POSTPRINT VERSION. The final version is published here: Deldar, Z., Blanchette, I., & Piché, M. (2021). Reduction of Pain and Spinal Nociceptive Transmission by Working Memory is Load Dependant. The Journal of Pain. [ONLINE AHEAD OF PRINT] http://dx.doi.org/https://doi.org/10.1016/j.jpain.2021.02.001

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

Zoha Deldar[a,b], Isabelle Blanchette [c], and Mathieu Piché[a,b*]

[a]Department of Anatomy, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada, G9A 5H7.
[b]CogNAC Research Group, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada, G9A 5H7.
[c]Department of Psychology, Université Laval, Québec, QC, Canada.

Number of pages: 26
Number of figures: 5
Number of tables: 1

***Corresponding author:**
Mathieu Piché, DC, PhD
Department of Anatomy
Université du Québec à Trois-Rivières
3351 boul. des Forges, C.P. 500
Trois-Rivières, Québec, Canada G9A 5H7
Ph.: 819-376-5011 Ext. 3998
Fax: 819-376-5204
E-mail: mathieu.piche@uqtr.ca
Web: www.uqtr.ca/cognac

Disclosures

This work was supported by a grant from the Natural Science and Engineering Research Council of Canada (MP: 06559). The contribution of MP was supported by the Fonds de recherche du Québec en Santé (FRQS). The contribution of Zoha Deldar was supported by the Department of Anatomy and the Center de Recherche en Neuropsychologie et Cognition (CERNEC) at Université de Montréal.

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 difficultly) 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 cm2; 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 [36, 47, 72] 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 [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 [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 (η_p^2). RT and accuracy values were transformed using the 1/x function and the 2*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, $p < 0.001$, $\eta_p^2 = 0.22$), but this effect was not significantly different between the 2-back and 3-back groups (interaction: $F_{2, 68} = 0.9$, $p = 0.4$, $\eta_p^2 = 0.02$). 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: $F_{3, 102} = 8.7$, $p < 0.001$, $\eta_p^2 = 0.2$), but was not significantly different between conditions and the 2-back and 3-back groups (interaction: $F_{3, 102} = 0.5$, $p = 0.7$, $\eta_p^2 = 0.01$). In contrast, accuracy was significantly different between conditions (main effect: F3, 102 = 12.2, $p < 0.001$, ηp2 = 0.26) and this effect was significantly different between the 2-back and 3-back groups (interaction: F3, 102 = 4.2, $p = 0.007$, ηp2 = 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 [18, 19] and indicating that cognitive engagement regulates pain [43, 61]. The interaction between cognition and pain can be explained by limited attentional capacity theories [8, 30, 31, 39]. According to these theories, conscious processing of all sensory information would overload the cognitive system, resulting in competition between stimuli [8, 21, 30, 31, 39]. Consistent with this, the availability of cognitive control resources, including WM, determines the capacity to inhibit irrelevant distractors [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 [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 [44, 61]. 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 [2, 24, 32, 44, 61]. Therefore, cognitive tasks must be designed to be sufficiently engaging, demanding, unrelated to pain, and involve WM functions in order to inhibit pain [44]. 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 [43]. 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 [35, 68] that interferes with goal-directed behaviors [34, 54, 68]. 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 [28]. 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 [68], 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 [26] and increase interference by noxious stimuli [34, 68]. 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 [11, 23, 58]. Previous research also revealed that attention manipulation can induce pain inhibition by activating different pain-related brain regions [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 [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 [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 [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 [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 [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 [49]. The findings available in the current literature do not allow the reconciliation of conflicting results [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 [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 [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 [43, 56, 57] and with previous findings showing pain inhibition by WM engagement [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 [8, 30, 31, 39]. Moreover, other factors usually not measured in WM tasks may affect the interaction between WM and pain, including cognitive effort [52, 69], affective and motivational factors [13, 22, 61, 64, 66], individual differences in WM capacity [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 [33], cognitive effort [29, 55, 65], individual differences in WM capacity [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 in part, on cerebrospinal mechanisms.

Acknowledgements

Figure 1 was prepared with BioRender.com.

References

1. Awh E, Vogel EK, Oh SH. Interactions between attention and working memory. *Neuroscience.* 139:201-208, 2006

2. Baddeley A: Working Memory: Theories, Models, and Controversies, ANNUAL REVIEWS, PALO ALTO, 2012, pp. 1-29.

3. Baddeley AD, Hitch G: Working Memory. In: Psychology of Learning and Motivation.(Bower, G.H., Ed.), Academic Press, 1974, pp. 47-89.

4. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. *Brain.* 125:310-319, 2002

5. Barrett LF, Tugade MM, Engle RW. Individual differences in working memory capacity and dual-process theories of the mind. *Psychol Bull.* 130:553-573, 2004

6. Berti S, Schröger E. Working memory controls involuntary attention switching: evidence from an auditory distraction paradigm. *European Journal of Neuroscience.* 17:1119-1122, 2003

7. Bjerre L, Andersen AT, Hagelskjær MT, Ge N, Mørch CD, Andersenl OK. Dynamic tuning of human withdrawal reflex receptive fields during cognitive attention and distraction tasks. *European Journal of Pain.* 15:816-821, 2011

8. Broadbent DE. Perception and communication. *New York: Pergamon.*, 1958

9. Buhle J, Wager TD. Performance-dependent inhibition of pain by an executive working memory task. *Pain.* 149:19-26, 2010

10. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience.* 14:502-511, 2013

11. Bushnell MC, Duncan GH, Dubner R, Jones RL, Maixner W. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. *J Neurosci.* 5:1103-1110, 1985

12. Coen SJ, Aziz Q, Yágüez L, Brammer M, Williams SCR, Gregory LJ. Effects of Attention on Visceral Stimulus Intensity Encoding in the Male Human Brain. *Gastroenterology.* 135:2065-2074.e2061, 2008

13. Crombez G, Eccleston C, Baeyens F, Eelen P. Attentional disruption is enhanced by the threat of pain. *Behaviour Research and Therapy.* 36:195-204, 1998

14. D'Esposito M, Postle BR: The Cognitive Neuroscience of Working Memory, ANNUAL REVIEWS, PALO ALTO, 2015, pp. 115-142.

15. Danziger N, Fournier E, Bouhassira D, Michaud D, De Broucker T, Santarcangelo E, Carli G, Chertock L, Willer JC. Different strategies of modulation can be operative during hypnotic analgesia: a neurophysiological study. *Pain.* 75:85-92, 1998

16. de Fockert JW. Beyond perceptual load and dilution: a review of the role of working memory in selective attention. *Front Psychol.* 4:287, 2013

17. Defrin R, Peleg S, Weingarden H, Heruti R, Urca G. Differential effect of supraspinal modulation on the nociceptive withdrawal reflex and pain sensation. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 118:427-437, 2007

18. Deldar Z, Rustamov N, Blanchette I, Piche M. Improving working memory and pain inhibition in older persons using transcranial direct current stimulation. *Neurosci Res.* 2019
19. Deldar Z, Rustamov N, Bois S, Blanchette I, Piche M. Enhancement of pain inhibition by working memory with anodal transcranial direct current stimulation of the left dorsolateral prefrontal cortex. *The journal of physiological sciences : JPS.* 2018
20. Dowman R. Attentional set effects on spinal and supraspinal responses to pain. *Psychophysiology.* 38:451-464, 2001
21. Duncan J. The locus of interference in the perception of simultaneous stimuli. *Psychological Review.* 87:272-300, 1980
22. Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull.* 125:356-366, 1999
23. Eippert F, Finsterbusch J, Bingel U, Büchel C. Direct Evidence for Spinal Cord Involvement in Placebo Analgesia. *Science.* 326:404-404, 2009
24. Engle RW, Tuholski SW, Laughlin JE, Conway ARA. Working Memory, Short-Term Memory, and General Fluid Intelligence: A Latent-Variable Approach. *Journal of Experimental Psychology: General.* 128:309-331, 1999
25. Gazzaley A, Nobre AC. Top-down modulation: bridging selective attention and working memory. *Trends Cogn Sci.* 16:129-135, 2012
26. Gieseler K, Inzlicht M, Friese M. Do people avoid mental effort after facing a highly demanding task? *Journal of Experimental Social Psychology.* 90:104008, 2020
27. Halin N, Marsh JE, Hellman A, Hellström I, Sörqvist P. A shield against distraction. *Journal of Applied Research in Memory and Cognition.* 3:31-36, 2014
28. Hsu C-F, Propp L, Panetta L, Martin S, Dentakos S, Toplak ME, Eastwood JD. Mental effort and discomfort: Testing the peak-end effect during a cognitively demanding task. *PloS one.* 13:e0191479, 2018
29. Inzlicht M, Shenhav A, Olivola CY. The Effort Paradox: Effort Is Both Costly and Valued. *Trends Cogn Sci.* 22:337-349, 2018
30. Kahneman D. Attention and effort. *The American Journal of Psychology.* 88, 1973
31. Kahneman D, Treisman A. Changing views of attention and automaticity. In R. Parasuraman & D.R. Davis (Eds.), Varieties of attention (pp. 29-61). *Orlando: Academic Press.*, 1984
32. Kane MJ, Bleckley MK, Conway AR, Engle RW. A controlled-attention view of working-memory capacity. *Journal of experimental psychology. General.* 130:169-183, 2001
33. Konstantinou N, Beal E, King J-R, Lavie N. Working memory load and distraction: dissociable effects of visual maintenance and cognitive control. *Attention, perception & psychophysics.* 76:1985-1997, 2014
34. Kool W, Botvinick M. Mental labour. *Nature human behaviour.* 2:899-908, 2018
35. Kurzban R. The sense of effort. *Current opinion in psychology.* 7:67-70, 2016
36. Ladouceur A, Rustamov N, Dubois JD, Tessier J, Lehmann A, Descarreaux M, Rainville P, Piche M. Inhibition of Pain and Pain-Related Brain Activity by Heterotopic Noxious Counter-Stimulation and Selective Attention in Chronic Non-Specific Low Back Pain. *Neuroscience.* 2017

37. Ladouceur A, Tessier J, Provencher B, Rainville P, Piche M. Top-down attentional modulation of analgesia induced by heterotopic noxious counterstimulation. *Pain.* 153:1755-1762, 2012
38. Lavie N. Distracted and confused?: selective attention under load. *Trends Cogn Sci.* 9:75-82, 2005
39. Lavie N, Hirst A, de Fockert JW, Viding E. Load theory of selective attention and cognitive control. *Journal of experimental psychology. General.* 133:339-354, 2004
40. Legrain V, Bruyer R, Guérit J, Plaghki L. Involuntary orientation of attention to unattended deviant nociceptive stimuli is modulated by concomitant visual task difficulty. Evidence from laser evoked potentials. *Clinical Neurophysiology.* 116:2165-2174, 2005
41. Legrain V, Bruyer R, Guerit JM, Plaghki L. Involuntary orientation of attention to unattended deviant nociceptive stimuli is modulated by concomitant visual task difficulty. Evidence from laser evoked potentials. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 116:2165-2174, 2005
42. Legrain V, Crombez G, Mouraux A. Controlling attention to nociceptive stimuli with working memory. *PloS one.* 6:e20926, 2011
43. Legrain V, Crombez G, Plaghki L, Mouraux A. Shielding cognition from nociception with working memory. *Cortex; a journal devoted to the study of the nervous system and behavior.* 49:1922-1934, 2013
44. Legrain V, Damme SV, Eccleston C, Davis KD, Seminowicz DA, Crombez G. A neurocognitive model of attention to pain: behavioral and neuroimaging evidence. *Pain.* 144:230-232, 2009
45. Legrain V, Mancini F, Sambo CF, Torta DM, Ronga I, Valentini E. Cognitive aspects of nociception and pain: bridging neurophysiology with cognitive psychology. *Neurophysiologie clinique = Clinical neurophysiology.* 42:325-336, 2012
46. Lv JY, Wang T, Qiu J, Feng SH, Tu S, Wei DT. The electrophysiological effect of working memory load on involuntary attention in an auditory-visual distraction paradigm: an ERP study. *Exp Brain Res.* 205:81-86, 2010
47. Piche M, Bouin M, Arsenault M, Poitras P, Rainville P. Decreased pain inhibition in irritable bowel syndrome depends on altered descending modulation and higher-order brain processes. *Neuroscience.* 195:166-175, 2011
48. Postle BR, Awh E, Jonides J, Smith EE, D'Esposito M. The where and how of attention-based rehearsal in spatial working memory. *Brain Res Cogn Brain Res.* 20:194-205, 2004
49. Roy M, Lebuis A, Peretz I, Rainville P. The modulation of pain by attention and emotion: a dissociation of perceptual and spinal nociceptive processes. *Eur J Pain.* 15:641.e641-610, 2011
50. Ruscheweyh R, Kreusch A, Albers C, Sommer J, Marziniak M. The effect of distraction strategies on pain perception and the nociceptive flexor reflex (RIII reflex). *Pain.* 152:2662-2671, 2011
51. SanMiguel I, Corral M-J, Escera C. When Loading Working Memory Reduces Distraction: Behavioral and Electrophysiological Evidence from an Auditory-

Visual Distraction Paradigm. *Journal of Cognitive Neuroscience.* 20:1131-1145, 2008

52. Sarter M, Gehring WJ, Kozak R. More attention must be paid: the neurobiology of attentional effort. *Brain research reviews.* 51:145-160, 2006

53. Scharinger C, Soutschek A, Schubert T, Gerjets P. Comparison of the Working Memory Load in N-Back and Working Memory Span Tasks by Means of EEG Frequency Band Power and P300 Amplitude. *Frontiers in human neuroscience.* 11:6-6, 2017

54. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature reviews. Neuroscience.* 12:154-167, 2011

55. Shenhav A, Musslick S, Lieder F, Kool W, Griffiths TL, Cohen JD, Botvinick MM. Toward a Rational and Mechanistic Account of Mental Effort. *Annual review of neuroscience.* 40:99-124, 2017

56. Soto D, Heinke D, Humphreys GW, Blanco MJ. Early, involuntary top-down guidance of attention from working memory. *Journal of experimental psychology. Human perception and performance.* 31:248-261, 2005

57. Soto D, Hodsoll J, Rotshtein P, Humphreys GW. Automatic guidance of attention from working memory. *Trends Cogn Sci.* 12:342-348, 2008

58. Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C. Attention modulates spinal cord responses to pain. *Current biology : CB.* 22:1019-1022, 2012

59. Terkelsen AJ, Andersen OK, Molgaard H, Hansen J, Jensen TS. Mental stress inhibits pain perception and heart rate variability but not a nociceptive withdrawal reflex. *Acta physiologica Scandinavica.* 180:405-414, 2004

60. Torta DM, De Laurentis M, Eichin KN, von Leupoldt A, van den Broeke EN, Vlaeyen JWS. A highly cognitive demanding working memory task may prevent the development of nociceptive hypersensitivity. *PAIN.* 161, 2020

61. Torta DM, Legrain V, Mouraux A, Valentini E. Attention to pain! A neurocognitive perspective on attentional modulation of pain in neuroimaging studies. *Cortex; a journal devoted to the study of the nervous system and behavior.* 89:120-134, 2017

62. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* 55:377-391, 2007

63. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. *Pain.* 109:399-408, 2004

64. Van Damme S, Legrain V, Vogt J, Crombez G. Keeping pain in mind: a motivational account of attention to pain. *Neuroscience and biobehavioral reviews.* 34:204-213, 2010

65. Van den Bussche E, Alves M, Murray YPJ, Hughes G. The effect of cognitive effort on the sense of agency. *PloS one.* 15:e0236809-e0236809, 2020

66. Van Ryckeghem D, Crombez G. Pain and Attention: Towards a Motivational Account. *Oxford University Press.* 2018

67. Van Ryckeghem DML, Crombez G, Eccleston C, Legrain V, Van Damme S. Keeping pain out of your mind: The role of attentional set in pain. *European Journal of Pain.* 17:402-411, 2013

68. Vogel TA, Savelson ZM, Otto AR, Roy M. Forced choices reveal a trade-off between cognitive effort and physical pain. *eLife.* 9:e59410, 2020
69. Westbrook A, Braver TS. Cognitive effort: A neuroeconomic approach. *Cognitive, Affective, & Behavioral Neuroscience.* 15:395-415, 2015
70. Wiech K. Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science.* 354:584-587, 2016
71. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci.* 12:306-313, 2008
72. Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain.* 3:69-80, 1977

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

Figure1

Click here to access/download;Figure;figure1-ExperimentalProtocol.tiff

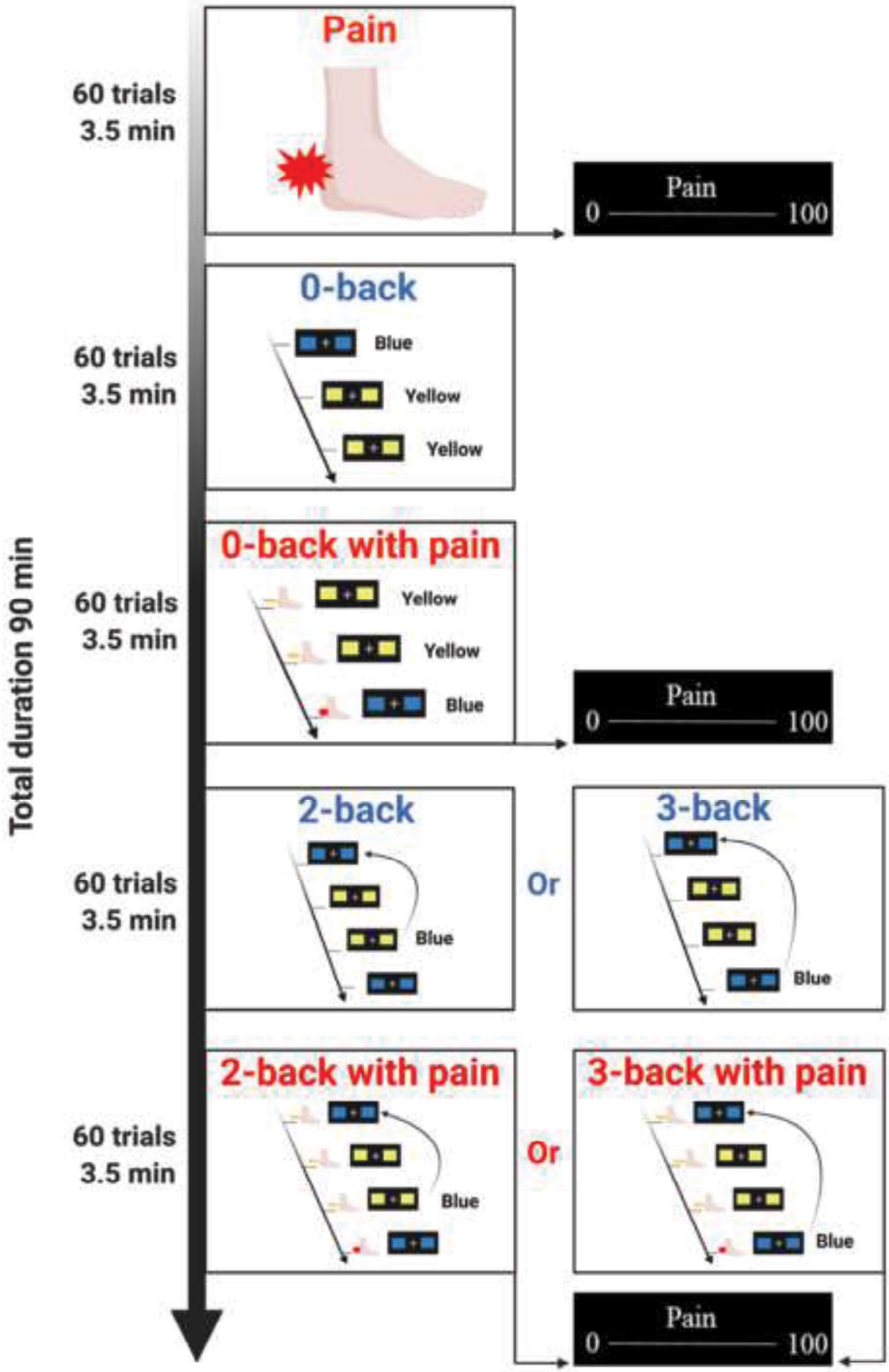


Figure2

Click here to access/download;Figure;Figure2-Pain.tiff

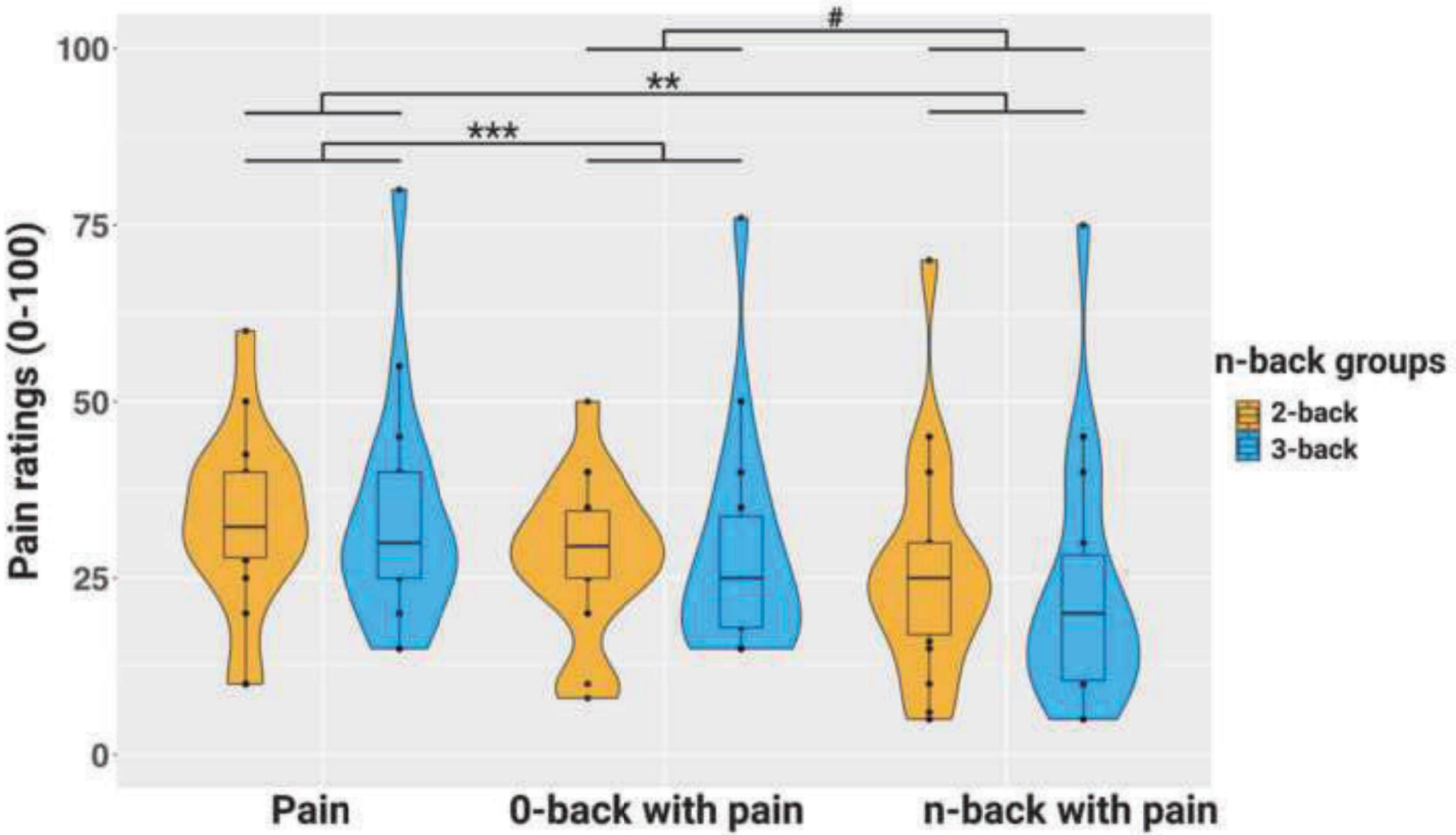


Figure3

Click here to access/download;Figure;Figure3-NFR.tiff

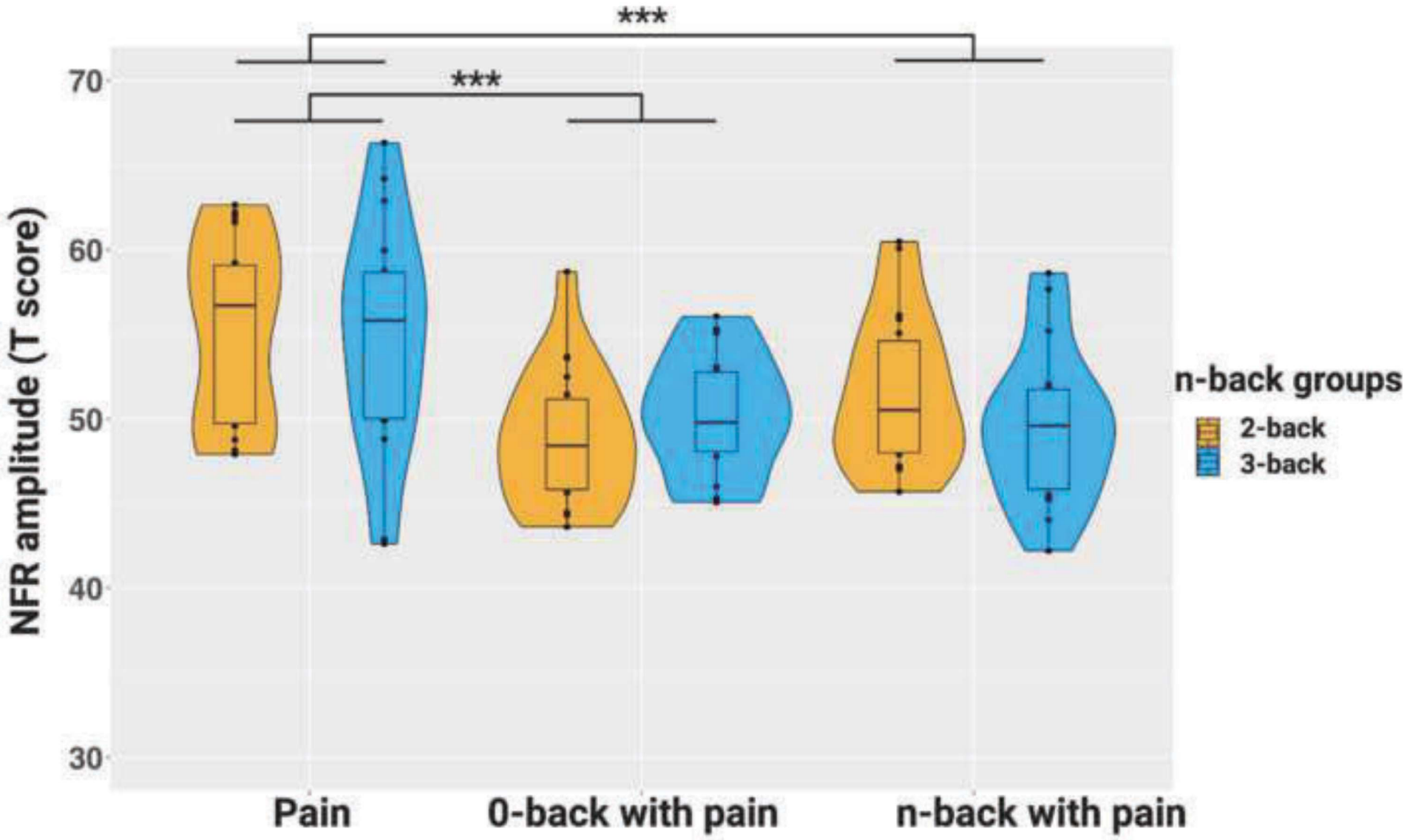


Figure4

Click here to access/download;Figure;Figure4-Responsetime.tiff

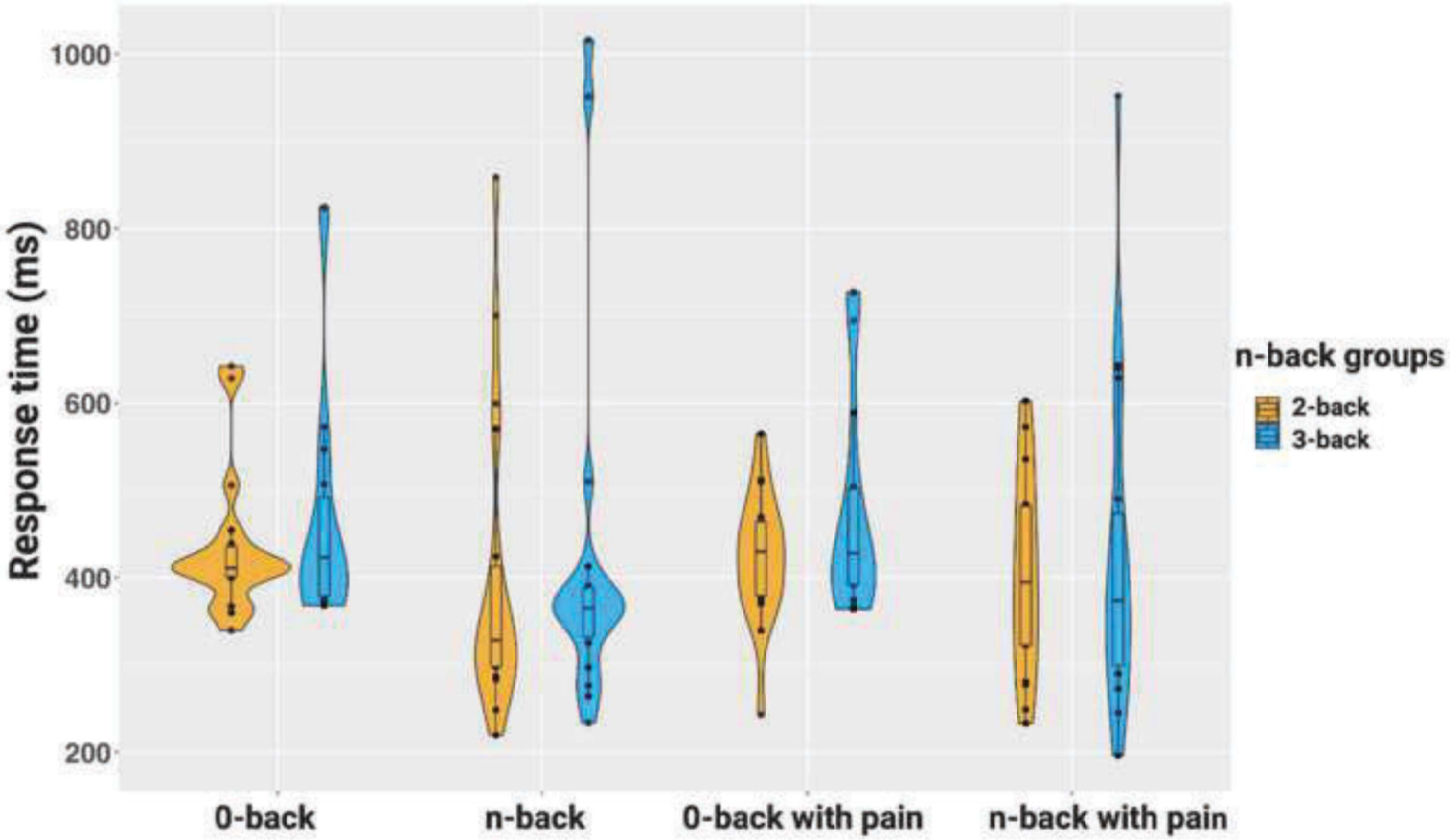
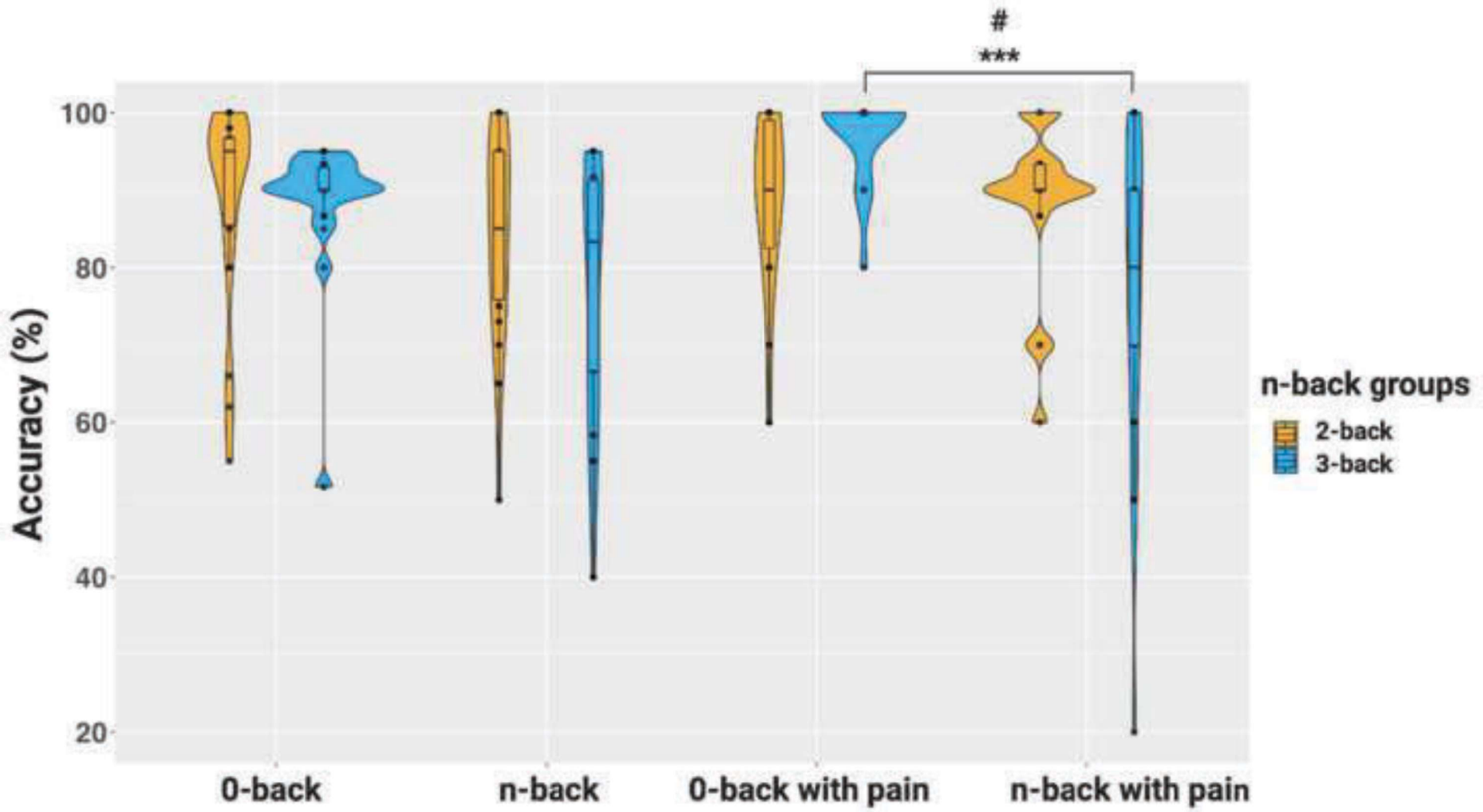


Figure5

Click here to access/download;Figure;Figure5-Accuracy.tiff



n-back groups	Measures	Pain	0-back	n-back	0-back with pain	n-back with pain
2-back group	**RT (ms)**	–	433.63 ± 79.99	396.47 ± 167.59	422.67 ± 71.13	404.1 ± 109.94
	RA (%)	–	88 ± 0.13	83 ± 0.13	88 ± 0.10	88 ± 0.10
	Pain ratings (0–100)	32.97 ± 12.16	–	–	27.77 ± 10.68	26.11 ± 15.13
	NFR (Z score)	0.51 ± 0.52	–	–	–0.10 ± .39	0.16 ± 0.43
3-back group	**RT (ms)**	–	476.05 ± 138.06	431.51 ± 207.44	481.95 ± 121.16	434.9 ± 181.08
	RA (%)	–	88 ± 0.09	76 ± 0.16	97 ± 0.05	77 ± 0.21
	Pain ratings (0–100)	33.16 ± 15.25	–	–	28.55 ± 15.18	23.22 ± 16.91
	NFR (Z score)	0.47 ± 0.64	–	–	0.02 ± 0.34	0.04 ± 0.43

Values are mean ± SD