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RESEARCH ARTICLE

# Effect of high level of bladder filling on spinal nociception and motoneuronal excitability

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**Abstract** To verify whether high level of bladder distension may counteract the inhibitory effect of descending pathways on sacral spinal cord neurons and to investigate which spinal circuitries are possibly involved in such a viscero-somatic interaction. Nociceptive withdrawal reflex (NWR), cutaneous silent period (CSP), and H-reflex were recorded in both lower and upper limbs of twenty-eight healthy subjects. Subjects were examined during baseline (empty bladder, no voiding desire), high level of bladder filling (urgency desire), and control (empty bladder, no voiding desire) sessions. Results showed that the NWR and its related pain perception were reduced in the upper limbs, while only a pain perception reduction in males was observed in the lower limbs. The H-reflex was inhibited in both limbs. No effects were found on the CSP duration. The decrease in both the NWR and its related pain perception in the upper limbs confirms the presence of a bladder distension-induced descending inhibitory modulation on nociception at spinal level. The lack of a similar inhibitory effect in the lower limbs suggests that excitatory nociceptive inputs from bladder afferents counterbalance the inhibitory effect on sacral spinal cord. The lack of the descending inhibitory effect may be a mechanism aimed at forcing the micturition phase to avoid bladder damage caused by bladder sovradistension.

**Keywords** Pain modulation · Viscero-somatic interaction · Nociceptive reflexes · Bladder distension

**Abbreviations**

| | |
|---|---|
| PAG | Periaqueductal gray |
| NRM | Nucleus raphe magnum |
| LC | Locus coeruleus |
| CNS | Central nervous system |
| NWR | Nociceptive withdrawal reflex |
| CSP | Cutaneous silent period |
| RT | Reflex threshold |
| NRS | Numerical rating scale |
| WDR | Wide dynamic range |
| DNIC | Diffuse noxious inhibitory control |

## Introduction

Bladder function and pain pathways seem to share peripheral and central neural pathways, including peripheral afferents, spinothalamic tract, periaqueductal gray (PAG), nucleus raphe magnum (NRM), and nucleus locus coeruleus (LC) and use common neurotransmitters such as serotonin and norepinephrine (Fields et al. 2006; Fowler et al. 2008; Birder et al. 2010; Mennini and Testa 2010). However, so far, only few experimental evidences have been

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provided in this regard. Previous studies on animal models (Evans and McPherson 1958, 1959) have shown that high level of bladder distension induced an inhibition of the polysynaptic flexor reflexes in anaesthetized and decerebrated but not in spinalized cats, suggesting an activation by bladder nociceptors of the descending inhibitory pathways on the spinal interneurons mediating flexor reflexes. Furthermore, the authors found an increase in reflex excitability in spinalized cats probably due to the unmasking of the segmental spinal excitatory mechanisms. Very recently, we found similar results in humans too by investigating flexion reflexes during different levels of bladder distension (Serrao et al. 2014). We observed that progressive distensions of the bladder can inhibit the magnitude of the nociceptive withdrawal reflex (NWR) and its related individuals' pain sensation in healthy subjects. Since NWR inhibition took place both in the upper and in the lower limbs, it suggested an activation of supraspinal descending antinociceptive pathways, (i.e., periaqueductal gray, PAG) (Serrao et al. 2014). Such an inhibitory effect may be exerted on the neural substrate mediating the NWR, i.e., the wide dynamic range neurons, which relay the neural inputs from several painful and no-painful afferents and is strongly modulated by descending pathways (Sandrini et al. 2005). Bladder distension-induced inhibitory effect seems to occur also at the level the motoneurons, since the bladder filling reduces also the H-reflex magnitude (Inghilleri et al. 2001). The overall inhibitory effect may represent a safety mechanism to maintain continence during painful stimuli and pain-related motor responses that may increase intra-abdominal pressure (Serrao et al. 2014).

In our previous study (Serrao et al. 2014), we investigated several degrees of bladder distension corresponding to no desire, moderate desire, and strong desire of voiding. However, to fully understand the effect of bladder distension on the spinal neurons, it would be helpful to investigate also the effect of physiological maximal bladder distension, which corresponds to the urgency of voiding in humans. Urgency is currently described as sudden, compelling desire to pass urine that is not possible to defer (Abrams et al. 2002). Theoretically, very high bladder distension levels represent a painful and potential dangerous condition (Wyndaele and De Wachter 2002; Madersbacher et al. 2012) for the bladder, leading to an increase in the A-delta and C fibers excitatory inputs onto the sacral spinal cord neurons which may suppress or lessen the descending inhibitory effects.

The first purpose of this study was to verify the hypothesis whether very high levels of bladder distension, with bladder filling volumes reaching or exceeding the bladder functional capacity, i.e., until urgency sensation of voiding, could counteract the effect of the descending inhibitory influences at sacral spinal level. As a secondary objective, we studied which spinal circuitries are possibly involved in such a viscero-somatic interaction. For these purposes, we recorded polysynaptic painful excitatory and inhibitory reflexes, namely NWR and cutaneous silent period (CSP), and monosynaptic H-reflex, in both lower and upper limbs of a sample of healthy subjects during urgency sensation of voiding.

## Methods

### Participants

Twenty-eight healthy volunteers (mean age 28.4 years; gender 15 men, 13 women) were enrolled in the study and gave their written informed consent to participate in the study. The study was approved by the local ethics committee and complied with the Helsinki Declaration. All participants reported no previous bladder problems or pain disorders, and were not taking medications on the date of the study enrollment.

### NWR recordings

Subjects were seated in a comfortable armchair with their lower limbs positioned with the knee flexed at 130° and the ankle at 90°. The upper limb was resting on a horizontal support, slightly flexed at the elbow, the wrist situated in the supine position, and the fingers spontaneously flexed. To elicit the lower limb NWR, the sural nerve was stimulated percutaneously using a pair of disposable surface Ag/AgCl electrodes (Medelec, Oxford, UK) positioned immediately below (+) and behind (−) the lateral malleolus. To elicit the upper limb NWR, the digital nerve was stimulated through a pair of surface electrodes placed on the skin of the index fingertip (−) and the proximal phalanx (+). The stimulus consisted of 25-ms trains of five rectangular pulses (1-ms duration, 200 Hz frequency) delivered through a constant current electrical stimulator (Digitimer DS7A, UK) that were triggered by a data acquisition and analysis interface (CED Power 1401, UK). The electromyographic (EMG) signals were amplified with a Digitimer D360 amplifier (band-pass 0.05–2000 Hz, gain 1000), recorded at a sample rate of 5 kHz, and collected on a computer. Reflex threshold (RT) was assessed using a staircase method and consisted of three series of ascending and descending intensity stimuli. The RT was defined as the minimum stimulation intensity at which it was possible to evoke a stable reflex response in at least three out of five trials. For both upper and lower limbs, the intensity of the electrical stimuli used for the electrophysiological measurements was then adjusted to 1.5 × RT.

The subjects were asked to score their pain perception after each stimulus on a 0- to 10-point numerical rating scale (NRS) anchored by "no pain" (score of 0) and "worst imaginable pain" (score of ten). The electrical stimuli were delivered at varied intervals of at least 40 s to avoid reflex habituation (Willer 1977).

EMG activity was unilaterally recorded through a pair of Ag/AgCl surface electrodes (Medelec, Oxford, UK) positioned over the belly of the biceps femoris (short head) in the lower limb and biceps brachialis in the upper limb.

The root mean square (RMS) amplitude in pre- and post-stimulus time windows (100 ms before and 80–180 ms after) was calculated. The EMG reflex activity was expressed as the difference between post- and pre-stimulus RMS. Reflex magnitude was calculated as the mean RMS of five trials.

### CSP recording

The CSP was unilaterally recorded for the lower limb from the tibialis anterior muscle during an isometric submaximal contraction of this muscle against a fixed bar. The cutaneous electrical stimuli were delivered through a pair of disposable surface Ag/AgCl electrodes (Medelec, Oxford, UK) positioned immediately below (+) and behind (−) the lateral malleolus. For the upper limb, the CSP was recorded during an isometric contraction of the first dorsal interosseous (FDI) muscle on a horizontal plane against a fixed bar, while cutaneous electrical stimuli were delivered through a pair of surface Ag/AgCl electrodes (Medelec, Oxford, UK), placed on the index finger.

The stimulus consisted of 25-ms trains of five rectangular pulses (1-ms duration, 200 Hz frequency) delivered through an electrical stimulator (Digitimer DS7A, UK) that were triggered by a data acquisition and analysis interface (CED Power 1401, UK). The stimulus intensity used to evoke the CSP was set at 1.5 times the NWR threshold recorded in upper limb. Five consecutive CSPs were full-wave rectified and averaged. During stimulations, subjects were instructed to perform a constant isometric contraction of either the TA or FI muscles for about 3 s. Interstimulus intervals of 20 s were used to avoid muscle fatigue. CSP duration was obtained by measuring the arithmetic difference between the CSP onset and offset latencies, which were taken, respectively, when the averaged signal dropped below and returned to above 50 % of the baseline electromyographic level (obtained during a 100-ms epoch preceding the stimulus).

### H/M ratio recording

The H-reflex in both upper and lower unilateral limbs was unilaterally measured using a bipolar surface Ag–AgCl electrode (Medelec, Oxford, UK) and an electrical stimulator (Digitimer DS7A, UK) triggered by a data acquisition and analysis interface (CED Power 1401, UK).

In the lower limb, the recording electrodes were placed over the soleus muscle at the middle point of the line connecting popliteal fossa and Achilles tendon. The soleus H-reflexes were elicited by stimulating the tibial nerve in the popliteal fossa of the leg. Electrical stimuli duration was set at 1 ms, and the intensity was gradually increased to obtain the maximum H-reflex amplitude and the maximum M wave amplitude (Kimura 2001).

In the upper limb, the recording electrodes were placed over the muscle flexor carpi radialis at the proximal third of the distance between the medial epicondyle at the elbow and the radial styloid process at the wrist. The flexor carpi radialis H-reflexes were elicited by stimulating the median nerve in the medial bicipital groove of the arm. Electrical stimuli duration was set at 0.5 ms, and the intensity was gradually increased to obtain the maximum H-reflex amplitude and the maximum M wave amplitude (Kimura 2001).

### Bladder filling technique

All participants were asked to urinate and completely empty the bladder. After micturition, participants were instructed to gradually drink water and hold their urine until a urgency sensation to void occurred. Urinary urgency was defined according to the "Standardization of terminology in lower urinary tract function: report from the standardization sub-committee of the International Continence Society" (Abrams et al. 2002) and to "Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies", as a sudden, compelling urge to urinate that is difficult to defer (Bates et al. 1979; Abrams et al. 2002; Schäfer et al. 2002).

All the participants were submitted to suprapubic ultrasound evaluation (Aloka model: SSD-1400): (i) to verify the complete bladder emptying and the absence of residue of urine; (ii) to measure the bladder filling level; and (iii) to exclude potential pathological conditions of the bladder which could have conditioned the experiment.

### Procedure

Neurophysiological data and suprapubic ultrasound evaluations were recorded from subjects in the following three sessions: (i) no voiding desire (baseline, empty bladder); (ii) urgency sensation (very high level of bladder filling); and (iii) no voiding desire (control session, empty bladder).

In no voiding desire sessions, all participants were invited to void in a way to start with the recording sessions at empty bladder.

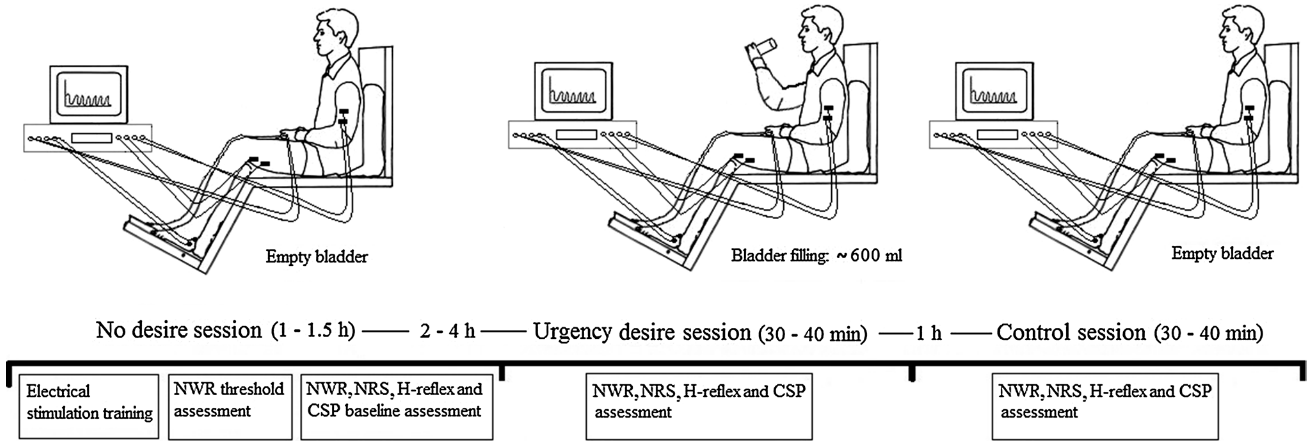


**Fig. 1** Scheme of the experimental design

For NWR recording, in order to avoid possible influences due to menstrual cycle or gastric or rectal distensions (Sandrini et al. 2005), the NWR measurements were always performed during the follicular phase in women, at least 2 h after meals and without a desire to evacuate.

### Statistical analysis

Three-way repeated-measures ANOVA was performed (SPSS ver. 15, Chicago, IL) to evaluate the effect of bladder filling (three-level within-subject factor), upper and lower limbs (two-level between-subject factor), and gender (two-level between-subject factor) on each electrophysiological variable, after having performed the Kolmogorov–Smirnov test for normal distribution. Greenhouse–Geisser correction was used to circumvent violations of sphericity. The Bonferroni adjustment for multiple comparisons was used for pairwise post hoc analyses. The results are presented as mean values ± standard error of the mean (SEM).

## Results

Mean delays between baseline and urgency sessions and between urgency and control sessions were 147.4 ± 56.4 and 71.4 ± 33.6 min, respectively.

For all subjects, cystometric capacities were in the normal range. Bladder filling mean value, during urgency session, was 605.4 ± 11.8 ml (Fig. 1).

### NWR and related NRS scores findings

A significant main effect of bladder filling sessions × limbs interaction was found on NWR magnitude ($F_{(2,104)} = 3346$, $p = 0.039$), while no significant main effects were found for bladder filling sessions, limbs, gender, and bladder filling × gender and gender × limbs interactions (all, $p > 0.05$). Post hoc analysis revealed significant lower

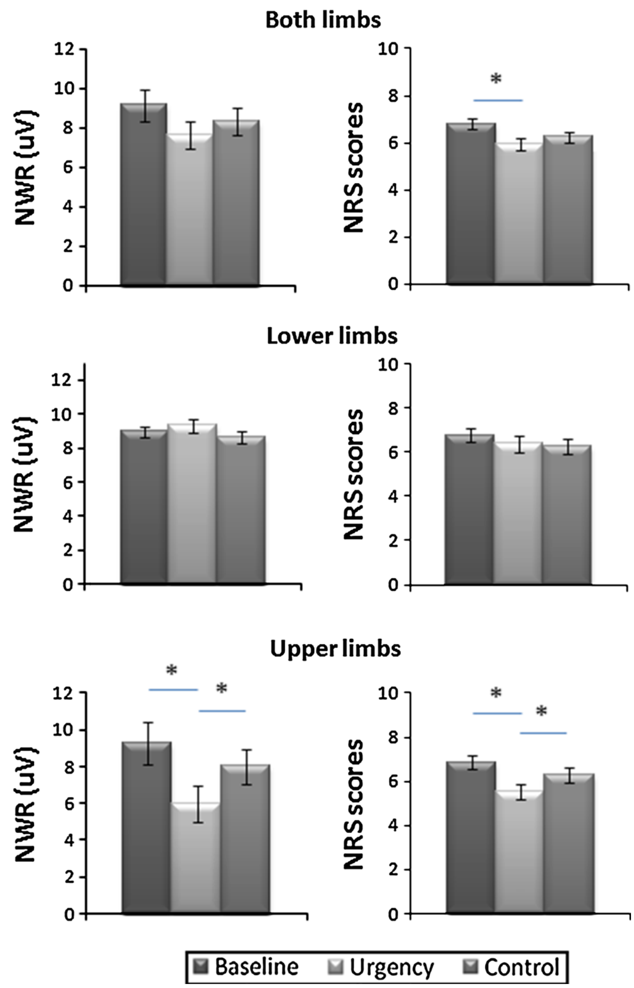


**Fig. 2** Limb effect on NWR magnitude and NRS scores during bladder filling sessions. *$p < 0.05$, at post hoc analysis

values of the NWR magnitude during urgency session compared to both baseline and control sessions only in the upper limbs, whereas no differences were found in the lower limbs (Fig. 2).

A significant main effect of bladder filling sessions ($F_{(2,104)} = 8.771$, $p > 0.001$), bladder filling sessions × limbs ($F_{(2,104)} = 3.450$, $p = 0.035$) and bladder filling sessions × gender × limbs ($F = 3.651$, $p = 0.029$) interactions was found on the NRS scores (Fig. 2). No significant main effect was found for limbs, gender, and limbs × gender interactions (all, $p > 0.05$).

Post hoc analysis revealed significant lower NRS values during urgency than during baseline session when considering both limbs (Fig. 2). Significant lower NRS values were found during urgency session compared to both baseline and control sessions in the upper limbs, whereas no differences were found in the lower limbs (Fig. 2). Significant lower values of the NRS scores were found in the lower limbs of males compared to baseline session, whereas no differences were found in females (Fig. 3). Significant lower NRS scores were found in both males and females during urgency compared to both baseline and control sessions in the upper limbs (Fig. 3).

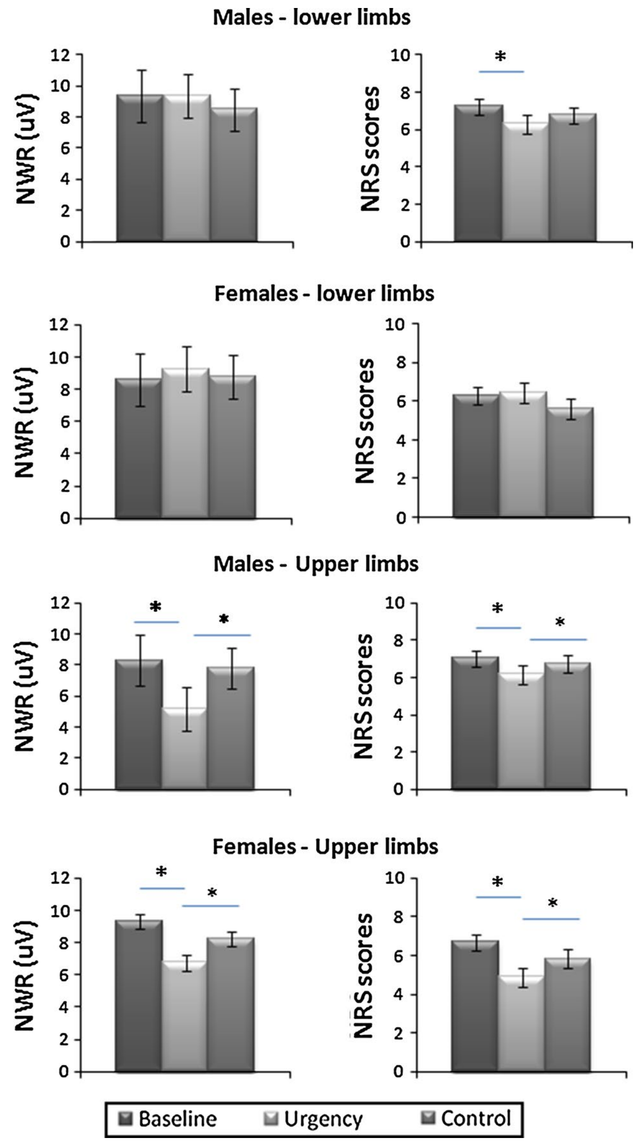


**Fig. 3** Gender effect on NWR magnitude and NRS scores during bladder filling sessions in *lower* and *upper limbs*. *$p < 0.05$, at post hoc analysis

### H-reflex findings

H-reflex data were obtained from 26 out of 28 subjects because two subjects did not show a detectable upper limb H-reflex and thus excluded from the statistical analyses. A significant main effect of bladder filling sessions was found on H–M ratio in both limbs ($F_{(2,96)} = 11.651$, $p < 0.001$), and no significant main effects were found for limbs, gender, and all the interactions (all, $p > 0.05$). Post hoc analysis revealed lower H/M value during urgency session compared to both baseline ($20.2 \pm 2.2$ vs $25.3 \pm 2.4$, $p < 0.001$) and control sessions ($20.2 \pm 2.2$ vs $23.7 \pm 2.3$, $p = 0.003$), whereas no differences were found between baseline and control sessions (all, $p > 0.05$).

### CSP findings

CSP data were obtained from all the 28 subjects. No significant effects of bladder filling sessions, limbs, gender, and all the interactions were found on the CSP duration (all, $p > 0.05$).

The effect of bladder filling on all spinal reflexes of a representative subject is illustrated in Fig. 4.

## Discussion

In the present study, we have investigated the effect of high level of bladder filling, corresponding to urgency sensation of voiding, on the spinal cord circuitries excitability as evaluated by both polysynaptic and monosynaptic spinal reflexes. This study extends previous investigations on the same topic (Inghilleri et al. 2001; Carbone et al. 2002; Palleschi et al. 2014; Serrao et al. 2014). The main results we obtained can be summarized as follows: (i) both NWR and its related pain perception were reduced only in the upper limbs; conversely, the H-reflex was inhibited in both limbs; (ii) NWR pain-related perception (NRS) was decreased in males in both limbs, while in females, no significant changes were observed in lower limbs; and (iii) no effects were found on the CSP duration.

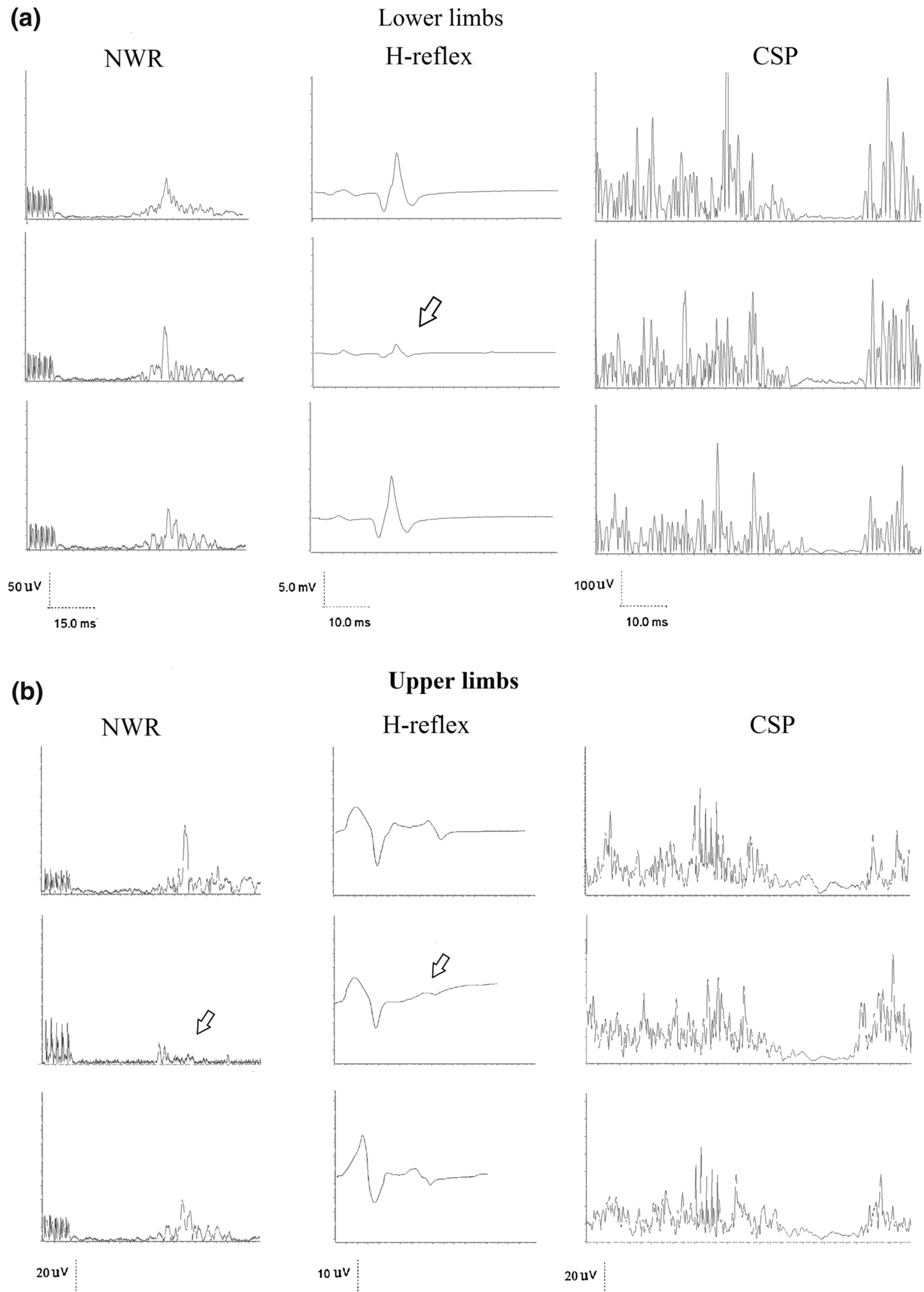


**Fig. 4** NWR, H-reflex, and CSP recordings during bladder filling sessions in a representative subject in *lower* (**a**) and *upper* (**b**) *limbs*. *Arrows* indicate recordings during bladder filling session

The decrease in both the NWR and its related pain perception in the upper limbs confirms the presence of a bladder distension-induced inhibition on nociception and pain processing at spinal level (Serrao et al. 2014). In our previous study, we investigated patients at low and high bladder filling levels, the last corresponding to a strong voiding desire. In that study, we found a significant inhibition of the NWR of both upper and lower limbs. In the present study, we investigated patients at higher bladder filling level corresponding to compelling desire to pass urine which is difficult to defer (urgency). The lack of the inhibitory effect on the lower limbs, found in the present experiment, suggests that excitatory nociceptive inputs from bladder A-delta and C afferents, during high level of bladder distension, counterbalance the inhibitory effect at spinal sacral level. Evidences of a coexistence of excitatory segmental and inhibitory supraspinal inputs on nociceptive reflexes have been previously reported in both animal models, during distension of the bladder (Evans and McPherson 1959), and humans, during acute or gradual distension of other viscera (stomach and rectum) (Bouhassira et al. 1994, 1998). Both inhibitory (descending) and excitatory (segmental) effects are very likely exerted on the wide dynamic range (WDR) neurons which are known also to mediate the NWR reflexes (Sandrini et al. 2005).

These neurons are activated by multimodal non-noxious and noxious somatic and visceral stimuli (Cadden and Morrrison 1991; Cervero 1995; Drewes et al. 2003) which may represent a basic somesthetic and visceral activity when transmitted to higher centers and thus could constitute a ''noise'' from which CNS must extract a clear pain signal. It is possible that, during high level of bladder distension, bladder signals to the CNS a painful and potential dangerous condition, thus allowing the CNS to increase the signal/noise ratio.

The reduction in the H-reflex amplitude as well as the lack of a significant effect on CSP reflexes in both limbs indicates that the inhibitory descending modulation is selectively exerted throughout the spinal cord. Indeed, whereas spinal motoneurons mediating H-reflex and WDR neurons mediating upper limb NWR are inhibited, the inhibitory premotor interneurons mediating the CSP reflex (Puja et al. 2012, 2014; Rossi et al. 2003) are not involved.

What are the neural structures involved in and what will be the functional significance may be only indirectly inferred. A likely scenario is that the inhibitory descending pathways are exerted by PAG activation, a midbrain structure involved in the control of both micturition and analgesia (Behbehani 1995; Fields et al. 2006; Suzuki et al. 2009; Benarroch 2010). Interestingly, beyond its role in the micturition and pain control, PAG plays a role in the "defense reaction," defined as the pattern of behavioral and cardiovascular change characteristic of an animal's reaction to threatening or stressful stimuli (Bandler and Carrive 1988; Bandler and Shipley 1994; Monassi et al. 1999). It is possible that, at very high levels of bladder filling, suppression of nociception and motor neurons activity, throughout the spinal cord, may be part of a defense reaction leading to analgesia and immobility. The suppression of the descending inhibition at spinal cord sacral level may "prepare" (facilitate) the sacral neurons to the micturition phase to avoid bladder damage caused by bladder sovradistension.

Anyway, the involvement of more than one supraspinal modulatory systems in mediating the interaction between bladder afferents and mono/polysynaptic reflexes cannot be ruled out (Bouhassira et al. 1990; Villanueva and Le Bars 1995; Serrao et al. 2004).

In the present study, we found a significant effect of sex × session × limbs interaction on NRS scores, with males showing a decreased of pain perception in lower limbs during urgency session with no inhibition of the NWR. A dissociation between NWR and pain-related perception has been reported in the literature due to either damages in the descending modulatory pathways or emotional reactions and expectation (for review see Sandrini et al. 2005). In this view, a gender-related difference in expectation and emotional reactions during urgency sensation of voiding could be hypothesized. Furthermore, anatomical and functional differences may explain some aspects of gender-related differences in pain modulation during bladder filling. Studies targeting the interactions between male and female urogenital neural circuitries have been limited, despite the very high incidence of gender-related bladder function disorders. However, in animals models, the presence of sex differences in the medullary reticular formation (MRF) responses to stimulation of the sensory fibers of the pudendal nerve branches related to their roles in various aspects of urogenital functions has been shown (Hubscher et al. 2013). Given the established role of MRF neurons in sexual function, it is possible that MRF neurons may participate in different sexual-related behavioral reactions (e.g., urination is inhibited during sexual activity). Anyway, further studies on humans are required to investigate which are the main gender-related differences in terms of behavioral reactions induced by bladder filling.

In conclusion, the effect of high level of bladder filling on NWR may represent a useful tool to investigate the interaction between bladder and pain pathways. It would be interesting to evaluate whether this effect is impaired in either somatic (i.e., low back pain) or visceral (i.e., bladder pain and irritable bowel pain) chronic pain syndromes.

**Compliance with ethical standards**

**Conflict of interest** Authors declare no conflict of interest.

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