 26; 30; 47; 73]. Although the CDA onset was around 300 ms, the CDA analysis time window was determined to account for the A-β and A-δ fibers' conduction velocity and the latency of their corresponding event-related cortical responses, in order to maximize the detection of an interaction between somatosensory/nociceptive stimuli and visual WM [10-12; 37].

The number of trials with a control stimulus was three times greater than that of trials with a nociceptive stimulus. This was necessary to keep nociceptive stimuli unpredictable and salient and to prevent habituation. To avoid the bias of trial number difference when comparing CDA amplitude between conditions, the number of trials with a control stimulus was matched to the number of trials with a nociceptive stimulus. To avoid a selection bias, trials with a control stimulus were randomly selected for analysis, using EEGLAB. Two sets of random control stimuli were used to repeat the analysis and confirm the stability of the results. Thus, any difference between conditions cannot be explained by a difference in the number of trials.

2.9 Laser-evoked potentials

Laser-evoked potentials (LEPs) were analyzed offline using EEGLAB v.13.5.4b [13]. After applying a 0.5–30 Hz finite impulse response (FIR) band-pass filter and re-referencing to the common average, data were segmented into epochs extending from -400 ms to +800 ms relative to stimulus onset. Epochs were baseline corrected using the -400 to -200 ms window and then visually inspected to reject those most likely to contain artifacts (amplitude value exceeding ± 100 μV). The -400 to -200 ms baseline window was selected instead of the -200 to 0 ms window, which was contaminated by visual evoked potentials. Next, an Infomax independent component analysis (ICA) was applied using the in-built EEGLAB function Runica to identify and remove components associated with noise (e.g., eye movements and blinks, and cardiac and muscle artifacts). Finally, average waveforms were computed for each participant in order to obtain the N2 and P2 components [28; 31; 51; 57]. The N2 was defined as the first major negative deflection occurring between 170

and 350 ms with a maximum amplitude at the vertex (Cz), and the P2 was defined as the first major positive deflection occurring between 280 and 500 ms with a maximum amplitude at the vertex (Cz). The N2 and P2 components evoked by nociceptive laser stimuli are sensitive to cognitive processes. Pain-related goals result in increased N2 and P2 amplitude, while WM engagement into a cognitive task results in reduced N2 and P2 amplitude [37; 40]. In the present study, N2 and P2 amplitudes were used as secondary variables to confirm the lack of inhibition (reduced amplitude) when nociceptive stimuli disrupted WM.

2.10 Statistical analysis

Statistical analysis was conducted using Statistica v13.1 (Dell Inc., Tulsa, OK, USA). All results are expressed as mean ± SD. Statistical threshold was set at $P \leq .05$. Data distribution was assessed for normality with the Kolmogorov-Smirnov test, and the data were transformed if the normality assumption was not met, in order to obtain normal distributions. Accuracy values were transformed with the 2*ArcSin(sqrt(x)) function [46]. Accuracy and response times were compared between conditions using repeated-measures analysis of variance (ANOVA) with 3 within-subject factors: change (change versus no change), load (set size 2 versus set size 4), and stimulus type (nociceptive vs innocuous control). Mean CDA amplitude was compared between conditions using a repeated-measures ANOVA with 2 within-subject factors: load (set size 2 versus set size 4) and stimulus type (nociceptive vs innocuous control). N2 and P2 peak amplitude were compared between set sizes 2 and 4 with paired t-tests. For ANOVAs, effect sizes are

reported based on partial eta-squared (η^2_p). The standardized effect size (*dz*) and the minimal detectable effect (MDE) are also reported for the planned contrasts.

3. Results

3.1 Working memory performance

Response times and accuracy values are reported in Table 1 and presented in Figures 2 and 3. Response time was significantly increased by load (main effect: $F_{1,20}$ = 164.7, $P < .001$, $\eta^2_p = .89$), by the change between the two visual arrays (main effect: $F_{1,20}$ = 18.9, $P < .001$, $\eta^2_p = .49$), and by nociceptive stimuli (main effect: $F_{1,20} = 10.5$, $P = .004$, $\eta^2_p = .34$). Moreover, compared with control stimuli, nociceptive stimuli increased response time in the low load condition (set size 2) when a change occurred between the two visual arrays compared with no change, and this effect was significantly different compared with the corresponding changes in the high load condition (set size 4) (interaction: $F_{1,20} = 9.3$, $P = .006$, $\eta^2_p = .32$). Bonferroni-corrected planned contrasts revealed that nociceptive stimuli increased the response time compared with the control stimuli in the low load condition (set size 2) when a change occurred between the two visual arrays (MD±SD: 43.8±47.9, $P = .002$, *dz*: 0.87; MDE:0.77). Nociceptive stimuli also increased the response time compared with control stimuli in the high load condition (set size 4) when no change occurred between the two visual arrays (MD±SD: 70.1±55.2, $P < .001$; *dz:* 1.29; MDE:0.17). In the least demanding task (i.e., in the low load condition (set size 2) when no change occurred between the two visual arrays), nociceptive stimuli did not increase response time (MD±SD: 29.2±66.5, $P = .2$; *dz*: 0.44; MDE:0.19). In the most demanding task (i.e., in the high load condition (set size 4) when a change occurred between the two

visual arrays), nociceptive stimuli did not increase response time (MD±SD: 1.1±92.9, P = 1.0; dz: 0.01; MDE:0.53).

Response accuracy was significantly decreased by load (main effect: $F_{1,20}$ = 98.6, P < .001, η^2_p = .83) and by the change between the two visual arrays (main effect: $F_{1,20}$ = 128.6, P < .001, η^2_p = .87) but not by nociceptive stimuli (main effects: $F_{1,20}$ = 2.0, P = .17, η^2_p = .09). However, similarly to response time, nociceptive stimuli decreased response accuracy in the low load condition (set size 2) when a change occurred between the two visual arrays compared with no change, and this effect was significantly different compared with the corresponding changes in the high load condition (set size 4) (interaction: $F_{1,20}$ = 4.4, P = .048, η^2_p = .18; dz: 0.54; MDE:0.53). Bonferroni-corrected planned contrasts revealed no other effect (all P > .1).

In summary, based on response time and accuracy, task demands increased between tasks in the following order: set size 2 with no change between the two visual arrays, set size 4 with no change between the two visual arrays, set size 2 with a change between the two visual arrays, and set size 4 with a change between visual arrays. The results indicate that nociceptive stimuli disrupted WM depending on task demands, with more impact at intermediate levels.

3.2 Contralateral delay activity

Grand average waveforms for the CDA are presented in Figure 4. CDA amplitude is reported in Table 2 and presented in Figure 5. To avoid the bias of trial number difference when comparing CDA amplitude between conditions, the number of trials with a control stimulus was matched to the number of trials with a nociceptive stimulus. To avoid a

selection bias, trials with a control stimulus were randomly selected for analysis. To confirm the stability of the results, two sets of random stimuli were used in separate analyses. Overall, the mean amplitude of the CDA was not significantly modulated by load (set size 2 versus 4) (main effect: $F_{1,20} = 0.5$, $P = .48$, $\eta^2_p = .03$) or by nociceptive stimuli (main effect: $F_{1,20} = 0.1$, $P = .8$, $\eta^2_p < .01$) for the first set of random stimuli. However, the CDA amplitude was affected differently by load for nociceptive versus control stimuli (interaction: $F_{1,20} = 5.5$, $P = .03$, $\eta^2_p = .22$). Bonferroni-corrected planned contrasts revealed that, as expected, the CDA amplitude was increased by load when a control stimulus was delivered (MD±SD: 0.5±1, $P = .04$; *dz*: 0.43; MDE:0.32), but this effect was abolished by nociceptive stimuli (MD±SD: 0.4±1.3, $P = .4$; *dz*: 0.34; MDE:0.56).

Similar effects were observed for the second analysis with another random set of control stimuli, where the mean amplitude of the CDA was not significantly modulated by load (set size 2 versus 4) (main effect: $F_{1,20} = 0.8$, $P = .38$, $\eta^2_p = .04$) or by nociceptive stimuli (main effect: $F_{1,20} = 0.01$, $P = .9$, $\eta^2_p < .01$). Again, the CDA amplitude was affected differently by load for nociceptive versus control stimuli (interaction: $F_{1,20} = 8.1$, $P = .01$, $\eta^2_p = .29$). Bonferroni-corrected planned contrasts also revealed that the CDA amplitude was increased by load when a control stimulus was delivered (MD±SD: 0.7±1.3, $P = .03$; *dz*: 0.59; MDE:0.53), but this effect was abolished by nociceptive stimuli (MD±SD: 0.4±1.3, $P = .4$; *dz*: 0.28; MDE:0.56).

To explore other effects with no a priori hypothesis, including the apparent increase in CDA amplitude as a result of the nociceptive stimulation compared with the control stimulation in set size 2, the Tuckey honestly significant difference test was used. The

results revealed no other significant effect for either analyses (either sets of randomly selected control stimuli).

In a secondary analysis, we examined the interaction of load and pain while considering the change between visual arrays, with the idea that the load x pain interaction should not be affected by change since the CDA is measured before the presentation of the second visual array. Indeed, the CDA amplitude was affected differently by load for nociceptive versus control stimuli (interaction: $F_{1,20} = 4.9$, $P = .04$, $\eta^2_p = .20$), but this effect was not affected by the change between visual arrays (interaction: $F_{1,20} = 0.7$, $P = .4$, $\eta^2_p = .03$).

3.3 Laser-evoked potentials

Grand average waveforms for the N2 and P2 at Cz are presented in Figure 6. N2 and P2 peak amplitude and latency are reported in Table 3 and presented in Figure 7. The N2 and P2 peak amplitude was not significantly modulated by load (MD±SD: 0.1±0.9, $t_{(20)} = 0.7$, $P = .5$; *dz*: 0.17; MDE:0.68 and MD±SD: 0.2±1, $t_{(20)} = 0.8$, $P = .5$; *dz*: 0.16; MDE: 0.68, respectively). Likewise, N2 and P2 peak latency was not significantly modulated by load (MD±SD: 0.2±49.6, $t_{(20)} = 0.02$, $P = .99$; *dz*: 0.01; MDE: 1.1 and MD±SD: 8.1±38.8, $t_{(20)} = 0.95$, $P = .35$; *dz*: 0.21; MDE: 0.60, respectively). This indicates that the balance between bottom-up and top-down processing of nociceptive stimuli led to comparable LEP amplitude between low and high WM load conditions. It also suggests that nociceptive stimuli captured attention equally in low and high WM load conditions.

4. Discussion

4.1 Reduction of working memory performance by nociceptive stimuli

In the present study, task demands were varied by manipulating WM load (set size 2 versus set size 4) and the content of visual arrays (change versus no change between the two visual arrays). The effect of nociceptive stimuli on WM performance seems to follow an inverted-U function with maximal effect when cognitive requirements are at intermediate levels (low load, change trial; high load, no change), and no effect when cognitive requirements are very low (low load, no change) or very high (high load, change).

The results at the intermediate levels are consistent with previous studies in which participants directed attention towards nociceptive stimuli even when nociceptive stimuli were irrelevant to the task-related goal [40; 41; 52; 58; 65; 66]. The results are also consistent with the motivational account model of attention to pain, which predicts that pain, as a general motive, captures attention during the pursuit of a current goal unrelated to pain [9; 16; 67; 69; 70].

By contrast, nociceptive stimuli did not disrupt WM in the least demanding condition, consistent with previous studies showing that attention and WM are not affected by painful stimuli when task demands are low [10-12].

In the most demanding conditions, nociceptive stimuli also did not disrupt WM. Based on the limited-capacity account, this likely occurred because task demands were already too high (response accuracy of 49.8%, slightly below chance level), and cognitive resources were insufficient to process task-relevant information. A related explanation, based on the motivational account, would suggest that goal-shielding mechanisms, necessary to maintain attention towards current goals, were less efficient under these

conditions. Indeed, allocating attention to task-relevant information depends on task demands [10; 37; 39]. Moreover, cognitive resources are limited when attention is captured by nociceptive stimuli [25; 36; 37; 39; 56; 62]. A recent study has shown that pain as a distractor can be inhibited by WM engagement and that increasing WM load increases this effect, although only to a certain threshold [10]. Thus, we propose that in the present study, in conditions where task demands were above a certain threshold, cognitive ressources became insufficient to process all information (nociceptive and task-related stimuli) and WM performance decreased. Below that threshold, cognitive ressources were sufficient to process information from both the nociceptive stimulus and the task, and WM performance was unaffected. Altogether, these behavioral results explain differences between studies concerning the interaction between pain and cognition.

4.2 Disruption of brain activity related to working memory by nociceptive stimuli

The CDA amplitude was increased by WM load (set size 4 versus set size 2) when control stimuli were delivered. This is consistent with the specific increase in CDA amplitude with the number of objects encoded and maintained in visual WM [30; 32; 35; 42; 43; 45; 72]. By contrast, the increase in CDA amplitude from set size 2 to set size 4 did not occur when nociceptive stimuli were delivered. This suggests that nociceptive stimuli occurring during the delay period disrupted the maintenance of information in WM when 4 objects were presented. Previous studies have shown that a sudden onset of task-irrelevant but salient information captures attention [20; 22; 61; 74] and negatively impacts ongoing WM representations [6; 26; 27; 68]. The present results suggest that attentional capture by nociceptive stimuli disrupts WM and that this disruption is reflected in

decreased CDA amplitude. Consistent with this interpretation, LEP amplitude was not decreased for set size 4 versus set size 2, in contrast to what is expected during engagement of WM in a task unrelated to pain, especially with higher WM load [10]. It should be noted that the effect of nociceptive stimuli on WM and the CDA may be produced by other intense or salient stimuli (e.g. intense auditory stimulus) and may not be specific to pain. It has been reported that both painful and nonpainful stimuli may interrupt cognitive activity [24].

Another interpretation is that attentional capture by nociceptive stimuli was equivalent between set size 4 and set size 2 (no difference in LEP amplitude) and that a similar amount of cognitive ressources was allocated to process nociceptive stimuli in both conditions. However, because WM load was higher in the set size 4, cognitive resources became insufficient to process all task-relevant information and WM performance decreased.

Notably, the CDA and its amplitude are calculated for trials with correct responses. The present results therefore suggest that despite the decrease in CDA amplitude, participants could still provide correct responses. The decreased CDA amplitude may reflect the maintenance of partial information, especially in the condition with set size 4 and no change between the two visual arrays, where response accuracy was 83.7%. Based on the comparable CDA amplitude between set size 2 and set size 4 with nociceptive stimuli, we could speculate that 2 of the 4 objects may have been maintained in WM and that this was sufficient to provide a correct response in most trials. However, providing a correct response with the same partial information may be more difficult when a change occurs between the two visual arrays. This is consistent with the lack of a significant

difference in CDA amplitude between trials with a change and trials with no change, and with the lower response accuracy of 49.8 % for the set size 4 with nociceptive stimuli condition. Thus, we propose that some of the correct responses may have been correct only by chance or due to a response bias, especially in the condition with set size 4 and a change between the visual array, in which response accuracy was just below chance level.

Another possibility to consider is that attentional control may modulate the CDA [59]. Attentional control plays a crucial role in selecting and maintaining information in WM [27], akin with the idea of goal shielding promoted by motivational theories [67]. Thus, the CDA may reflect more than just the number of objects maintained in WM, and a decrease in CDA amplitude may result from decreased attentional control. Attentional control is also affected by task demands and stimulus saliency during active maintenance of information in WM [8; 14; 59; 63]. The specific relative effects of the amount of information and attentional control remain to be investigated in future studies.

4.3 Limitations and future directions

In the present study, the effects of painful laser stimuli were compared with the effects of nonpainful electrical stimuli (control) as in previous studies [11; 12; 37]. Although the nonpainful electrical stimulus controls for somatosensory activation, it could be argued that some aspects of the painful stimulus were not matched. For instance, the intensity of nociceptive stimuli must be high enough to activate high-threshold receptors (nociceptors) and to evoke pain. Moreover, painful stimuli are intrinsically salient and capture attention [36; 67], which is not the case of nonpainful stimuli. Furthermore, novelty was different between the painful and nonpainful stimuli; to prevent habituation, more

nonpainful than painful stimuli were delivered [11; 12; 37]. Although this was necessary for the purpose of the experiment, the impact of these different factors should be addressed in future studies. In addition, although the slight difference in stimulus duration (2 ms vs 4 ms) is unlikely to explain the present results, it would be possible to match duration for all stimuli. Painful stimuli could be compared with intense auditory stimuli matched for salience and novelty. Indeed, the effects of painful stimuli on WM and the CDA may be produced by other intense, salient and novel stimuli and may not be specific to pain. This is consistent with a previous report showing that painful and intense nonpainful stimuli that interrupt a cognitive task both alter the resumption of the task [24]. In that study, the goal was to examine the effect of task interruptions resulting from painful and nonpainful stimuli, and not of the stimuli themselves. Hence, more research is necessary to determine whether the impact of pain on WM is specific or shared with other intense sensory stimuli.

Another potential limitation is that response bias may contribute to observed differences in behavioural response to change and no change conditions for the behavioral results. However, this cannot explain the difference between nociceptive and tactile stimuli [29]. Another factor that may have affected RT is that the response keys were not counterbalanced for change and no change conditions, implicating possible motor effects. However, the main comparisons and the most relevant effects are between nociceptive and tactile stimuli in the different conditions, for which the motor responses were consistently produced with the index and middle fingers. Moreover, the electrophysiological data reflect processing that occurs before the motor response. Lastly, the sample size was limited to 21 participants so the present results should be reproduced in future studies.

5. Conclusion

In summary, the present study shows that WM may shield cognition from nociception, but nociception disrupts WM when cognitive resources become insufficient to process information from nociception and the task. This warrants future studies to examine the modulation of the interaction between pain and cognition by WM and attentional control capacity, as well as cognitive effort.

Availability of data and materials

The dataset supporting the conclusions of this article is available from the corresponding author on reasonable request.

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Author contributions

AWT and MP contributed to all aspects of the study. ZD contributed to data collection, analyses, and interpretation, as well as manuscript writing. SN contributed to data analyses and interpretation. IB and BB contributed to the experimental design, data interpretation,

and manuscript writing. IB, BB, and MP obtained funding for the study. All authors approved the final version of the manuscript.

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Figure legends

Figure 1. Change detection task. The task comprised 8 conditions, including set size 2 with change or no change and set size 4 with change or no change, with an innocuous

electrical stimulus (control) or a nociceptive laser stimulus delivered during the retention period. Each trial lasted 3.2 s with a self-paced inter-trial interval. The nociceptive and control stimuli were delivered at 120 and 200 ms after the retention interval onset, based on the conduction velocity of nociceptive A-δ fibers and non-nociceptive A-β fibers. This allowed the interaction between somatosensory and visual processes during the retention interval, around 500 ms after the onset of the memory array. Two representative trials are shown: set size 4 with a change between visual arrays (left) to be recalled, and set size 2 with no change between visual arrays (right) to be recalled. The first display contained a fixation cross with an arrow indicating to which hemifield the participant was to attend. The next display contained the memory array, followed by a retention interval of 900 ms, and then the test array was presented. The visual arrays were both presented for 100 ms. A maximum of 2 s was allowed for the participant response. When a change occurred between the two visual arrays to be recalled, one of the four attended objects had a different orientation, as highlighted by the red circles in the example on the left.

Figure 2. Response time. Mean response time for each of the 8 conditions. Control conditions are depicted with black bars, and nociceptive conditions are depicted with gray bars. Individual data are shown with white circles. Response time was significantly increased by load (set size 4 versus set size 2) (main effect: $P < .001$), by the change between the two visual arrays (main effect: $P < .001$), and by nocieptive stimuli (main effect: $P = .004$). Moreover, compared with control stimuli, nociceptive stimuli increased response time in the low load condition (set size 2) when a change occurred between the two visual arrays compared with no change, and this effect was significantly different

compared with the corresponding changes in the high load condition (set size 4) (interaction: $P = .006$). Bonferroni-corrected planned contrasts revealed that nociceptive stimuli increased the response time compared with the control stimuli in the low load condition (set size 4) when a change occurred between the two visual arrays ($P = .002$). Moreover, nociceptive stimuli increased the response time compared with control stimuli in the high load condition (set size 4) when no change occurred between the two visual arrays ($P < .001$). ** $P < .01$; *** $P < .001$.

Figure 3. Response accuracy. Mean response accuracy for the 8 conditions. Control conditions are depicted with black bars, and nociceptive conditions are depicted with gray bars. Individual data are shown with white circles. Raw data are used for illustration purposes. Statistical analyses were conducted with transformed data using the 2*ArcSin(sqrt(x)) function. Response accuracy was significantly decreased by load (main effect: $P < .001$) and by the change between the two visual arrays (main effect: $P < .001$), but not by nociceptive stimuli (main effects: $P = .17$). However, similarly to response time, nociceptive stimuli decreased response accuracy in the low load condition (set size 2) when a change occurred between the two visual arrays compared with no change, and this effect was significantly different compared with the corresponding changes in the high load condition (set size 4) (interaction: $P = .048$). Bonferroni-corrected planned contrasts revealed no other effect (all $P > .1$). * $P < .05$

Figure 4. Contralateral Delay Activity. Grand average of contralateral delay activity (CDA) time-locked to the onset of the memory array. Trials with control stimuli are

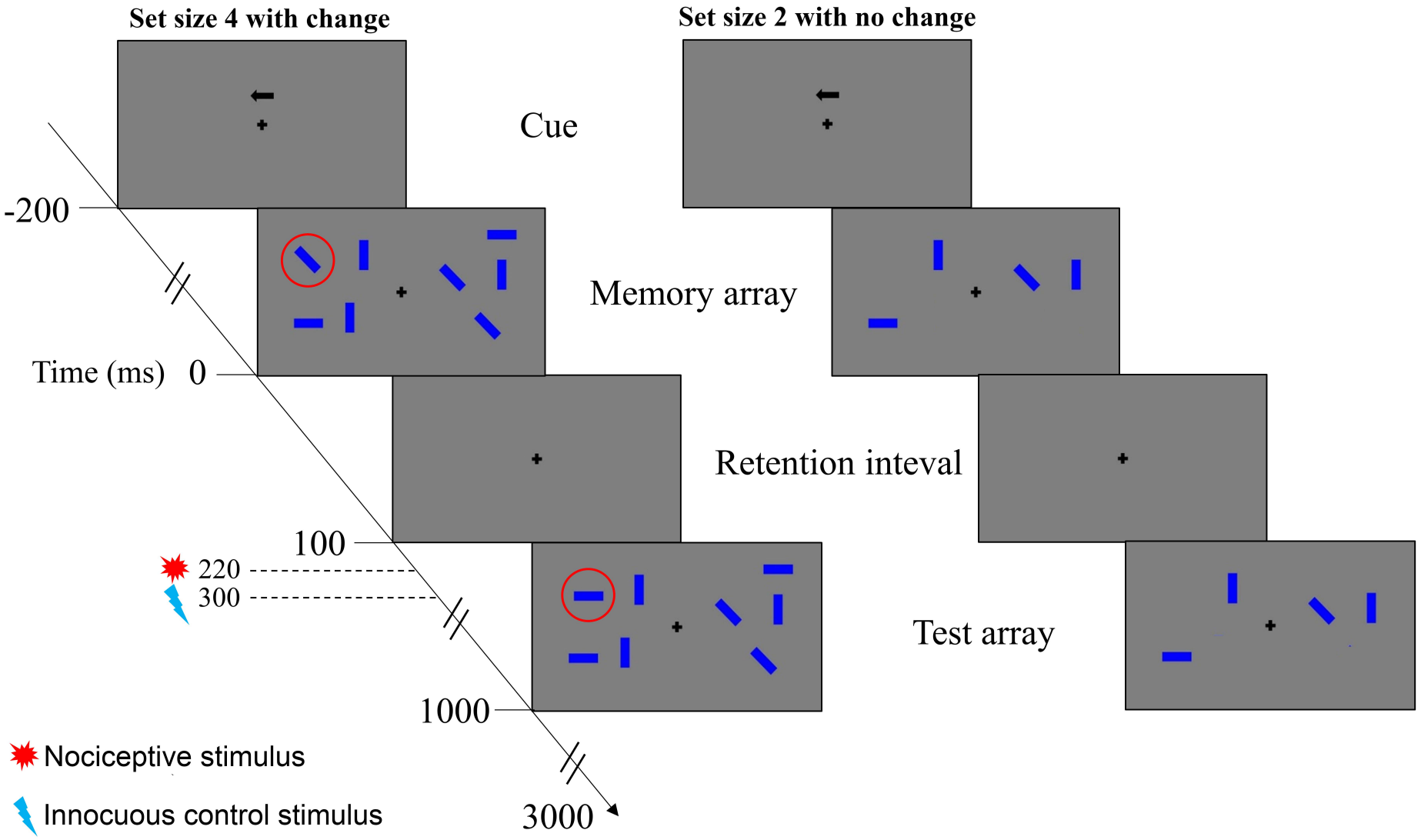
presented in A, and trials with nociceptive stimuli are presented in B. CDA for set size 2 conditions are shown as full black lines. CDA for set size 4 conditions are shown as dashed black lines. Note that the conditions with a change and those with no change between the two visual arrays are combined because the CDA occurs before the presentation of the second visual array, creating 4 conditions for this analysis. The nociceptive and control stimuli were delivered 220 and 300 ms after the memory array onset, based on the conduction velocity of nociceptive A-δ fibers and non-nociceptive A-β fibres. This allowed recording of the CDA when the interaction between somatosensory and visual processes occurred, during the retention interval, around 500 ms after the memory array onset. Baseline was calculated as the mean signal value between -200 and 0 ms. The CDA is observed as a slow wave between 300 and 900 ms. CDA mean amplitude was measured between 500 and 800 ms, as indicated by the gray window.

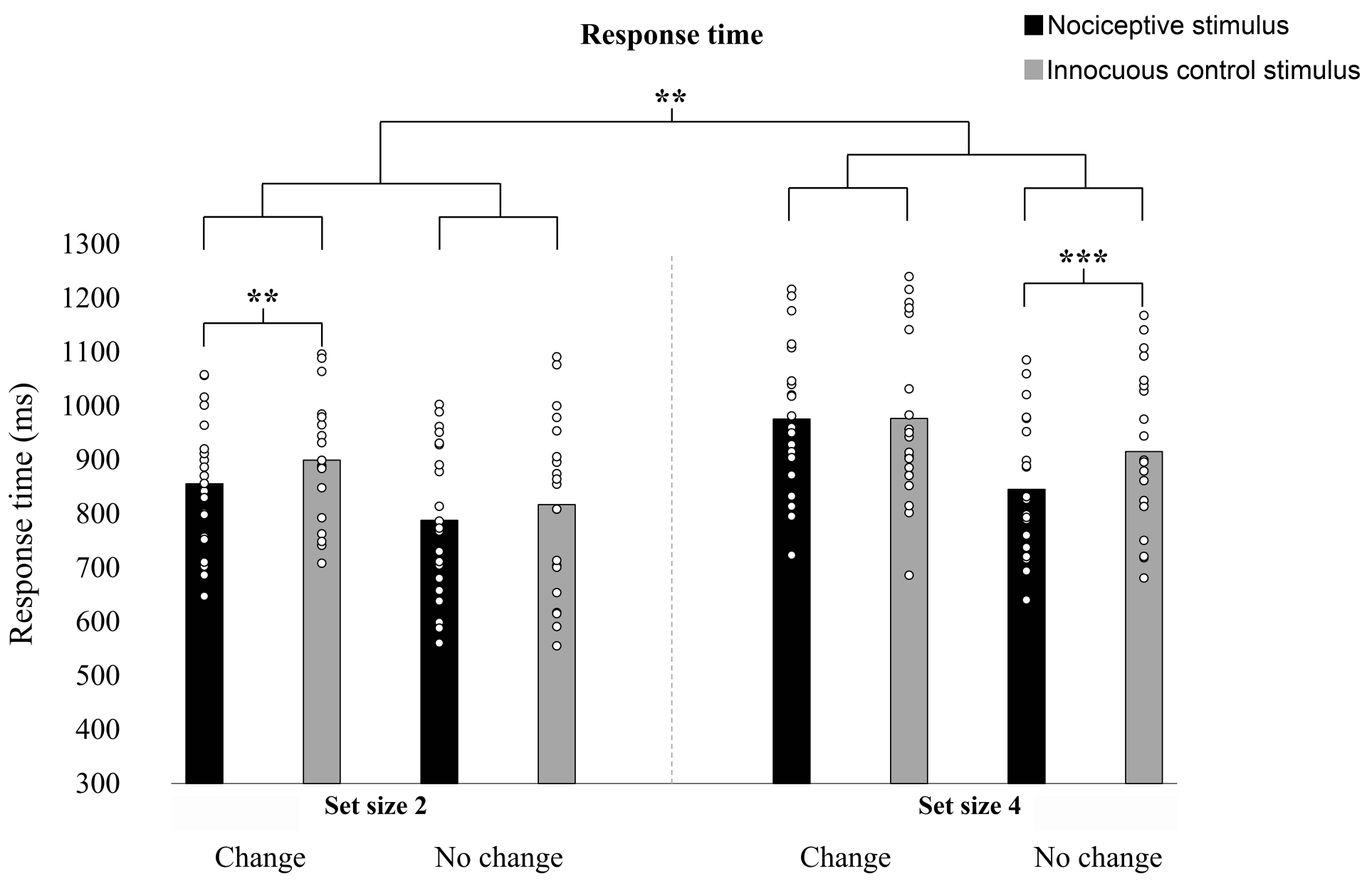
Figure 5. Modulation of Contralateral Delay Activity. Mean CDA amplitude with individual data represented as white circles. Note that the conditions with a change and those with no change between the two visual arrays are combined because the CDA occurs before the presentation of the second visual arrays, creating 4 conditions for this analysis. The CDA amplitude was affected differently by load (set size 2 versus set size 4) for nociceptive versus control stimuli (interaction: $P = .03$). Bonferroni-corrected planned contrasts revealed that, as expected, the CDA amplitude was increased by load when a control stimulus was delivered ($P = .04$), but this effect was abolished by nociceptive stimuli ($P = .4$). * $P < .05$.

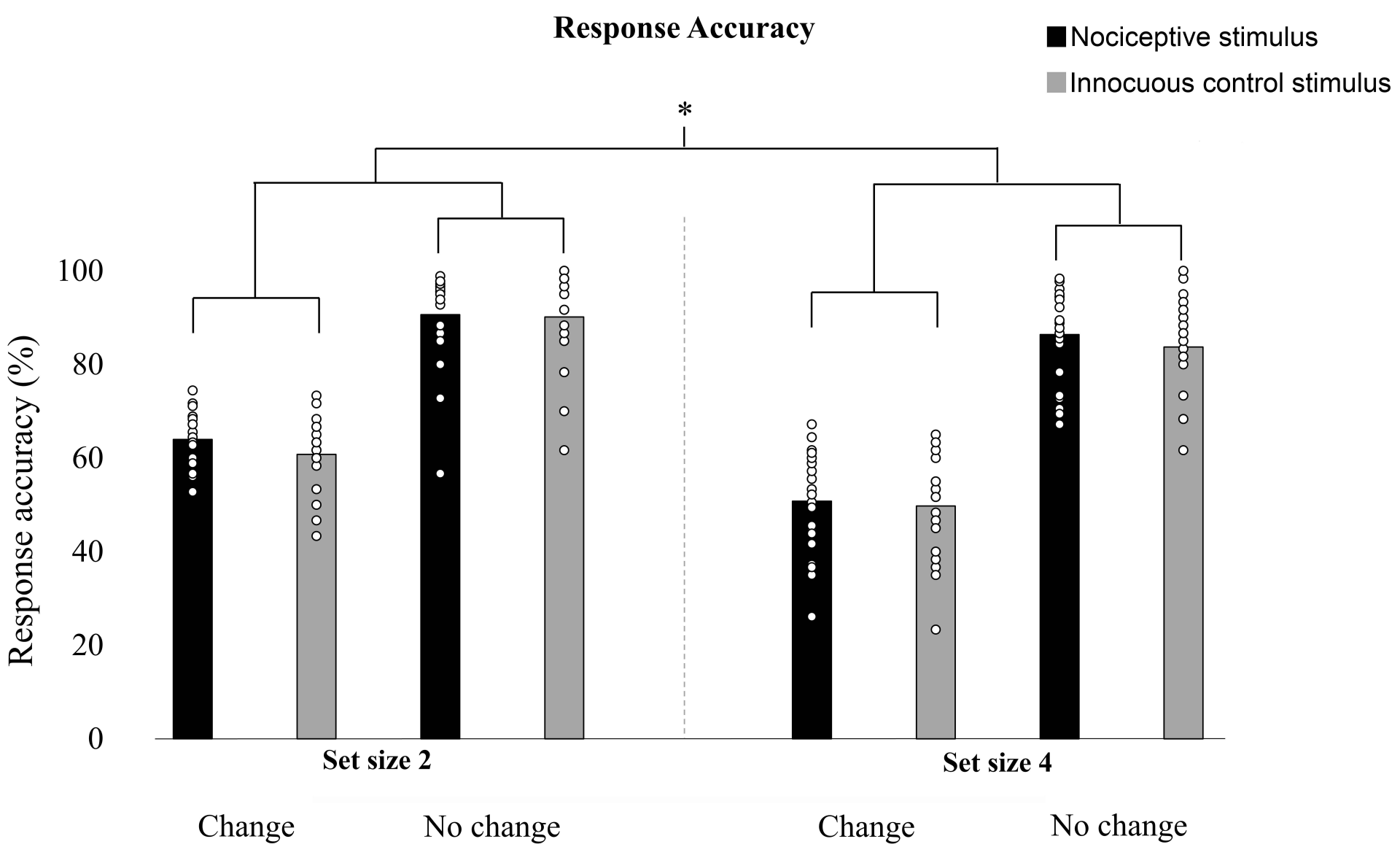
Figure 6. Laser-evoked potentials at Cz. Grand average laser-evoked potentials time-locked to laser stimulation, recorded at Cz, for the 2 conditions with nociceptive stimuli (set sizes 2 and set size 4). Note that the conditions with a change and those with no change between the two visual arrays are combined because laser-evoked potentials occur before the presentation of the second visual arrays, creating 2 conditions for this analysis. The set size 2 condition is depicted as a black line and the set size 4 condition is depicted as a gray line. The dashed gray and red vertical lines represent the onset of the visual memory array (-220 ms) and the laser stimulus (0 ms), respectively. Baseline was calculated as the mean value between -400 and -200 ms to avoid including the visual evoked potential produced by the memory array presentation. A 180 ms window from 170 ms to 350 ms was used to calculate the N2 peak amplitude and latency. A 220 ms window from 280 ms to 500 ms was used to calculate the P2 peak amplitude and latency.

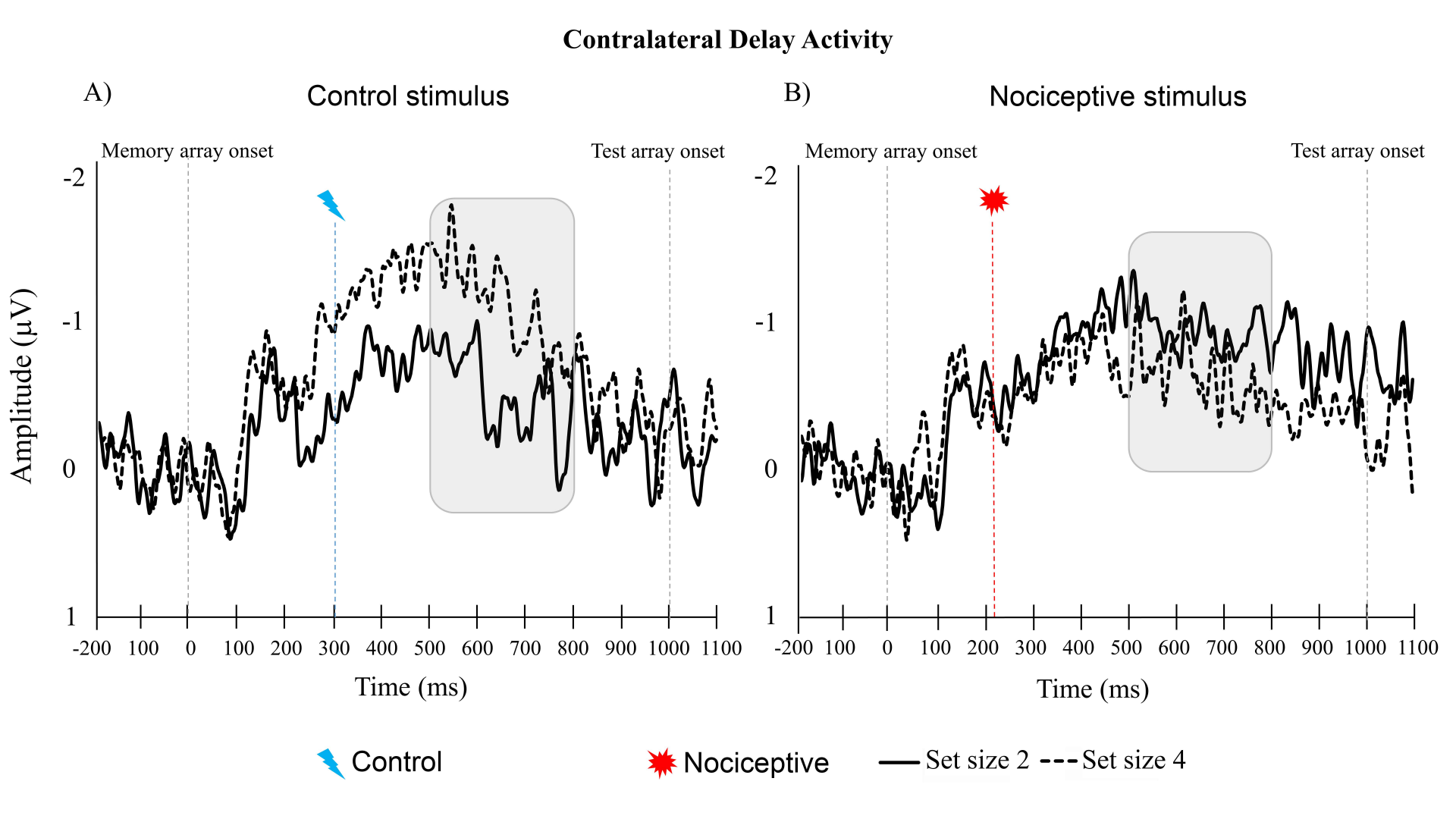
Figure 7. N2 and P2 peak amplitude. Mean N2 and P2 peak amplitude is shown for the 2 conditions. The N2 and P2 peak amplitude was not significantly modulated by load (set size 2 versus set size 4) both $P = .5$).

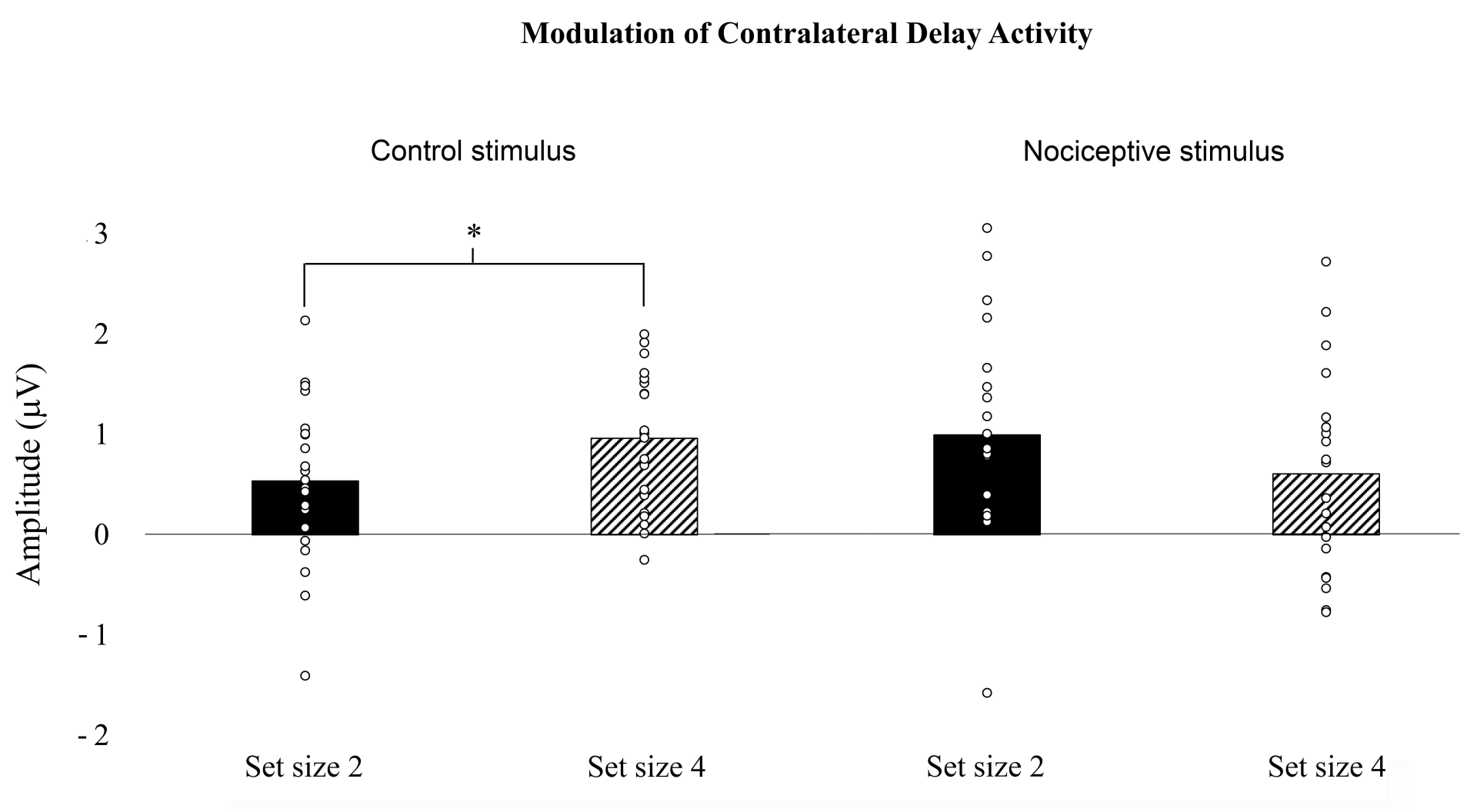
Change detection task

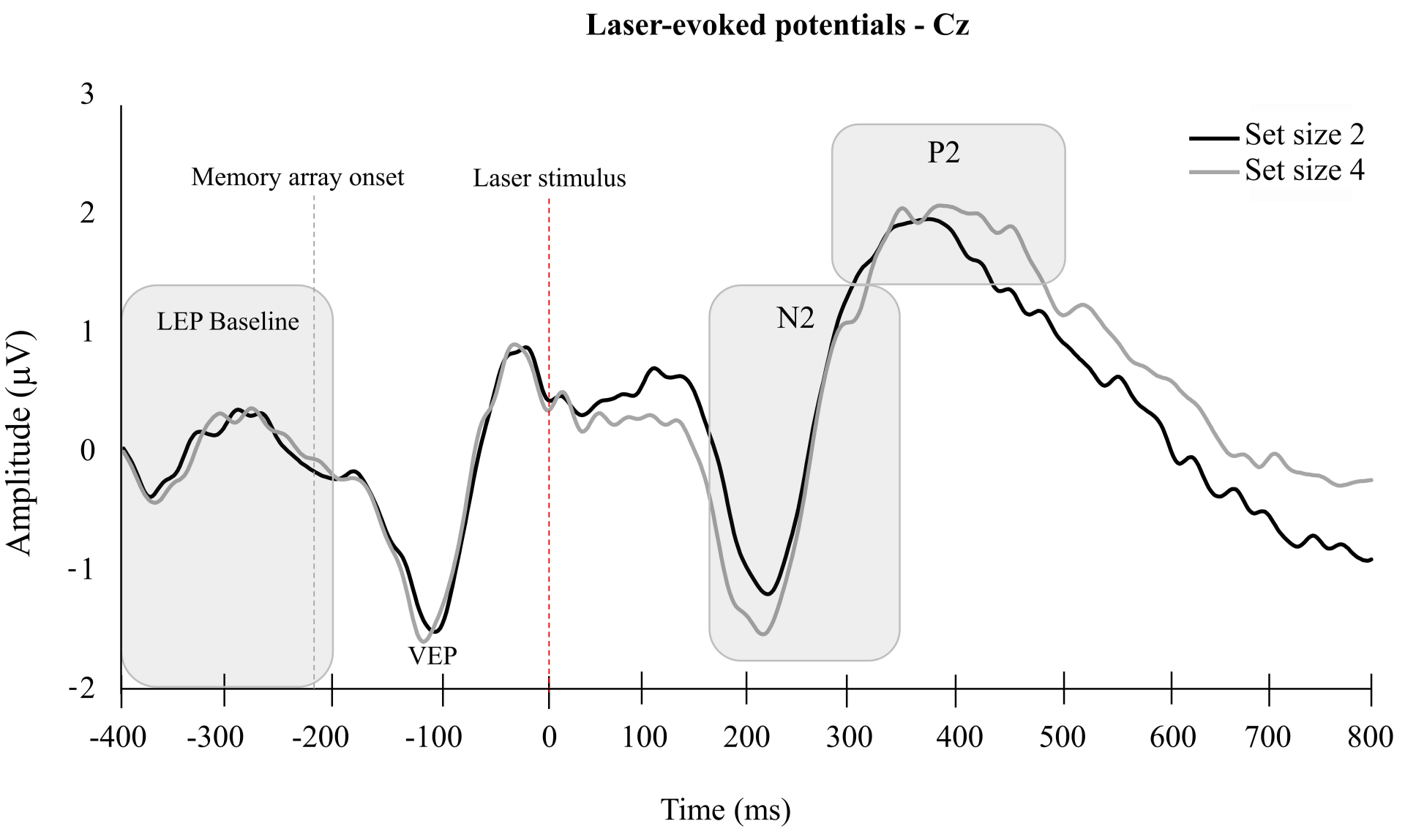



Response time
Nociceptive stimulus
Innocuous control stimulus
**
**
***
1300
1200
1100
1000
900
800
700
600
500
400
300
Response time (ms)
Set size 2
Set size 4
Change
No change
Change
No change


Response Accuracy
Nociceptive stimulus
Innocuous control stimulus
*
Response accuracy (%)
100
80
60
40
20
0
Set size 2
Set size 4
Change
No change
Change
No change


Contralateral Delay Activity
A)
Control stimulus
B)
Nociceptive stimulus
Memory array onset
Test array onset
Memory array onset
Test array onset
Amplitude (μV)
-2
-1
0
1
-200 100 0 100 200 300 400 500 600 700 800 900 1000 1100
Time (ms)
-2
-1
0
1
-200 100 0 100 200 300 400 500 600 700 800 900 1000 1100
Time (ms)
Control
Nociceptive
Set size 2
Set size 4


Modulation of Contralateral Delay Activity
Control stimulus
Nociceptive stimulus
Amplitude (μV)
3
2
1
0
- 1
- 2
*
Set size 2
Set size 4
Set size 2
Set size 4


Laser-evoked potentials - Cz
Set size 2
Set size 4
Memory array onset
Laser stimulus
LEP Baseline
VEP
N2
P2
Amplitude (μV)
Time (ms)
3
2
1
0
-1
-2
-400
-300
-200
-100
0
100
200
300
400
500
600
700
800

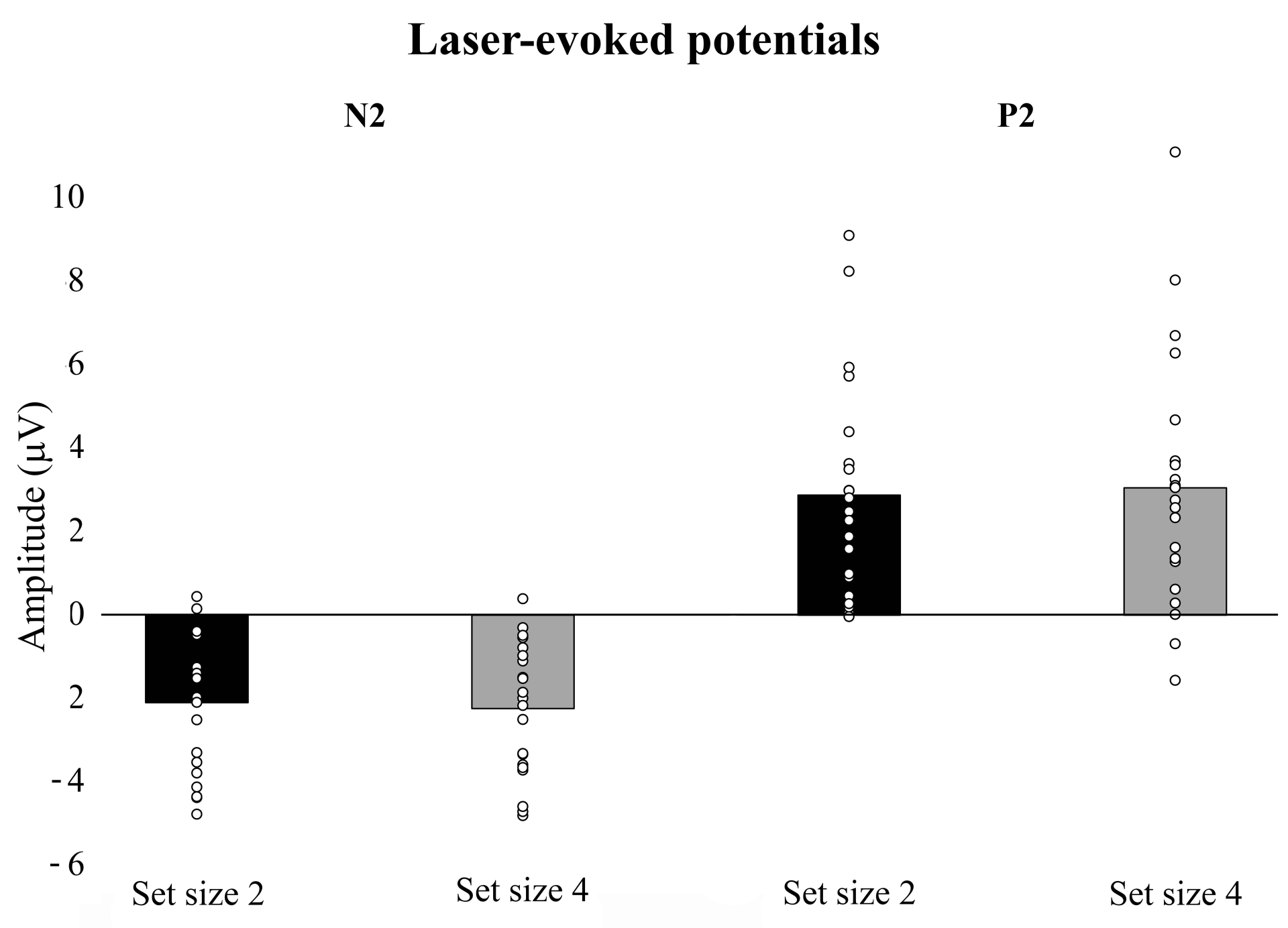

Laser-evoked potentials
N2
P2
10
8
6
4
2
0
2
4
6
Amplitude (μV)
Set size 2
Set size 4
Set size 2
Set size 4

Table 1. Response time and accuracy (mean ± SD)

		set size 2		set size 4	
	Stimulus	**Change**	**No change**	**Change**	**No change**
RT (ms)	Control	855.7 ± 121.3	787.9 ± 141.0	975.8 ± 137.1	845.3 ± 129.3
	Nociceptive	899.4 ±109.6	817.1 ± 159.9	976.8 ± 155.9	915.4 ± 147.1
Accuracy (%)	Control	64.0 ± 5.6	90.6 ± 10.4	50.8 ± 11.3	86.4 ± 10.3
	Nociceptive	60.8 ± 8.0	90.2 ± 10.6	49.8 ± 11.4	83.7 ± 10.5

Table 2. Contralateral delay activity (mean ± SD)

	Stimulus	set size 2	set size 4
CDA amplitude	Control	0.51 ± 0.80	0.95 ± 0.74
	Nociceptive	0.96 ± 1.23	0.60 ± 0.96

Table 3. Laser-evoked potential amplitude and latency (mean ± SD)

		set size 2	set size 4
N2	Amplitude	-2.1 ± 1.6	-2.2 ± 1.6
	Latency	247.0 ± 38.3	246.9 ± 35.8
P2	Amplitude	2.9 ± 2.6	3.1 ± 3
	Latency	402.8 ± 56.3	410.9 ± 62.3