Shielding cognition from nociception with working memory

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ABSTRACT

Because pain often signals the occurrence of potential tissue damage, nociceptive stimuli have the capacity to capture attention and interfere with ongoing cognitive activities. Working memory is known to guide the orientation of attention by maintaining goal priorities active during the achievement of a task. This study investigated whether the cortical processing of nociceptive stimuli and their ability to capture attention are under the control of working memory. Event-related brain potentials (ERPs) were recorded while participants performed primary tasks on visual targets that required or did not require rehearsal in working memory (1-back vs. 0-back conditions). The visual targets were shortly preceded by task-irrelevant tactile stimuli. Occasionally, in order to distract the participants, the tactile stimuli were replaced by novel nociceptive stimuli. In the 0-back conditions, task performance was disrupted by the occurrence of the nociceptive distracters, as reflected by the increased reaction times in trials with novel nociceptive distracters as compared to trials with standard tactile distracters. In the 1-back conditions, such a difference disappeared suggesting that attentional capture and task disruption induced by nociceptive distracters was suppressed by working memory, regardless of task demands. Most importantly, in the conditions involving working memory, the magnitude of nociceptive ERPs, including ERP components at early latency, were significantly reduced. This indicates that working memory is able to modulate the cortical processing of nociceptive input already at its earliest stages, and could explain why working memory reduces consequently ability of nociceptive stimuli to capture attention and disrupt performance of the primary task. It is concluded that protecting cognitive processing against pain interference is best guaranteed by controlling the disengagement of attention away from nociceptive stimuli by keeping out of working memory pain-related information.

49 **KEY WORDS**

50 Pain, attention, distraction, executive control, event-related potentials

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1. INTRODUCTION

Alleviating pain is a central question motivating many researchers in the field pain research.

The manipulation of attention is a potentially efficient method, partially constituting the common feature underlying the analgesic effect of hypnotic suggestion, meditation, cognitive behavioral therapy, etc. Several studies showed that distracting people from pain, i.e. directing attention away from a nociceptive stimulus, can decrease the perception of pain generated by that stimulus (see Van Damme et al., 2010 for a review).

The attention paid to a given stimulus depends on its salience (Egeth and Yantis, 1997). For this reason, nociceptive stimuli have a strong capacity to capture attention independently of voluntary control. Therefore, it was recently proposed that an efficient approach to reduce the attention paid to nociceptive stimuli should take into account the following three main factors (Legrain et al., 2009b). First, attention should be engaged in mental activities that are unrelated to pain and, more generally, to bodily sensations. Indeed, when performing a cognitive task, a mental set of information is defined to guide attention towards the stimuli that are relevant to the task (Folk et al., 1992). As a consequence, any sensory event sharing common features with the mental set will automatically attract attention. Therefore, the greater the segregation between competing task-relevant and task-irrelevant stimuli, the better attentional capture by irrelevant distracters is avoided. Second, the engagement of attention should be effortful: the more attention is loaded to perform a task, the less it will be prone to process distracter stimuli (e.g. see Allport, 1987; Lavie, 2005). Third, the engagement of attention should be controlled by executive functions in order to inhibit the interference of distracters (Posner and Petersen, 1990). Among the various executive functions, the role of working memory has been put forward (Olivers, 2008; Soto et al., 2008). Working memory contributes to optimize attention by keeping a memory trace of the

97 attentional set during the achievement of the task (Desimone and Duncan, 1995) and by
98 protecting task execution from the intrusion of distracters (Szmales et al., 2011). Working
99 memory was shown to facilitate the orientation of attention to any stimuli sharing common
100 features of the task set (Downing, 2000; Soto et al., 2005; Soto and Humphreys, 2007).
101 Moreover, working memory can control the intrusion of irrelevant distracters and,
102 therefore, can protect task performance (SanMiguel et al., 2008), by reducing the cortical
103 processing of the distracters (de Fockert et al., 2001; Berti and Schröger, 2003; SanMiguel et
104 al., 2008). Conversely, such a control is less efficient if the resources of working memory are
105 used in a second unrelated task (de Fockert et al., 2001; Lavie and de Fockert, 2005; Dalton
106 et al., 2009).

107 Recently, we showed that the disruptive effect induced by nociceptive distracters, i.e. the
108 decrease in task performance due to the interference from task-irrelevant nociceptive
109 stimuli, can be reduced by working memory (Legrain et al., 2011a, 2011b). Indeed, when
110 participants performed a visual task requiring the use of working memory, task-irrelevant
111 nociceptive stimuli lost their ability to capture attention and to disrupt the task, as compared
112 to conditions in which working memory was not used. In these experiments, we adapted a
113 paradigm from research on auditory attention (Escera and Corral, 2007). In this paradigm,
114 stimuli are delivered in pairs consisting of a task-irrelevant distracter immediately followed
115 by a task-relevant target. In order to manipulate attentional capture and distraction,
116 occasionally and unexpectedly, the standard distracter is replaced by a stimulus mismatching
117 the standard distracters according to at least one parameter. In our experiments, task-
118 relevant targets were visual stimuli and task-irrelevant distracters were tactile
119 somatosensory stimuli occasionally replaced by a nociceptive somatosensory stimulus
120 (Legrain et al., 2011a, 2011b). The low probability of occurrence of the mismatching

distracter is an important factor since the novelty of a stimulus is a key factor determining stimulus salience and attentional capture (Näätänen, 1992; Escera and Corral, 2007). Indeed, it was shown that the ability of a nociceptive stimulus to capture attention is strongly determined by the context in which it occurs, such as its novelty (Legrain et al., 2009, 2011c). Comparing task performance when the visual targets were preceded by a standard tactile distracter vs. a novel nociceptive distracter confirmed that the occurrence of novel nociceptive stimuli triggered an involuntary shift of attention and disrupted task performance, as indexed by the increased reaction times to the visual targets preceded by a novel nociceptive distracter (Legrain et al., 2011a, 2011b). However, and most importantly, comparing task performance in conditions involving working memory and conditions not involving working memory, showed that the novel nociceptive stimuli lost their ability to disrupt task performance in the working memory condition, as revealed by the disappearance of the difference in reaction times between the trials with standard tactile distracters and the trials with novel nociceptive distracters. This result suggests that working memory is able to suppress the attentional capture triggered by the novel nociceptive distracters and consequently, the disruptive effect on primary task performance. Another important point was the relative independency of the attentional control by working memory from task demands and attentional overload. Indeed, the reduction of distraction observed in the working memory conditions was significant both during high-demanding and low-demanding working memory tasks (Legrain et al., 2011a). Here, using event-related brain potentials (ERPs) to sample stimulus-evoked cortical activity, we tested the hypothesis that suppression of distraction by working memory results in a reduction of the cortical processing of nociceptive inputs. More specifically, we predicted that nociceptive stimuli would elicit ERPs of reduced magnitude when participants rehearsed

145 the properties of concurrent visual stimuli in working memory, as compared to conditions in
146 which working memory was not engaged. Such as in our previous studies (Legrain et al.,
147 2011a, 2011b), participants performed a task on visual target stimuli. The presentation of
148 each visual target was shortly preceded by the presentation of a task-irrelevant
149 somatosensory stimulus which was either a standard innocuous tactile stimulus in 83% of
150 the trials or a novel nociceptive stimulus in the remaining 17% of trials. In the 0-back control
151 conditions, participants were asked to perform the task on each visual target directly after
152 its presentation. In the 1-back working memory conditions, participants were asked to
153 respond based on the features of the visual target presented one trial before. Hence,
154 participants were required to maintain information about the visual targets in working
155 memory during the presentation of somatosensory distracters in the 1-back conditions but
156 not in the 0-back conditions. As in our previous study (Legrain et al., 2011a), two different
157 types of tasks were used in order to avoid the possible confounding effect of tasks demand
158 and attentional load. In the first type of task, performing the working memory condition was
159 more demanding than performing the control condition (matching tasks), whereas in the
160 other type of task, performing the working memory condition was not more demanding
161 (discrimination tasks). We expected that, during the two working memory conditions, the
162 reduction of distraction, as indexed by reaction times to the visual targets, would be
163 accompanied by a reduction of the cortical activity elicited by the nociceptive distracters.
164 Specifically, in both types of tasks, we expected that nociceptive distracters would
165 significantly increase reaction times to the visual targets in the 0-back condition but not in
166 the 1-back condition. Furthermore, we hypothesized that if working memory is able to
167 modulate the cortical processing of the nociceptive distracters, this could translate into a

measurable difference in the magnitude of nociceptive ERPs between 0-back and 1-back conditions.

2. METHODS

2.1. Participants

Participants were 16 healthy volunteers (mean age 25 ± 3 years; 6 women; 2 left-handed), with normal or corrected-to-normal vision, no prior history of neurological, psychiatric or chronic pain disorder and no current use of psychotropic or analgesic drugs. Experimental procedures were approved by the Ethics Committee of the Université catholique de Louvain. Written informed consent was obtained. Participants were randomly assigned to one of two groups of equal size. Each group was assigned to one of two tasks.

2.2. Stimuli

Nociceptive somatosensory stimuli were 50 ms pulses of radiant heat generated by a CO₂ laser (10.6 μ m wavelength; Université catholique de Louvain, Belgium), delivered to the dorsum of the left hand, within the sensory territory of the superficial radial nerve. Beam surface area on the skin was ~ 80 mm². Stimulus energy ($M = 720 \pm 80$ mJ, ranging from 560 to 850 mJ, no difference between the two groups: $t_{14} = .0192$, $p = .850$, $d = .096$) was adjusted individually to elicit a clear pinprick sensation, perceived as slightly painful and related to the activation of A δ -fiber skin nociceptors (Plaghki and Mouraux, 2005). To prevent nociceptor fatigue, sensitization and skin overheating, the laser beam was slightly displaced after each stimulus.

Innocuous tactile somatosensory stimuli were 0.5 ms constant current square-wave electrical pulses (DS7 Stimulator, Digitimer Ltd, Letchworth Garden City, UK) delivered with a

pair of electrodes (0.7 cm diameter, 2.5 cm inter-electrode distance) placed over the superficial branch of the left radial nerve, at the level of the wrist. Intensity was set at 1.5 times the absolute detection threshold. This intensity ($M = 0.89 \pm 0.21$ mA, ranging from 0.50 to 1.30 mA, no difference between groups: $t_{14} = -1.254$, $p = .230$, $d = .095$) was above the threshold of tactile A β -fibers, but well below the threshold of nociceptive A δ - and C-fibers (Mouraux and Plaghki, 2007). At such intensity, these electrocutaneous stimuli were felt as a non-painful vibrotactile sensation.

Visual stimuli were presented on a 17" CRT monitor placed 70 cm in front of the participant. Stimuli consisted of two 6 cm blue (RGB 0*0*255) or yellow (RGB 255*255*0) colored disks (6 cm diameter) displayed on a black background. The centers of the circles were positioned respectively 6 cm left and right of a white 1.7 cm central fixation cross.

2.3. Procedure

The experiment started with a practice block of the 1-back condition (see below) with ~20 visual stimuli without any concurrent somatosensory stimuli. After electrode placement and impedance check, the detection thresholds to electrocutaneous tactile stimuli and laser nociceptive stimuli were measured with the method of limits (Churyukanov et al., 2012). Next, participants were presented with 8 blocks of 60 trials per block. A fixation cross remained at the center of the monitor for the entire duration of the block. Each trial started with a somatosensory stimulus (tactile or nociceptive) shortly followed by a visual stimulus presented briefly during 500 ms. The inter-stimulus time interval (ISI) between the onset of the somatosensory stimulus and the onset of the visual stimulus varied according to the type of somatosensory stimulus, in order to account for the faster conduction velocity of A β -fibers conveying the tactile input vs. A δ -fibers conveying the nociceptive input: ISI was 220

ms for tactile-visual trials and 300 ms for nociceptive-visual trials (Legrain et al., 2011b). The inter-trial time interval (ITI) between the onsets of two consecutive visual stimuli was 3000 ms.

Within each block, trials were delivered in a pseudo-random order, using the following restrictions. To maximize the novelty of nociceptive distracters relatively to tactile distracters, (1) the probability of occurrence was 0.83 for tactile-visual trials (50 per block) and 0.17 for nociceptive-visual trials (10 per block), (2) nociceptive-visual trials were preceded by at least three tactile-visual trials and (3) the first four trials of a block never included a nociceptive-visual trial. To prevent any preference for a given response, and to prevent any association between the type of trial and the type of response, (4) the probabilities of each of the two possible responses were equivalent, (5) each type of somatosensory distracter was equally often associated with each type of response, (6) each type of response was equally likely to be preceded by the same or a different type of response and (7) this equivalence was maintained across the two types of somatosensory distracters. The blocks were separated by short pauses of 2 to 5 minutes.

In one group, participants performed a *color discrimination task* (Figure 1a). The color of the two disks constituting the visual target was either both blue or both yellow (i.e. blue-blue, yellow-yellow). Immediately following the onset of the visual target, they were instructed to respond according to the color of the current visual target (0-back condition, 4 blocks) or the color of the visual target presented one trial before (1-back condition, 4 blocks). In other words, in the 1-back condition, participants were required to rehearse in working memory the color of the correct response and to delay their response until the presentation of the next target (i.e. during the presentation of the somatosensory distracter). In the other group, participants performed a *color matching task* (Figure 1b). During the 4 blocks of the 0-back

condition, the two colored disks of each visual target could be either matching (blue-blue, yellow-yellow) or non-matching (yellow-blue, blue-yellow) and the participants were asked to report whether the two disks were of matching color. During the 4 blocks of the 1-back condition, the two colored disks were either both blue or both yellow (blue-blue, yellow-yellow) and the participants were asked to report whether the color of the current target matched the the color of the preceding target. This 1-back condition required to rehearse in working memory the color of the preceding target during the presentation of the somatosensory distracter, in order to be able to compare it to the color of the upcoming target. The order of the blocks was balanced with the restriction of having in each half of the experiment the same amount of blocks for each condition.

For all conditions, participants were asked to respond as accurately and as fast as possible. Responses were produced by pressing one of two keys on a numerical keypad with their right middle or index fingers ("*blue*" vs. "*yellow*" in the discrimination task, "*same*" vs. "*different*" in the matching task). They were instructed to keep both fingers on the response keys in order to prevent using the target finger as a proprioceptive or visual cue in the 1-back color discrimination task. In order to keep the somatosensory distracters irrelevant for the tasks, no intensity rating was asked for the somatosensory stimuli during the experiment (Legrain et al., 2002).

2.4. Measures

2.4.1. Performance of the visual task.

The percentage of errors was used as a measure of response accuracy. The mean reaction time (RTs) was used as a measure of response speed (excluding RTs associated to the first response of each block, incorrect responses, anticipated responses [RT < 150 ms], and

missed responses [RT > 1500 ms]). Tactile-visual trials that immediately followed a nociceptive-visual trial were not included in the analysis (Legrain et al., 2009).

2.4.2. Event-related potentials.

The electro-encephalogram (EEG) was recorded using 64 Ag-AgCl electrodes placed on the scalp according to the international 10/10 system (Waveguard64 cap, Cephalon A/S, Denmark). Eye blinks and eye movements were monitored by an electrooculogram (EOG) recorded from two pairs of electrodes placed at the upper-left and lower-right sides of the right eye (vertical EOG) and close to the lateral canthi of the left and right eyes (horizontal EOG). Electrode impedances were kept below 50 k Ω . Signals were recorded using an average reference, amplified and digitized using a 1000 cps sampling rate (ASA-Lab, ANT, The Netherlands). Off-line analyses were carried out using Brain Vision Analyzer 1.05 (Brain Products GmbH, Germany) and LetsWave 4.0 (Université catholique de Louvain, Belgium). The continuous EEG recordings were band-pass filtered (0.3-30 Hz, 12dB/octave) and segmented into 2000 ms long epochs (-500 to 1500 ms for nociceptive and tactile ERPs, and -800 to 1200 ms for visual ERPs, relative to stimulus onset). Artifacts produced by eye blinks and eye movements were corrected using ICA (Hyvarinen and Oja, 2000) and epochs with activities exceeding ± 100 μ V were excluded (less than 10% of the epochs). Signals were re-referenced to the mastoid electrodes (M1M2) and baseline-corrected (from -500 to 0 ms for nociceptive and tactile ERPs; from -800 to -300 ms for visual ERPs). Finally, epochs were sorted and averaged according to experimental conditions (1-back vs. 0-back for nociceptive and tactile ERPs; 1-back vs. 0-back*nociceptive vs. tactile distracter for visual ERPs).

Identification of nociceptive and tactile ERP components was based on latency and scalp topography. Three components of the nociceptive ERPs were identified, N1, N2 and P2. The N2 component was first identified at Cz as a negative component peaking between 150 and 250 ms after laser stimulus onset. The P2 was identified at Cz as the positive component following the N2 around 300-400 ms after laser stimulus onset. The N1 was isolated by re-referencing the contralateral temporal electrode (T8) to Fz (Kunde & Treede, 1993) and was identified as a negative component peaking 100-200 ms after laser stimulus onset. Two components of the tactile ERPs were identified, N1 and P2. The N1 was identified as a negative component peaking at C4 around 80-150 ms and the P2 as a positive component peaking at Cz around 150-200 ms after electrical stimulus onset. No earlier ERP components were consistently identified in response to tactile stimuli across subjects and conditions. Peak latencies of were measured from stimulus onset (in millisecond), peak amplitudes from baseline to peak (in microvolt).

Identification of visual ERP components was based on latency and scalp topography. Three early-latency components of the visual ERPs were identified at PO7 and PO8: P1 (70-120 ms after visual stimulus onset), N1 (100-200 ms) and P2 (150-250 ms). In addition, the N2 (200-300 ms) and P3 (250-500 ms) components were identified Fz and Pz. Peak latencies were measured from visual stimulus onset. Peak amplitudes were measured from peak to peak (P1-N1, N1-P2, N2-P3), since baseline-to-peak amplitudes were contaminated by the presence of the preceding somatosensory ERPs.

2.5. Analyses

2.5.1. Performance of the visual task.

Eight conditions resulted from the combination of one between-subjects variable (*task*: discrimination vs. matching task) and two within-subjects variables (*working memory*: 0-back vs. 1-back; *somatosensory distracter*: frequent tactile vs. novel nociceptive). The reaction times and the percentages of error were compared using a 3-factor repeated-measures ANOVA with *task* as between-subjects factor (2*2*2 conditions).

2.5.2. Nociceptive and tactile event-related potentials.

The latencies and amplitudes of the nociceptive and tactile ERPs were submitted to a 2-factor repeated-measures ANOVA with *working memory* as within-subjects factor (0-back vs. 1-back) and *task* as between-subjects factor (discrimination vs. matching task).

In a next step we investigated whether *working memory* and *task* similarly influenced the ERPs elicited by nociceptive stimuli vs. those elicited by tactile stimuli. Despite the fact that the P2 elicited by nociceptive stimuli and the P2 elicited by tactile stimuli are thought to partially share similar mechanisms (Treede et al., 1988; Kunde & Treede, 1993; Mouraux & Iannetti, 2009), there is no evidence to consider them as strictly the same component, i.e. the same dependent variable. Therefore, a multivariate analysis of variance (MANOVA)¹ was performed using two dependent variables (*P2 elicited by nociceptive vs. tactile stimuli*), one within-subjects factor (*working memory*) and one between-subjects factor (*task*).

2.5.3. Visual event-related potentials.

¹ Because there is no argument to relate the tactile N1 to either the nociceptive N1 or the nociceptive N2 (Treede et al., 1988; Kunde & Treede, 1993; Valeriani et al., 1996), the MANOVA was not performed on these negative components.

The latencies and peak-to-peak amplitudes of visual ERPs were submitted to a 4-factor ANOVA with *task* as between-subjects factor, and *working memory*, *somatosensory distracter* and *electrode* (PO7 vs. PO8 for P1-N1 and N1-P2; Fz vs. Pz for N2-P3) as within-subjects factors.

When appropriate, contrast analyses were used. Size effects were measured with partial Eta-squared (η^2) for ANOVAs and Cohen's *d* for *t*-tests. Significance level was set at $p < 0.05$.

3. RESULTS

3.1. Performance of the visual task

Participants anticipated 9.2% of the responses in the 1-back condition of the discrimination task. They never anticipated the responses in the other conditions. Overall, participants made few errors (3.4%), and error rates were not affected by the experimental variables (all $p > .114$, all $\eta^2 < .169$). Reaction times were significantly modulated by the experimental variables. Indeed, the ANOVA revealed a significant main effect of *working memory* ($F_{1,14} = 7.156$, $p = .018$, $\eta^2 = .338$) with a significant interaction between *working memory* and *task* ($F_{1,13} = 45.006$, $p < .001$, $\eta^2 = .793$). Contrast analyses showed that, in the group performing the discrimination task, participants were faster in the 1-back than in the 0-back condition ($F_{1,7} = 113.814$, $p < .001$, $\eta^2 = .942$). Conversely, in the group performing the matching task, participants tended to be slower in the 1-back condition than in the 0-back condition ($F_{1,7} = 5.043$, $p = .060$, $\eta^2 = .419$) (Figure 2a). In other words, working memory improved performance in the discrimination task, but tended to reduce performance in the matching task. This confirms that overall task demands of the two working tasks were not the same and that the matching working memory tasks tended to be more difficult to perform. In line

with our hypothesis, the ANOVA also revealed a significant main effect of the type of *somatosensory distracter* ($F_{1,14} = 63.855$, $p < .001$, $\eta^2 = .820$) with a significant interaction with *working memory* ($F_{1,13} = 78.764$, $p < .001$, $\eta^2 = .849$). In line with the results of our previous studies (Legrain et al., 2011a, 2011b), contrast analyses showed that RTs in nociceptive-visual trials were significantly greater than RTs in tactile-visual trials in the 0-back condition ($F_{1,14} = 265.871$, $p < .001$, $\eta^2 = .950$) but not in the 1-back condition ($F_{1,14} = .679$, $p = .424$, $\eta^2 = .046$) (Figure 2a). This confirms that behavioral distraction, i.e. slower reaction times due to the occurrence of a novel distracter, was not observed in the working memory conditions. Most importantly, this interaction was not dependent on the type of working memory task (*group*working memory*somatosensory distracter* interaction: $F_{1,13} = .064$, $p = .805$, $\eta^2 = .005$), indicating that the suppression of distraction was present both when participants performed the discrimination task and when they performed the matching task (Figure 2b).

3.2. Electrophysiological data

3.2.1. Nociceptive event-related potentials.

Group-level average waveforms are shown in Figure 3. The latencies of the N1, N2 and P2 components were not affected by the experimental conditions (all $p \geq .274$, all $\eta^2 \leq .085$). Analysis of N1 amplitude revealed a main effect of the factor *working memory* ($F_{1,14} = 5.226$, $p = .038$, $\eta^2 = .272$) without a main effect of the factor *task* ($F_{1,14} = 1.057$, $p = .321$, $\eta^2 = .070$) and without interaction between the two factors ($F_{1,13} = .321$, $p = .580$, $\eta^2 = .022$), indicating a similar reduction of N1 amplitude by working memory in both the discrimination task and the matching task. Similar results were observed for the N2 as its amplitude was significantly affected by the factor *working memory* ($F_{1,14} = 4.779$, $p = .046$, $\eta^2 = .254$) with no effect of

the factor *task* (main effect of *task*: $F_{1,14} = .856$, $p = .370$, $\eta^2 = .058$) and no interaction between the two factors ($F_{1,13} = .673$, $p = .426$, $\eta^2 = .046$). Analysis of P2 amplitude revealed a main effect of the factor *working memory* ($F_{1,14} = 7.079$, $p = .019$, $\eta^2 = .336$), but also a significant interaction with the factor *task* ($F_{1,14} = 5.482$, $p = .035$, $\eta^2 = .281$). Contrast analyses showed that P2 amplitude was significantly reduced by working memory in the group of participants performing the discrimination task ($t_7 = 4.533$, $p = .003$, $d = .723$), but not in the group of participants performing the matching task ($t_7 = .191$, $p = .854$, $d = .053$). The main effect of *task* was not significant ($F_{1,13} = .086$, $p = .773$, $\eta^2 = .006$). To summarize, the magnitude of nociceptive ERPs was significantly reduced in the working memory conditions: the magnitude of the N1 and N2 nociceptive components was significantly reduced in the working memory conditions of both the matching and the discrimination tasks, whereas the magnitude of the nociceptive P2 component was significantly reduced only in the working memory condition of the discrimination task.

3.2.2. Tactile event-related potentials.

Group-level average waveforms are shown in Figure 4. The latencies of the N1 and P2 components were not affected by the experimental variables (all $p \geq .196$, all $\eta^2 \leq .117$). Analysis of N1 amplitude revealed a main effect of the factor *working memory* ($F_{1,14} = 14.783$, $p = .002$, $\eta^2 = .541$), with no effect of the factor *task* (main effect of *task*: $F_{1,14} = .531$, $p = .478$, $\eta^2 = .037$) and no interaction between the two factors ($F_{1,13} = 2.093$, $p = .170$, $\eta^2 = .130$), indicating a similar reduction of N1 amplitude by working memory in both the discrimination task and the matching task. Amplitude of the P2 was also affected by the factor *working memory* ($F_{1,14} = 17.600$, $p = .001$, $\eta^2 = .557$) with no main effect of the factor *task* ($F_{1,14} = .079$, $p = .783$, $\eta^2 = .006$). Conversely to the P2 of the nociceptive ERPs, the

interaction between the factors *working memory* and *task* was not significant ($F_{1,13} = .429$, $p = .523$, $\eta^2 = .030$), despite the fact that the reduction of P2 amplitude was significant for the group of participants performing the discrimination task ($t_7 = 4.016$, $p = .005$, $d = .511$), while such a difference failed to reach significance level in the group of participants performing the matching task ($t_7 = 2.221$, $p = .062$, $d = .495$). To summarize, the magnitude of the N1 and P2 components of tactile ERPs was significantly reduced in the working memory conditions of both the matching and the discrimination tasks.

The univariate tests suggest that the present experimental manipulations differently affected the P2 component elicited by nociceptive stimuli and the P2 component elicited by tactile stimuli. This difference was confirmed by the MANOVA showing that the effect of the *working memory*task* interaction on the magnitude of the tactile P2 component was significantly different from its effect on the nociceptive P2 component (multivariate test of the *working memory*task* interaction: $F_{2,13} = 4.545$, $p = .032$, $\eta^2 = .411$).

3.2.3. Visual event-related potentials.

Group-level average waveforms are shown in Figure 5. None of the latencies of the visual ERP components were significantly affected by the experimental variables (all $p \geq .093$, all $\eta^2 \leq .214$). The P1-N1 peak-to-peak amplitude was also unaffected (all $p \geq .056$, all $\eta^2 \leq .253$). Comparison of the N1-P2 amplitude showed a significant interaction between the factors *working memory* and *somatosensory distracter* ($F_{1,14} = 6.821$, $p = .021$, $\eta^2 = .328$; all other $p \geq .096$, all $\eta^2 \leq .186$). The N1-P2 amplitude was reduced in the 1-back condition compared to the 0-back condition when the visual targets followed a novel nociceptive distracter ($F_{1,14} = 4.557$, $p = .051$, $\eta^2 = .246$), but not when they followed a standard tactile distracter ($F_{1,14}$

=.014, $p = .907$, $\eta^2 = .375$). Comparison of the N2-P3 amplitude showed a significant interaction between the factors *working memory* and *electrode* ($F_{1,13} = 5.630$, $p = .034$, $\eta^2 = .302$), and between the factors *somatosensory distracter* and *electrode* ($F_{1,13} = 7.645$, $p = .016$, $\eta^2 = .370$), without any other significant effect (all $p \geq .100$, all $\eta^2 \leq .194$). At electrode Pz, N2-P3 amplitude was decreased in the 1-back condition compared to the 0-back condition ($F_{1,13} = 5.567$, $p = .035$, $\eta^2 = .300$). At electrode Fz, N2-P3 amplitude was larger when the visual stimuli were preceded by a novel nociceptive distracter as compared to when they were preceded by a standard tactile distracter ($F_{1,13} = 8.489$, $p = .012$, $\eta^2 = .395$).

4. DISCUSSION

The results of the present study are summarized in the following three points. First, in line with the results of our previous studies (Legrain et al., 2011a, 2011b), behavioral distraction induced by unexpected task-irrelevant novel nociceptive stimuli was suppressed when a concomitant visual task required working memory, regardless of the type of task, i.e. regardless of task demands. Second, suppression of nociceptive distraction by working memory was related to a reduction of the magnitude of the cortical responses elicited by the nociceptive stimulus. Importantly, working memory affected the earliest cortical responses to nociceptive stimuli, i.e. the N1 component of nociceptive ERPs, indicating that working memory is able to exert an effect already at the very early stages of nociceptive processing. Third, contrasting with the effect of working memory on the magnitude of the nociceptive N1 and N2 components, the effect of working memory on the magnitude of the P2 component of nociceptive ERPs was dependent on the type of task (working memory significantly modulated the P2 component in the discrimination task, but not in the matching

task). This suggests that, unlike the N1 and N2 components, the P2 component reflects processing stages that are dependent on aspects differentiating the two tasks.

4.1. Effect of working memory on behavioral distraction

Present behavioral results clearly replicate the results obtained in our previous studies. First, when subjects performed a relatively simple visual task, their performance was disrupted by the occurrence of a novel nociceptive distracter, as reflected by the increased reaction times to the visual targets preceded by a novel nociceptive distracter as compared to visual targets preceded by a standard tactile distracter (Escera and Corral, 2007; Legrain et al., 2009a, 2011a, 2011b). Second, the distraction induced by the novel and irrelevant nociceptive stimuli was suppressed when the task involved working memory, as revealed by the suppression of the difference in the reaction times to the visual target preceded by novel nociceptive distracter and the visual targets preceded a standard tactile distracter in the 1-back conditions (Legrain et al., 2011a, 2011b). Crucially, the reduction of distraction was present in the working memory conditions of both tasks, even though the two tasks showed distinct effects of working memory involvement on the global performance of the participants. Overall, as compared to their respective control conditions, reaction times were faster in the working memory condition of the discrimination task, whereas reaction times were slower in the working memory condition of the matching task (Legrain et al., 2011a). There were also more errors in the working memory condition of the matching task. This pattern of results suggests that the working memory condition of the matching task was more demanding than its corresponding control condition, while there was no evidence of a difference in demand between the working memory and control conditions of the discrimination task. Therefore, the fact that a similar reduction of distraction was observed

in the working memory condition of both the discrimination task and the matching task indicates that the suppression of nociceptive distraction was specifically due to the executive control of working memory, regardless of the attentional overload induced by task demands (Legrain et al., 2011a).

4.2. Effect of working memory on the N1 and N2 components of nociceptive ERPs

In both tasks, the control of distraction by working memory was associated with a reduction of the magnitude of the N1 and N2 component of nociceptive ERPs. The N1 component of nociceptive ERPs is thought to reflect, at least partially, activity originating from the secondary somatosensory cortex (reviewed in Garcia-Larrea et al., 2003), and, probably also the primary somatosensory cortex contralateral to the stimulated side (Tarkka and Treede, 1993; Schlereth et al., 2003; Valentini et al., 2012). The N2 component is thought to be mainly generated by activity originating from insular and cingulate cortices (reviewed in Garcia-Larrea et al., 2003). Our finding that both the N1 and N2 components were reduced by working memory thus suggests that most of the cortical areas usually shown to respond to nociceptive stimuli are under the control of working memory. Most importantly, the finding that working memory modulated the N1 component of nociceptive ERPs indicates that working memory is able to modulate the earliest stages of nociceptive cortical processing. Our observation of an early modulatory effect of working memory on the cortical processing of irrelevant sensory input is in line with the results of previous studies having shown similar effects of working memory on the early-latency responses to auditory distracters (Berti and Schröger, 2003; Pratt et al., 2011), although this finding was not observed in some others studies (Harmony et al., 2000; Muller-Gass and Schröger, 2007; SanMiguel et al., 2008). Our observation is also in line with the results of Fockert et al. (2001)

showing, with functional magnetic resonance imaging, that working memory can modulate the activity elicited by visual distracters in extrastriate visual cortices. Interestingly, previous studies have shown that selective attention modulates the magnitude of the N1 component (Legrain et al., 2002, 2009a; Schlereth et al., 2003). This effect has been proposed to result from a top-down modulation of the responsiveness of the cortical areas involved in processing the attended sensory inputs (Desimone and Duncan, 1995). Event-related potential studies support that such an enhancement by selective attention can be observed at very early latencies, suggesting a modulation of primary sensory cortical areas (Hillyard et al., 1998; Rausse et al., 2011). Therefore, one can hypothesize that working memory can control the selectivity of the processing of sensory inputs already at the earliest stages of cortical processing. In other words, our results suggest that the ability of nociceptive stimuli to capture attention and to interfere with the processing of relevant information can be modified by working memory because working memory can modulate the responsiveness of the cortical areas involved in their processing. Based on previous data, one may wonder whether working memory could exert an effect at subcortical stages of nociceptive processing, such as at thalamic (Bantick et al., 2002; Valet et al., 2004) or even spinal level (Willer et al., 1979).

4.3. Effect of working memory on the P2 component of nociceptive ERPs

Contrasting with the N1 and N2 components, the P2 component of nociceptive ERPs was significantly reduced by working memory in the discrimination task but not the matching task. Despite a similar trend, this interaction was not found for the P2 component of tactile ERPs. This could be explained by a larger contribution of attention-related mechanisms to the generation of the nociceptive P2, especially because the occurrence of nociceptive

distracters was made rare in the present experiment (Legrain et al., 2002, 2009). Indeed, it is now increasingly recognized that the P2 component of nociceptive ERPs does not reflect cortical activity directly and specifically related to nociception and the perception of pain (Legrain et al., 2011c). For instance, there is increasing evidence suggesting that the nociceptive P2 component reflects, at least partially, brain processes similar to those underlying the auditory P3a component (Legrain et al., 2002, 2009a) which is specifically elicited by the occurrence of novel mismatching auditory stimuli (Näätänen, 1992) and is thought to reflect the attentional shift towards the novel sounds (Escera and Corral, 2007). The finding that the P2 component of nociceptive ERPs was not reduced in the working memory condition of the matching task is somewhat unexpected. Indeed, previous studies have almost always observed a decrease of P3a amplitude by working memory (Berti and Schröger, 2003; Harmony et al., 2000; Muller-Gass and Schröger, 2007; SanMiguel et al., 2008). For this reason, our observation that the P2 component of nociceptive ERPs is not necessarily reduced by working memory suggests that it may reflect more than pure attentional shifting. Furthermore, the observed reduction of P2 amplitude in the working memory condition of the discrimination task cannot be attributed to differences in attentional load and task difficulty. Indeed, the behavioral results showing reduced reaction times in the 1-back condition of the discrimination task and increased reaction times in the 1-back condition of the matching task suggests that, on the contrary, the 1-back condition of the matching task was the more demanding and thus more likely to overload attentional resources. This leads us to hypothesize that the amplitude modulation of the P2 component by working memory could be dependent on the type of information that is maintained in working memory. In other words, we hypothesize that the processing stage represented by the P2 component competed with the information manipulated by working memory in the

visual discrimination task, but not with the information manipulated by working memory in the visual matching task. In the working memory condition of the matching task, participants were forced to maintain in working memory the sensory-discriminative features of the visual stimulus (i.e. its color) delivered during the preceding trial in order to compare them to the features of the upcoming visual stimulus (Owen et al, 2005; Smith and Jonides, 1997). In the working memory condition of the discrimination task, because participants were just asked to delay their response, and because responding did not require then to compare the features of the previous visual target to the features of the upcoming visual target, the participants could prepare their response during the inter-trial interval. Therefore, each new target could be considered as a *go signal* prompting the execution of the prepared and already selected response (Szmalec et al., 2009; Szmalec and Vandierendonck, 2007). In fact, the finding that, in the discrimination task, reaction times in the 1-back condition were significantly shorter than in the 0-back condition suggests that the response was indeed already prepared before the *go signal* (i.e. the next visual stimulus). As a consequence, during the 1-back condition of the discrimination task, the information maintained in working memory was probably the representation of the motor response associated to the target stimulus (Szmalec and Vandierendonck, 2007). Hence, the 1-back condition of the discrimination task could be viewed as a *motor working memory task*, whereas the 1-back condition of the matching task could be viewed as a *sensory-perceptive working memory task*. The processes underlying the P2 component competed with the representation of the motor response to the visual targets in the 1-back condition of the discrimination task, but not with the representation of the visual stimulus in the 1-back condition of the matching task. For this reason, our results showing that the P2 component was modulated in the 1-back condition of the discrimination task but not in the 1-back condition of the matching

task could suggest that the P2 component of nociceptive ERPs reflects brain activities underlying the selection of the response associated to the nociceptive stimulus. This hypothesis is supported by studies having shown that nociceptive stimuli applied during the preparation of a motor response to a visual stimulus elicit ERPs of weaker magnitude if the nociceptive stimuli are applied on the hand used to respond vs. the contralateral hand (Le Pera et al., 2007). Furthermore, source analysis studies and intra-cortical recordings have suggested that the P2 reflects activity originating mainly from the midcingulate cortex (Garcia-Larrea et al., 2003; Frot et al., 2008), corresponding to the section of the cingulate gyrus connecting primary and supplementary motor areas (Torta and Cauda, 2011; Dum et al., 2009), hypothesized to be involved in motor reactions to significant sensory events (Vogt, 2005). Obviously, further studies will be needed to demonstrate the involvement of the P2 wave of nociceptive ERPs in the generation of motor responses.

4.4. Effect of working memory on task-relevant visual evoked potentials

Based on our previous results (Legrain et al., 2009a), we expected that the magnitude of the ERPs elicited by the visual targets, in particular the late-latency N2 and P3 components, would be reduced in the 0-back conditions when the preceding distracter was a novel nociceptive stimulus, as compared to a standard tactile stimulus. This would have suggested a disrupted analysis of the visual target consecutive to the attentional shift towards the novel distracter. Such a reduction was not observed. Indeed, visual ERPs did not appear to be affected by the occurrence of a novel nociceptive distracter in the 0-back conditions. Importantly, the results of previous studies relying on a similar experimental paradigm are also inconsistent (Alho et al., 1997; Escera et al., 1998; SanMiguel et al., 2008; Schröger, 1996). However, crucial difficulties in interpreting the ERPs elicited by the visual targets are

that they overlap with the ERPs elicited by the shortly-preceding somatosensory distracter, and that the results might have been affected by the relatively low number of trials in the nociceptive distraction conditions. In addition, the general pattern of results regarding the magnitude of the visual ERPs in the working memory condition is consistent with the previous literature since the reduction of N2-P3 over parietal electrodes during working memory tasks is a recurrent result (McEvoy et al., 1998; Watter et al., 2001; Wintink et al., 2001; SanMiguel et al., 2008) which might be interpreted as an index of decreased processing capacity in the working memory tasks (Kok, 2001).

5. CONCLUSION

In the present study, we confirm that working memory can suppress the capture of attention by nociceptive stimuli. Most importantly, we show that working memory exerts an effect already at the earliest cortical stages of nociceptive processing reflected by the N1 component of nociceptive ERPs. The later stages, reflected by the N2 and P2 components, were also modulated. However, the P2 component was only modulated during the working memory condition of the discrimination task, i.e. when working memory involved the representation of motor responses. In accordance with recent theories (Legrain et al., 2012), this observation suggests that the P2 component of nociceptive ERPs reflects processes that are functionally distinct from those underlying the N1 and N2 components, possibly related to the production of motor responses rather than nociceptive sensory processing.

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806 **FIGURE CAPTIONS**

807

808 **FIGURE 1. Experimental design.** One group of participants was assigned to a color-

809 discrimination task in which they had to respond to the color of each visual stimulus

constituted of two circles either both blue or both yellow (a). In the 0-back condition, they responded to the color of the current stimulus. In the 1-back condition, they responded to the color of the stimulus presented one trial before. The other group was assigned to a color matching task in which they responded according to whether the colors of the two targets were matched or unmatched (b). In the 0-back condition, they compared the color of the two circles of the current stimulus which were the same (yellow-yellow, blue-bleu) or different (yellow-blue, blue-yellow). In the 1-back condition, they compared the color of the current stimulus to the color of the preceding stimulus (in this case, the colors of the two circles in the same stimulus could only be the same, yellow-yellow vs. blue-blue, as in the discrimination task conditions. The visual stimuli were preceded by a tactile distracter in 83% of trials or by a nociceptive distracter in the remaining 17% of trials. The bottom left image details the timing of the trials. A grey fixation cross were present at the center of the screen during the entire stimulation block. Each trial started with a somatosensory stimulus (stimulation duration was 0.5 ms for tactile electrocutaneous stimuli and 50 ms for nociceptive laser stimuli). Somatosensory stimuli were followed by a visual stimulus of 500-ms duration. The inter-stimulus time interval was 220 ms for the tactile-visual trials and 300 ms for the nociceptive-visual trials. Performance in the visual task was measured in the time window running from 150 to 1500 ms after visual stimulus onset. The next trial started at a latency set so that the inter-trial time interval measured between the onsets of two consecutive visual stimuli was 3000 ms.

831

832 **FIGURE 2.** Responses speeds. (a) Mean reaction times to the visual targets (in milliseconds)

833 according to the task performed (discrimination vs. matching task), the involvement of

834 working memory (0-back vs. 1-back) and the type of somatosensory distracter (novel

835 nociceptive vs. standard tactile). Errors bars represent standard deviation corrected

836 according to the method of Cousineau (2005). (b) Mean distraction indexes assessed by

837 subtracting in each participant the mean RT to the visual targets associated to standard

838 tactile distracters from the mean RT to the visual targets associated to novel nociceptive

839 distracters. Errors bars represent standard deviations. Symbols represent the significance of

840 the p-values: ns, not significant; ~, $p = .06$; ***, $p < .005$.

841

Nociceptive ERPs

Discrimination task

Matching task

FIGURE 3. Nociceptive event-related potentials. Superimposition of blue and red waveforms represents the ERPs elicited by the novel nociceptive distracters during the 0-back condition and during the 1-back condition respectively, distinctly for the group of participants performing the discrimination task (left panel) and the group of participants performing the matching task (right panel). The figure illustrates the ERPs recorded from the vertex electrode (Cz referenced to mastoids; top waveforms) and the contralateral temporal electrode (T8 referenced to Fz, bottom waveforms). The dashed vertical lines represent the onsets of the nociceptive and the visual stimuli respectively. The three main nociceptive ERP

components, outlined by the grey boxes, are also depicted by their mean amplitude (illustrated by the column charts on the left side of each waveform; errors bars represent corrected standard deviation [Cousineau, 2005]; significance symbols: ns, not significant; *, $p < .05$; **, $p < .01$) and their scalp topography (illustrated by the top-view maps on the right side).

Tactile ERPs

Discrimination task

Matching task

— : 0-back condition
— : 1-back condition

5 μV
100 ms

FIGURE 4. Tactile event-related potentials. Superimposition of blue and red waveforms represents the ERPs elicited by the standard tactile distracters during the 0-back condition and during the 1-back condition respectively, distinctly for the group of participants

861 performing the discrimination task (left panel) and the group of participants performing the
862 matching task (right panel). The figure illustrates the ERPs recorded from the contralateral
863 central electrode (C4 referenced to mastoids; top waveforms) and the vertex electrode (Cz
864 referenced to mastoids; bottom waveforms). The dashed vertical lines represent the onsets
865 of the tactile and the visual stimuli respectively. The two main tactile ERP components,
866 outlined by the grey boxes, are also depicted by their mean amplitude (illustrated by the
867 column charts on the left side of each waveform; errors bars represent corrected standard
868 deviation [Cousineau, 2005]; significance symbols: ~, $p = .06$; **: $p < .01$) and their scalp
869 topography (illustrated by the top-view maps on the right part).

870

Visual ERPs

FIGURE 5. Visual event-related potentials. Superimposition of the different waveforms represents the ERPs elicited by the visual targets according the working memory conditions (0-back vs. 1-back) and the types of somatosensory distracters (nociceptive distracters on the left panel; tactile distracters on the right panel). Because the factor *task* did not show any significant effect on visual ERP amplitudes, data from the two groups were pooled and

877 merged together for grand-averaging. The figure illustrates the ERPs recorded from the
878 frontal (Fz; top waveform) and the parietal electrodes (Pz; middle waveform) over the
879 midline as well as from the right parieto-occipital electrode (PO8; bottom waveform). The
880 dashed vertical line represents the onset of the visual stimuli. The five main visual ERP
881 components, outlined by the grey boxes, are also depicted by their scalp topography
882 (illustrated by the top-view maps on the right side of the waveforms). The peak-to-peak
883 mean amplitudes are illustrated by the column charts on the central panel of the figure
884 (errors bars represent corrected standard deviation [Cousineau, 2005]; significance symbols:
885 ns, not significant; *: $p < .05$).

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