Reduction of pain and spinal nociceptive transmission by working memory is load dependant.

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Conflicts of interest

The authors declare no competing interests and no relationship that may lead to any conflict of interest.
Key points

- Pain was reduced by WM engagement and more so for high WM load.
- This effect partly depended on cerebrospinal mechanism, as indicated by NFR inhibition.
- Increasing WM load increased this effect, but only to a certain point.
- Beyond this point, additional load was not more effective.
Abstract

Working memory (WM) engagement produces pain inhibition. However, it remains unclear whether higher WM load increases this effect. The aim of this study was to investigate the interaction between WM load and pain inhibition by WM and examine the contribution of cerebrospinal mechanism. Thirty-eight healthy volunteers were assigned to one of two n-back groups for which WM load was different (2-back or 3-back). The experimental protocol comprised five counterbalanced conditions (0-back, n-back, pain, 0-back with pain, and n-back with pain). Pain and the nociceptive flexion reflex (NFR) were evoked by transcutaneous electrical stimulation of the sural nerve. Pain was significantly different between conditions, but not between n-back groups. Both the 0-back and n-back tasks reduced pain compared with pain alone, but the n-back task produced stronger pain inhibition compared with the 0-back task. NFR amplitude was significantly different between conditions but not between n-back groups. NFR was inhibited by the 0-back and n-back tasks, with no difference between the two tasks. These findings indicate that pain inhibition by WM is increased by WM load, but only to a certain point. NFR inhibition by WM suggests that inhibition of pain by WM depends, at least in part, on cerebrospinal mechanism.
Perspective

This behavioral and electrophysiological study shows that engaging in a cognitive task reduces pain by decreasing spinal nociceptive transmission, depending on task difficulty. These findings may yield better non-pharmacological pain therapies based on individual differences in working memory performance and capacity as well as several factors that regulate working memory.

**Keywords:** cognitive load, cognitive pain inhibition, nociceptive flexion reflex, attention, cognition, working memory.
Introduction

Cognitive-based approaches to pain regulation involve the engagement of attention and working memory (WM) \(^{42, 43, 61}\). Attention may facilitate or inhibit the processing of painful information \(^{45, 66, 67}\), while noxious stimuli involuntarily draw attention to protect the body from tissue damage \(^{64}\). However, this attentional capture is inhibited or reduced when performing a task that requires mental operations \(^{40, 60}\). These involuntary and voluntary processes interact to regulate the focus of attention \(^{51}\).

There is a link between attentional control and WM \(^{1, 25, 48, 51}\). WM regulates the balance between involuntary and voluntary attention \(^{1, 14, 25, 48, 51}\). WM allows the prioritization of task-relevant information when presented with task-irrelevant information \(^{2, 3, 14, 16}\), including pain. Effective cognitive control over pain requires both disengaging attention from task-irrelevant painful stimuli and maintaining attention toward task-relevant information by engaging WM \(^{43, 44}\). Accordingly, limited attentional capacity theories posit that consciously processing all available information overloads the cognitive system, leading to competition between the stimuli to be processed \(^{8, 30, 31, 39}\). For example, performing cognitively demanding tasks requires allocating more attentional resources to task-relevant information, leading to less resources available to process other information and shielding task performance from distractors \(^{41, 43}\).

Cognitive tasks that are adequately engaging, difficult, and unrelated to pain induce pain inhibition \(^{43, 44, 60}\). Increasing the difficulty of a cognitive task may improve the extent to which it shields against distraction \(^{27}\). Accordingly, performing a more difficult WM task may improve the inhibition of distractors \(^{6, 27, 46}\). For example, one study showed that
performing a difficult WM task (3-back task) reduced pain compared with a visually matched control condition that did not engage WM \(^9\). Thus, performing a difficult WM task may decrease pain processing. However, the specific effect of increasing WM load (task difficulty) has not been investigated systematically.

Previous studies that have compared the effect of different WM loads on pain inhibition have provided mixed results. Some showed that performing a high load WM task during painful stimulation reduces pain at the expense of increased response time \(^9\). In contrast, other studies showed that performing a high load WM task during painful stimulation reduces pain and improves response time \(^{18, 19}\). This discrepancy may result from confounding within-subject effects (e.g., learning or fatigue) or to different levels of WM load. Also, it is not clear if the difficulty of the tasks are comparable.

Another point to clarify in the interaction between pain and WM is whether pain inhibition is caused by cerebrospinal mechanisms. Brain imaging studies indicate that cerebrospinal mechanisms contribute to cognitive pain inhibition \(^4, 10, 62, 70, 71\). However, only a few studies measured spinal cord activity to support this interpretation, which relies mostly on the activation of brainstem structures involved in cerebrospinal pain regulation. Regulation of spinal nociceptive transmission can be assessed by measuring changes in the amplitude of the nociceptive flexion reflex (NFR). For example, pain reduction by distraction is accompanied by decreased NFR amplitude \(^{37, 50}\). However, experimental studies on cognition and cerebrospinal pain regulation have yielded mixed results and NFR inhibition by distraction is affected by task characteristics \(^7, 18-20, 50\).
WM is a multifaceted process. Many factors, including WM content, top-down control processes and WM load can affect WM processes and the interactions between WM and pain. The aim of this study was to investigate the interaction between WM load and pain perception and to determine whether cerebrospinal mechanism contribute to pain inhibition by WM, proportionally to WM load. We hypothesized that increasing the level of WM load decreases pain perception and NFR amplitude.

Methods

Ethics approval

All experimental procedures in this study 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 Quebec à Trois-Rivières. All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and received a financial compensation for their travel expenses, time, and commitment.

Participants

Thirty-six volunteers (18 women and 18 men; 18–38 years old, mean ± SD: 25.55 ± 4.98) were recruited by advertisements at the Université du Québec. Participants were included if they were between 18 and 40 years old with normal or corrected-to-normal vision. They were excluded if they had taken any medication within the two weeks prior to the experiment and if they had a history of chronic pain, suffered from acute or chronic neurological illness, or had a psychiatric disorder. Participants were assigned to one of two n-back groups of equal size (2-back and 3-back).
Experimental design

This experiment used a mixed design. A modified n-back task with different levels of difficulty was used to elicit WM engagement. The task involved color discrimination and was 0-back, 2-back, or 3-back (see details below) in order to manipulate WM load \(^{18,19,43}\). The experiment included two groups and five counterbalanced conditions for each group. The 2-back group performed the following conditions: pain alone, 0-back, 2-back, 0-back with pain, and 2-back with pain. The 3-back group performed the following conditions: pain alone, 0-back, 3-back, 0-back with pain, and 3-back with pain.

The painful stimuli were delivered alone or concurrently to the n-back task to test the effect of WM on pain. In the conditions with pain, sixty electrical stimuli were delivered randomly, among which ten stimuli were painful and fifty stimuli were non-painful. This distribution of stimuli increased saliency and novelty of painful stimuli.

Transcutaneous electrical stimulation

Transcutaneous electrical stimulation (trains of 10 1-ms pulses at 333 Hz) was delivered with two isolated DS7A constant current stimulators (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA) that was controlled by a stimulus presentation program (E-Prime2; Psychology Software Tools, Sharpsburg, PA, USA). The degreased skin was stimulated by two adjacent pairs of custom-made surface electrodes (1 cm\(^2\); inter-electrode distance 2 cm) placed over the retromalleolar path of the right sural nerve for the painful stimulus and on the dorsum of the foot for the tactile stimulus. For the painful stimuli, the
NFR threshold was determined using the staircase method with four series of stimuli of increasing and decreasing intensity. Each series began with a stimulus intensity of 1 mA, with subsequent stepwise increments of 1 mA, reaching a suprathreshold level between 15 and 25 mA (clearly above the threshold but adjusted individually to avoid severe pain). Stimulus intensity was then decreased in steps of 1 mA. After four of these series were completed, NFR amplitude was plotted against the stimulus intensity (recruitment curve), and the threshold was defined as the intensity producing a clear response that exceeded background EMG in at least 50% of trials. Background EMG was defined as the maximum artifact-free EMG activity observed in the same post-stimulus interval of 90–180 ms across all subthreshold stimuli. For tactile stimulation, the detection threshold was determined as the first stimulus intensity that produced a tactile sensation under the electrodes. The painful and tactile stimuli were always delivered with the same pair of electrodes. In both sessions, stimulus intensity was adjusted individually to 120% of the NFR threshold for painful stimulation and 150% of the detection threshold for tactile (non-painful) stimulation.

*Pain ratings*

After each condition, participants were instructed to rate pain verbally using a numerical rating scale that was displayed on the computer screen, ranging from 0 (“no pain”) to 100 (“worse pain imaginable”).

*NFR measurement and analysis*

Electromyography of the short head of the right biceps femoris was recorded with a pair of surface electrodes (EL- 508; Biopac Systems, Inc., Goleta, CA, USA). It was amplified 2000 times, band-pass filtered (10–500 Hz), sampled at 1000 Hz (Biopac
Systems, Inc.), and stored on a personal computer for off-line analyses. The raw EMG recordings were full-wave rectified, and the resulting signal was used to quantify the amplitude of NFR to each shock by extracting the integral value between 90 and 180 ms after stimulus onset. This amplitude was standardized using a within-subject Z-transformation. For group analyses, the mean response to ten painful stimuli was calculated for each condition.

*Modified n-back tasks*

In the modified n-back tasks, participants had to discriminate between blue and yellow squares with two levels of WM load (0-back and 2-back or 0-back and 3-back). In the 0-back condition, participants discriminated the color of the current stimulus immediately after its presentation. In the 2-back condition, they responded to the stimulus presented two trials before, while in the 3-back condition, they responded to the stimulus presented three trials before (see Figure 1) \(^{18,19,43}\). For clarity, we refer to n-back tasks when pooling data from 2-back and 3-back tasks to contrast with the 0-back task, although the 0-back task is also an n-back task. We selected the comparison n-back tasks based on previous study \(^{53}\). In this study, a significant decline in accuracy occurred between the 2-back and 3-back tasks, while no significant difference could be observed between the 3-back and 4-back tasks. Thus, we selected 0, 2 and 3 back tasks as three different load levels.

WM performance was assessed with two measures: response time (RT) and response accuracy (RA; the percentage of correct responses). The mean RT was calculated for each condition by including RT from each trial with a correct response. Trials with incorrect answers, trials defined as anticipated responses (RT < 150 ms), or trials with
missed responses were excluded from the mean RT calculation. For conditions with electrical stimulation during the n-back task (0-back or n-back), the task-relevant stimuli (blue or yellow squares presented for 500 ms) were preceded briefly by a task-irrelevant tactile stimulus (see Figure 1). Occasionally, the tactile stimulus was replaced by a painful stimulus, as described in a previous study\textsuperscript{18, 19, 43}, to keep the novelty of painful stimuli. The inter-stimulus interval (ISI) between the onset of the electrical stimulus and the onset of the task-relevant stimulus was 220 ms for tactile trials and 300 ms for painful trials to account for the conduction velocity of tactile and nociceptive fibers. The inter-trial interval (ITI) between the onsets of two consecutive task-relevant stimuli was 3000 ms\textsuperscript{18, 19, 43}.

**Experimental protocol**

Participants completed a 90-min session (see Figure 1). The same protocol was carried out for both n-back groups (2-back and 3-back). For the 0-back, 2-back, and 3-back conditions, the 60 trials were presented without any electrical stimulation. For the pain condition, the 60 trials included 50 tactile stimuli and 10 painful stimuli without the n-back task. For the 0-back, 2-back, and 3-back with pain conditions, 50 trials of the n-back task were preceded by the tactile stimulus, while the painful stimulus preceded ten trials. The order of the five conditions was counterbalanced between participants in both groups.

**Statistical analysis**

Data analysis was conducted using Statistica v13.1 (Dell, Inc., Tulsa, OK). All results are expressed as mean ± standard deviation, and the statistical threshold was set to \( p \leq 0.05 \) (two-tailed). Mixed ANOVAs evaluated changes in pain intensity, RIII-reflex
amplitude, response time, and response accuracy with GROUP (2-back vs. 3-back) as a between-subject factor and CONDITION as a within subject factor (pain, 0-back with pain, 2-back with pain or 3-back with pain). A priori hypotheses were tested with planned contrasts and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons, based on the number of contrasts for each independent analysis. All reported p-values are therefore corrected for multiple comparisons for all variables including pain, NFR amplitude, response time, and response accuracy. Effect sizes are reported based on partial eta-squared ($\eta_p^2$). RT and accuracy values were transformed using the $1/x$ function and the $2*\text{Arcsin}(*\sqrt{x})$ function, respectively. Statistical analyses were performed on transformed data but results are illustrated with the raw data for clarity.

Results

Pain and NFR inhibition by WM with different WM loads

Pain ratings and NFR amplitude were compared between conditions and groups using mixed ANOVAs (see Figure 2-3 and Table 1).

Pain was significantly different between conditions (main effect: $F_{2, 68} = 23.6, p < 0.001, \eta_p^2 = 0.40$), but this effect was not significantly different between the 2-back and 3-back groups (interaction: $F_{2, 68} = 1.3, p = 0.28, \eta_p^2 = 0.03$). For both groups combined (main effect of condition), Bonferroni-corrected planned contrasts revealed that pain was reduced by both the 0-back and n-back tasks (pooled data from 2-back and 3-back) (both $p < 0.001$), compared with the pain alone condition. However, the n-back tasks produced stronger pain inhibition compared with the 0-back task ($p = 0.015$).
NFR amplitude was significantly different between conditions (main effect: $F_{2,68} = 10.0, p < 0.001, \eta^2_p = 0.22$), but this effect was not significantly different between the 2-back and 3-back groups (interaction: $F_{2,68} = 0.9, p = 0.4, \eta^2_p = 0.02$). For both groups combined (main effect of condition), Bonferroni-corrected planned contrasts revealed that NFR amplitude was reduced by both the 0-back and n-back tasks (pooled data from 2-back and 3-back) ($p < 0.001$ and $p = 0.003$, respectively), compared with the pain alone condition. In this case, the n-back tasks produced similar effects compared with the 0-back task ($p = 1.0$).

Response time and accuracy

RT and accuracy were compared between conditions and groups using mixed ANOVAs (see Figure 4-5 and Table 1). RT was significantly different between conditions (main effect: $F_{3,102} = 8.7, p < 0.001, \eta^2_p = 0.2$), but was not significantly different between conditions and the 2-back and 3-back groups (interaction: $F_{3,102} = 0.5, p = 0.7, \eta^2_p = 0.01$). In contrast, accuracy was significantly different between conditions (main effect: $F_{3,102} = 12.2, p < 0.001, \eta^2_p = 0.26$) and this effect was significantly different between the 2-back and 3-back groups (interaction: $F_{3,102} = 4.2, p = 0.007, \eta^2_p = 0.11$). Bonferroni-corrected planned contrasts were used to examine whether WM performance was affected differently by pain depending on WM load (2-back vs. 3-back). Accuracy was lower in the 3-back with pain vs. the 0-back with pain task ($p < 0.001$), but not in the 2-back with pain vs. the 0-back with pain task ($p = 0.9$). Moreover, the reduction of accuracy in the 3-back with pain task relative to the 0-back with pain task was significantly greater than the corresponding contrast for the 2-back task ($p = 0.028$).
To examine the effect of pain on WM performance, accuracy was compared for each task (0-back, 2-back or 3-back) when performed with or without pain. Bonferroni-corrected planned contrasts revealed that pain did not alter accuracy in any task, including the 0-back task of both groups ($p = 1.0$ and $p = 0.063$), the 2-back task ($p = 1.0$) and the 3-back task ($p = 1.0$).

**Discussion**

The primary outcome of this study was the effect of WM load on pain, while the effect of WM load on WM performance was a secondary outcome. The findings indicate that pain can be inhibited by WM engagement and that increasing WM load increases this effect, but only to a certain point. Moreover, the NFR inhibition also suggests that inhibition of pain by WM depends, at least in part, on cerebrospinal mechanism.

*Cognitive pain inhibition*

Results showed that performing WM tasks (0-back and n-back tasks) reduces pain, replicating results from our previous studies\textsuperscript{18, 19} and indicating that cognitive engagement regulates pain\textsuperscript{43, 61}. The interaction between cognition and pain can be explained by limited attentional capacity theories\textsuperscript{8, 30, 31, 39}. According to these theories, conscious processing of all sensory information would overload the cognitive system, resulting in competition between stimuli\textsuperscript{8, 21, 30, 31, 39}. Consistent with this, the availability of cognitive control resources, including WM, determines the capacity to inhibit irrelevant distractors\textsuperscript{38}. Thus, engaging WM in a cognitive task allows voluntary shifting and maintenance of attention toward task-relevant information and away from task-irrelevant information\textsuperscript{18, 19, 43, 44, 60}. 
The neurocognitive model of pain suggests that decreasing the amount of attention to painful stimuli involves attentional load, attentional set, and WM. Attentional load is the amount of attention allocated to a task. When attentional load increases, less resources are available for painful stimuli. The attentional set is the maintenance of stimulus features in WM to prioritize goal-relevant information, where WM is a temporary storage system that allows active maintenance and manipulation of information. In Baddeley and Hitch’s model, attentional set is determined and prioritized by the central executive component of WM, while attentional load is determined and limited by WM capacity. Therefore, cognitive tasks must be designed to be sufficiently engaging, demanding, unrelated to pain, and involve WM functions in order to inhibit pain. In the current study, we focused on the manipulation of WM load to examine its effects on pain.

**Inhibition of pain by increasing working memory load**

Pain was reduced by both low (0-back) and high WM load (2-back and 3-back). Moreover, high WM load tasks were more effective than the low WM load task, consistent with previous findings. However, no significant difference in pain inhibition was observed between the 2-back and 3-back tasks, suggesting that WM load effects are not linear. Thus, factors other than WM load should also be considered, including cognitive effort and a ceiling effect.

Cognitive effort was described as an aversive experience that interferes with goal-directed behaviors. In a previous study on cognitive effort during a WM task with different difficulty levels, difficult trials were rated more effortful and were performed with
less accuracy. Thus, higher WM load may make a task more effortful and may mitigate the benefits of WM engagement during pain perception. In addition, it was shown that a painful stimulus may be preferred over cognitive effort, which further mitigate these effects. Therefore, the lack of difference in pain inhibition between the 2- and 3-back tasks may be explained by the interaction between cognitive effort and pain in the present study. Accordingly, greater task difficulty may alter the investment of cognitive effort in task execution and increase interference by noxious stimuli. This warrants future studies on the mediating role of cognitive effort in the interaction between cognition and pain.

The ceiling effect of pain inhibition by WM may also explain the lack of difference between the effects of the 2- and 3-back tasks on pain inhibition in the present study. The 3-back task did not produce greater pain inhibition compared with the 2-back task. We postulate that saturation occurs above a certain WM load and from that point, increasing the load does not enhance pain inhibition. In the present study, this point was between the 2-back and 3-back tasks. However, this may vary depending on the task and on individual differences in WM capacity. Future studies could examine this saturating point in individuals with different WM capacity.

Inhibition of the nociceptive flexion reflex by working memory

Our findings contribute to elucidating the mechanisms responsible for pain inhibition by WM engagement. Previous studies had provided equivocal results concerning the involvement of cerebrospinal mechanisms. In the present study, we investigated the regulation of spinal nociceptive activity by measuring the NFR during cognitive tasks with different levels of WM load. The results indicate that NFR amplitude was reduced by low
(0-back) and high (n-back) WM load tasks, consistent with pain reduction. The reduction of NFR amplitude suggests that cerebrospinal mechanisms were activated by cognitive processes. This is consistent with previous reports showing that cognitive pain inhibition is accompanied by decreased spinal nociceptive activity in humans and monkeys\textsuperscript{11, 23, 58}. Previous research also revealed that attention manipulation can induce pain inhibition by activating different pain-related brain regions\textsuperscript{10}. In particular, distraction has been shown to engage circuits involving connections between the orbitofrontal cortex, the anterior cingulate cortex (ACC), and the periaqueductal gray (PAG) matter\textsuperscript{63}. It is plausible that WM tasks, in which central executive attention is manipulated, activate cerebrospinal mechanisms through inhibitory networks including the ACC–PAG pathway\textsuperscript{58, 63}. However, the specific contribution of WM engagement, attention manipulation and cognitive effort to cerebrospinal pain regulation remains to be examined.

Notwithstanding, some studies have reported a dissociation between cognitive pain inhibition and spinal nociceptive transmission\textsuperscript{15, 17, 19, 59}. It has been proposed that the disinhibition of spinal nociception by WM engagement enhances protective reflexes while shielding cognition from pain signals in the brain to allow optimal task performance\textsuperscript{19}. Likewise, it has been shown that a simple distraction task involving the presentation of emotionally neutral pictures could decrease pain while increasing NFR amplitude\textsuperscript{49}. Disinhibition of spinal reflexes to promote automatic adaptive responses while the brain is engaged in an attentional task has been suggested as a potential mechanism underlying this sensorimotor dissociation\textsuperscript{49}. The findings available in the current literature do not allow the reconciliation of conflicting results\textsuperscript{10, 11, 15, 17, 19, 23, 49, 58, 59, 63}. It is possible that different types of cognitive manipulation lead to opposite effects, where spinal nociceptive
responses are either facilitated or inhibited \cite{15, 17, 19, 58, 59, 63}. In some tasks, inhibitory and facilitatory pathways may also compete, leading to no significant overall change in spinal nociceptive reflexes \cite{19}. Further research is needed to clarify this issue.

**Interaction between working memory performance and pain perception**

In the n-back task, response time improved but accuracy decreased compared with the 0-back task, while pain was reduced. The fact that pain was reduced indicates that WM was engaged in task execution, consistent with the rehearsal and updating of visual target features that prevent a bottom-up shift of attention toward the salient noxious distractors \cite{43, 56, 57} and with previous findings showing pain inhibition by WM engagement \cite{12, 57}. These results imply that cognitive pain inhibition may occur independently of performance. However, pain inhibition was not significantly different between the 2-back and 3-back tasks, while performance was lower in the 3-back task, which may indicate that poorer performance may offset the effects of greater WM load. This may be explained by the limited cognitive capacity and the competition between painful and visual stimuli \cite{8, 30, 31, 39}. Moreover, other factors usually not measured in WM tasks may affect the interaction between WM and pain, including cognitive effort \cite{52, 69}, affective and motivational factors \cite{13, 22, 61, 64, 66}, individual differences in WM capacity \cite{5}.

The sample size of this study could not be determined with a power calculation based on previous studies reporting the effects of 2-back and 3-back tasks on pain. Future studies are needed to allow *a priori* power calculation. The effects should also be confirmed with a larger sample and explored in clinical populations and other age groups. Other
factors that remain to be examined include WM content\textsuperscript{33}, cognitive effort\textsuperscript{29, 55, 65}, individual differences in WM capacity\textsuperscript{5} and the use of different pain stimuli.

**Conclusion**

The present results indicate that pain can be inhibited by WM engagement and that increasing WM load increases this effect, but only to a certain point, beyond which additional load is not more effective. Moreover, the NFR inhibition by WM suggests that inhibition of pain by WM depends, at least in part, on cerebrospinal mechanisms.

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Figure 1 was prepared with BioRender.com.
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Figure Legends

**Figure 1. Experimental protocol.** This figure depicts the five counterbalanced conditions for the two n-back groups (2-back and 3-back). The 2-back group performed the pain alone, 0-back, 2-back, 0-back with pain, and 2-back with pain conditions, while the 3-back group performed the pain alone, 0-back, 3-back, 0-back with pain, and 3-back with pain conditions. Each condition consisted of 60 trials and lasted 3.5 minutes. In the 0-back condition, participants discriminated the color of the current stimulus (blue or yellow) immediately after its presentation. In the 2-back condition, they responded to the color of stimulus (blue or yellow) presented two trials before, while in the 3-back condition, they responded to the color of stimulus (blue or yellow) presented three trials before. The painful stimuli were delivered alone or concurrently to the n-back task. In the conditions with pain, sixty electrical stimuli were delivered randomly to the right lower limb (ten stimuli were painful and fifty stimuli were non-painful). Pain ratings were prompted after each painful condition using a numerical rating scale with left (0) and right (100) anchors indicating “no pain” and “worse pain imaginable.”

**Figure 2. Pain inhibition by working memory with different loads.** Pain ratings were reduced during both the 0-back and n-back conditions (2- or 3-back) compared with the pain alone condition (both \( p < 0.001 \)). The 2- and 3-back tasks produced similar effects (\( p = 0.28 \)). However, the n-back tasks produced stronger pain inhibition compared with the 0-back task (\( p = 0.015 \)). *** \( p < 0.001 \); \# \( p = 0.015 \).

**Figure 3. Nociceptive flexion reflex (NFR) inhibition by working memory with different loads.** NFR amplitude was reduced by both the 0-back and n-back tasks (2- and 3-back) compared with the pain alone condition (\( p < 0.001 \) and \( p = 0.003 \), respectively). The 2- and 3-back tasks produced similar effects (\( p = 1.0 \)). *** < 0.001.

**Figure 4. Response time during different working memory loads.** RT were not significantly different between conditions (main effect: \( p = 0.14 \)) or between conditions and 2-back and 3-back groups (interaction: \( p = 0.9 \)).
Figure 5. Response accuracy during different working memory loads. Response accuracy was significantly different between conditions (main effect: $p < 0.001$) and this effect was significantly different between the 2-back and 3-back groups (interaction: $p = 0.004$). Accuracy was lower in the 3-back with pain vs. the 0-back with pain condition ($p < 0.001$), but not in the 2-back with pain vs. the 0-back with pain condition ($p = 1.0$). Moreover, the decrease in accuracy in the 3-back with pain vs. the 0-back with pain condition was significantly different compared with the corresponding contrast for the 2-back task. *** $p < 0.001$; # $p = 0.018$.

Table 1. Means and standard deviations of response time, accuracy, pain and NFR inhibition by WM with different WM loads
<table>
<thead>
<tr>
<th>n-back groups</th>
<th>Measures</th>
<th>Pain</th>
<th>0-back</th>
<th>n-back</th>
<th>0-back with pain</th>
<th>n-back with pain</th>
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</thead>
<tbody>
<tr>
<td>2-back group</td>
<td>RT (ms)</td>
<td>–</td>
<td>433.63 ± 79.99</td>
<td>396.47 ± 167.59</td>
<td>422.67 ± 71.13</td>
<td>404.1 ± 109.94</td>
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<tr>
<td>RA (%)</td>
<td>88 ± 0.13</td>
<td>88 ± 0.10</td>
<td>83 ± 0.10</td>
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<tr>
<td>Pain ratings (0–100)</td>
<td>32.97 ± 12.16</td>
<td>–</td>
<td>–</td>
<td>27.77 ± 10.68</td>
<td>26.11 ± 15.13</td>
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<tr>
<td>NFR (Z score)</td>
<td>0.51 ± 0.52</td>
<td>–</td>
<td>–</td>
<td>–0.10 ± 0.39</td>
<td>0.16 ± 0.43</td>
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<tr>
<td>3-back group</td>
<td>RT (ms)</td>
<td>–</td>
<td>476.05 ± 138.06</td>
<td>431.51 ± 207.44</td>
<td>481.95 ± 121.16</td>
<td>434.9 ± 181.08</td>
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<tr>
<td>RA (%)</td>
<td>88 ± 0.09</td>
<td>97 ± 0.05</td>
<td>76 ± 0.16</td>
<td>77 ± 0.21</td>
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<tr>
<td>Pain ratings (0–100)</td>
<td>33.16 ± 15.25</td>
<td>–</td>
<td>–</td>
<td>28.55 ± 15.18</td>
<td>23.22 ± 16.91</td>
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<tr>
<td>NFR (Z score)</td>
<td>0.47 ± 0.64</td>
<td>–</td>
<td>–</td>
<td>0.02 ± 0.34</td>
<td>0.04 ± 0.43</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD