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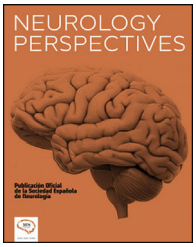

ORIGINAL

# Overactive bladder, lack of habituation, and central sensitisation: The sympathetic skin response as a possible diagnostic marker and neuromodulation as a treatment

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**KEYWORDS**
Overactive bladder;
Lack of habituation;
Posterior tibial neuromodulation;
Central sensitisation;
Sympathetic skin response

**Abstract**
*Objectives:* 1) to characterise clinically, neurophysiologically and manometrically the overactive bladder (OAB); 2) to objectify the lack of habituation in OAB; 3) to quantify the comorbidities associated with CS (central sensitisation); and 4) to evaluate the effect of neuromodulation (NM) of the tibialis posterior nerve in OAB.
*Material and methods:* Forty-seven patients, retrospective observational pre-post study.
Intervention: manometric biofeedback and posterior tibial transcutaneous NM (PTNM), 8 sessions.
Outcome variables: a) clinical (daytime urinary frequency [DUF] and nocturnal urinary frequency [NUF]), b) neurophysiological (latency, amplitude and percentage of habituation); c) comorbidities associated with CS; d) manometric (maximum and average pressure); at the beginning/end of treatment.
*Results:* Age, 58.91 ± 13.27 years. Comorbidities associated with CS, 1.98 ± 0.32 (range 1–5 pathologies). Percentage of habituation, 88.6%. PTNM decreased DUF (10.4 ± 4.86 to 6.21 ± 1.87 episodes; $P = .0001$), and NUF (3.02 ± 1.66 to 1.17 ± 1 episodes; $P = .0001$). PTNM increased maximum (38.46 ± 23.06 to 42.61 ± 19.46 mmHg; $P = .0964$), and mean (7.63 ± 3.56 to 8.66 ± 4.76 mmHg; $P = .1639$) pressure. NMTP modified latency (1.32 ± 0.32 to 1.38 ± 0.32 s; $P = .3397$), and reduced amplitude (1.98 ± 1.28 to 1.67 ± 1.44 mV; $P = .0004$) and habituation (88.6 ± 23.5% at 70 ± 30.2%; $P = .0001$) of sympathetic skin response (SSR).
*Conclusion:* The lack of habituation is a neurophysiological phenomenon present in OAB. PTNM improved clinical and neurophysiological variables. SSR is a neurophysiological test capable of objectifying lack of habituation and could characterize other response patterns (alteration of the ascending, central, descending or postganglionic pathway).

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**PALABRAS CLAVE**
Vejiga hiperactiva;
Falta de habituación;
Neuromodulación del tibial posterior;
Sensibilización central;
Respuesta simpático cutánea

**Vejiga Hiperactiva, falta de habituación y sensibilización central: la respuesta simpático cutánea como probable marcador diagnóstico y la neuromodulación como tratamiento**

**Resumen**

*Objetivos:* 1) caracterizar clínica, neurofisiológica y manométricamente la vejiga hiperactiva (VH); 2) objetivar la falta de habituación en VH; 3) cuantificar las comorbilidades asociadas a SC (sensibilización central); 4) evaluar el efecto de la neuromodulación (NM) del tibial posterior en VH.

*Material y Métodos:* 47 pacientes, estudio observacional retrospectivo (antes-después).

Intervención: biofeedback manométrico y NM transcutánea tibial posterior (NMTP), 8 sesiones.

Variables resultado: a) clínicas (frecuencia urinaria diurna [FUD] y nocturna [FUN]), b) neurofisiológicas (latencia, amplitud y porcentaje de habituación de la respuesta simpático cutánea [RSC]); c) comorbilidades asociadas a SC; d) manométricas (fuerza máxima y media); al inicio-término del tratamiento.

*Resultados:* Edad 58.91 ± 13.27 años. Comorbilidades asociadas a SC 1.98 ± 0.32 (rango 1−5 patologías). Porcentaje de habituación 88.6%. La NMTP disminuyó FUD (10.4 ± 4.86 a 6.21 ± 1.87 episodios; p = .0001), y FUN (3.02 ± 1.66 a 1.17 ± 1 episodios; p = .0001). La NMTP aumentó la Presión máxima (38.46 ± 23.06 a 42.61 ± 19.46 mmHg; p = .0964), y media (7.63 ± 3.56 a 8.66 ± 4.76 mmHg; p = .1639). La NMTP modificó la latencia (1.32 ± 0.32 a 1.38 ± 0.32 segundos; p = .3397), redujo la amplitud (1.98 ± 1.28 a 1.67 ± 1.44 mV; p = .0004), y la habituación (88.6 ± 23.5% a 70 ± 30.2%; p = .0001) de la RSC.

*Conclusión:* La falta de habituación es un fenómeno neurofisiológico presente en VH. La NMTP mejoró las variables clínicas y neurofisiológicas. La RSC es una prueba neurofisiológica capaz de objetivar falta de habituación y podría caracterizar otros patrones de respuesta (alteración de la vía ascendente, central, descendente o postganglionar).



## Introduction

Overactive bladder (OAB) is a highly prevalent condition, affecting as many as one in every 7 individuals in the United States, and has a financial impact on patients and healthcare systems due to the direct and indirect expenses it generates.[1]

OAB is defined as the presence of urinary urgency together with a daytime urinary frequency (DUF) higher than 8 (DUF > 8/day) and night-time urinary frequency (NUF) higher than 2 (NUF > 2/night), and sometimes urge incontinence.[2]

The pathophysiological mechanisms involved in OAB include dysfunction of afferent pathways of the bladder and central nervous system (CNS), resulting in bladder hyperactivity.[3] These mechanisms include an abnormal increase in afferent impulses from the bladder (mediated by C-fibre hyperactivity) or a decreased ability to modulate afferent signals to suppress the unconscious or unnecessary bladder sensations (habituation to the stimulus) and facilitate the necessary afferent signals to maintain balance (homeostasis). Published evidence shows that the CNS plays a major role in the development of OAB.[3]

Central sensitisation (CS) is defined as an increased response of nociceptive neurons to a normal or subthreshold afferent stimulus, which corresponds to a state of spinal hypersensitivity mediated initially by C-fibres and later by Aβ and Aδ mechanoreceptors, which would be amplified by heterosynaptic potentiation (secondary peripheral sensitisation).[3,4]

In the pathogenesis of CS, peripheral nerves work normally, whereas changes occur in central neurons. Thus, patients present increased pain in response to normally painful stimuli (hyperalgesia) and pain in response to normally nonpainful stimuli (allodynia).[4] The effects of perceiving these nonpainful stimuli may be particularly relevant to understanding the role of CS in OAB.[3] However, CS is believed to contribute to the pathophysiology not only of OAB but also of 50 diseases causing chronic pain and even such somatic conditions as endometriosis, irritable bowel syndrome, primary dysmenorrhea, interstitial cystitis, painful bladder syndrome, vulvodynia, vulvar vestibulitis, prostatitis, chronic male pelvic pain, migraine, tension-type headache, chronic lower back pain, whiplash injury, and myofascial temporomandibular disorder, among others.[3] Furthermore, these conditions may coexist in the same

individual: a patient with chronic pain may develop up to 5 CS-related comorbidities over 5 years.[5]

Data suggest that CS may lead to hypersensitivity of the afferent pathways (mediated by C- and Aδ-fibres) that participate in the generation of sensations related to bladder hyperactivity.[3] Both CS and OAB are mediated or induced by the activation of C-fibres of the afferent nerves. Thus, in animal models of OAB, silent C-fibres are spontaneously activated and become hypersensitive to low-intensity stimuli; these changes are mediated by second-order neurons in the spinal cord.[6] This reinforced activity of C-fibres has also been observed in CS.[7] Furthermore, primary dysfunction may arise from, for example, another organ, such as the intestine, with secondary involvement of the bladder due to the capacity of CS to expand to other organs (pelvic organ crosstalk).[3]

The absence of demonstrable bladder disease or lesions in OAB is also consistent with the concept of CS, as the current origin of C-fibre conditioning may have been activated remotely, either in anatomical or temporal terms. Thus, for example, previous urinary retention or infection may have been the trigger for sub-threshold stimulation of silent C-fibres, which would be activated and induce CS.[8]

No direct assessment method is currently available for CS. Different assessment methods include such questionnaires as the Chronic Sensitive Inventory (CSI) and the Pain Inventory (PI); psychophysiological tests such as Quantitative Sensory Testing (QST), which assesses sensory facilitation and inhibition and temporal summation; and imaging studies such as functional MRI, which assesses changes in brain function and morphology in patients with CS.[9]

Although CS and OAB develop in response to the continuous stimulus of C-fibres, typically associated with tissue injury and pain, there are no biochemical or neurophysiological markers that identify patients with OAB or delimit the pathophysiological mechanisms underlying the condition.[7]

The pathophysiology of OAB includes an alteration to the afferent nervous system, reflected as an abnormal increase in afferent signals of the bladder (mediated by C-fibres) and/or a decreased ability to modulate afferent signals in the CNS. Thus, hypersensitive neurons in patients with OAB amplify the afferent signals of mechanoreceptors at sub-threshold level, causing increased bladder sensitivity. In this context, it would be highly beneficial to have a neurophysiological test to objectively assess CS and OAB.[3] This ideal test would identify: *a)* a large increase in the afferent signals mediated by C-fibres; *b)* abnormal processing in the CNS; and *c)* a decrease in the activity of the descending pain inhibitory pathways.

In 1984, Shahani et al.[10] designed a neurophysiological test, the sympathetic skin response (SSR) test, with the aim of measuring the function of C-fibres with an easy-to-administer test using electromyography devices available in everyday practice. The SSR test assesses one part of the peripheral nervous system, specifically the unmyelinated C-fibres; therefore, the SSR is a reflex that reflects the function of afferent and efferent sympathetic fibres of the skin, as well as their integration at the level of the spinal cord and CNS. According to Shahani et al.,[10] lack of response is synonymous with axonal injury; as the amplitude of the response habituates with repeated stimuli, Shahani et al.[10] only considered the absence of response as an abnormal finding in the test.

In fact, the SSR is a polysynaptic reflex arc. This reflex involves: *a)* an afferent pathway made up of myelinated sensory fibres; *b)* a complex central integrative mechanism; and *c)* a sympathetic efferent pathway with postganglionic C-fibres. These postganglionic fibres or C-fibres extend from sympathetic ganglia to peripheral nerves and sweat glands.[11] This response may be evoked by different types of stimuli (visual, auditory, tactile, or electrical stimuli).[11]

There is controversy around the SSR, with Shahani et al.[10] and Vetrugno et al.[12] considering that only the absence of SSR should be interpreted as abnormal, whereas Hu,[11] Jazayeri,[13] and Eslahi[14] argue that increased latency should also be considered pathological.

However, decreased SSR amplitude is not considered pathological due to the habituation phenomenon.[11] In the SSR, habituation is the phenomenon by which the amplitude of the response decreases with repeated stimulation.[15] Habituation is dependent on the adaptation of neural and non-neural components to internal stimuli (type of stimulus, room temperature, age, etc). We know that after several minutes of stimulation with irregular stimuli and long intervals, the levels of selective attention decrease, leading to habituation.[15] Therefore, habituation is a physiological phenomenon of the cerebral cortex by which cerebral activity progressively decreases after receiving repeated stimuli of similar intensity.[15]

Habituation of the SSR may be reduced by: *a)* decreasing the duration of the test to 15 min, or *b)* applying irregular stimuli at intervals longer than 1 min.[15]

SSR may be qualitatively assessed by determining the presence or absence of a response (pathological sign of C-fibres) and quantitatively assessing the shortest latency and greatest amplitude of the first evoked potential, thus minimising the habituation phenomenon.[15]

Goizueta et al.[16] also added the percentage of habituation as a quantifier, establishing a cut-off point of 60%–70%. They establish that the persistence of up to 60%–70% of the response to stimuli is normal, whereas persistence of >60%–70% is considered abnormal (hyper-response, lack of inhibition, or lack of habituation). This test is useful to assess both the CNS and the peripheral nervous system.[16]

Finally, any nervous system lesion involving afferent pathways, supraspinal pathways (spinal cord), and even central pathways may lead to an absence of SSR. Some examples include spinal cord injury and amyotrophic lateral sclerosis.[11] In the same way, an incomplete spinal lesion may result in an SSR with increased latency and abnormal amplitude.[17]

Lack of habituation/persistence of the SSR has been described during the onset and progression of migraine, tension-type headache, and OAB.[3,18] The pattern of reduced habituation to nociceptive stimuli may favour the increase in pain and the CS phenomenon.[18] The exact mechanism and the relevance of habituation remain unclear and are probably varied. Habituation to a sensory stimulus is believed to be a state of cortical information processing that reduces the level of selective attention to the stimulus.[18] On the contrary, the lack of habituation in the conditions described (migraine, tension-type headache, OAB) suggests a cortical dysfunction of information

processing,[18] and probably CS, as has been shown in children with OAB and migraine.[18,19]

The lack of habituation/persistence of SSR may suggest CS, as indicated by: *a)* increased afferent impulse of C-fibres; *b)* abnormal processing at the CNS level; or *c)* a decrease in ascending inhibitory pathways and/or increase in the descending facilitating pathway (**Fig. 1**).[3]

First-line treatments for OAB include bladder retraining, biofeedback, and pharmacological treatment. Second-line options include peripheral (percutaneous or transcutaneous neuromodulation [NM] of the posterior tibial nerve) and central (sacral) NM. The aim of NM is to modify nerve impulses through excitation or inhibition to change the physiological behaviour of a system. The action of NM may be peripheral or central, acting on the ascending/descending pathways, supraspinal region, and even cortical areas (learning), which displays phenomena favouring cerebral plasticity, explaining the long-term effects of NM.[20]

Okuyucu et al.[21] have shown that transcutaneous electrical nerve stimulation (TENS) causes a reduction in the amplitude and a decrease in the latency of the SSR. Thus, TENS shows an inhibitory or modulating effect on the sympathetic or autonomous nervous system and on pain, due to an anatomical association between pain afferent fibres and sympathetic fibres.[21] Fernández-Cuadros et al.[20] have shown that posterior tibial nerve stimulation (PTNS) with TENS modifies SSR habituation in patients with OAB from 100% (lack of habituation/SSR persistence) to 50% (normal habituation), in addition to showing clinical and pelvic floor muscle strength improvements in those patients.

Finally, besides the absence of SSR, no author has considered the lack of habituation/SSR persistence, decreased amplitude, or increased latency as signs of dysfunction of the peripheral autonomic pathway (afferent or efferent) and/or central pathway.

We believe that the different SSR patterns, such as the lack of response, a lack of habituation/SSR persistence, and decreased amplitude with increased latency, may be correlated with alterations to afferent pathways (lack of response); central processing (lack of habituation); or efferent pathways, with involvement of postganglionic sympathetic fibres (decreased amplitude with increased latency), respectively (**Fig. 1**). This classification may place patients in different categories of a single mechanism: peripheral autonomic dysfunction (afferent/efferent), central autonomic dysfunction, or CS syndrome.[3,20]

The aims of the present study are: *1)* to clinically, neurophysiologically, and manometrically characterise patients with OAB; *2)* to confirm the status of lack of habituation/SSR persistence as a characteristic feature of patients with OAB; *3)* to determine the presence of CS-related comorbidities in patients with OAB; and *4)* to analyse the effect of PTNS on the clinical, manometric, and neurophysiological variables of SSR in patients with OAB.

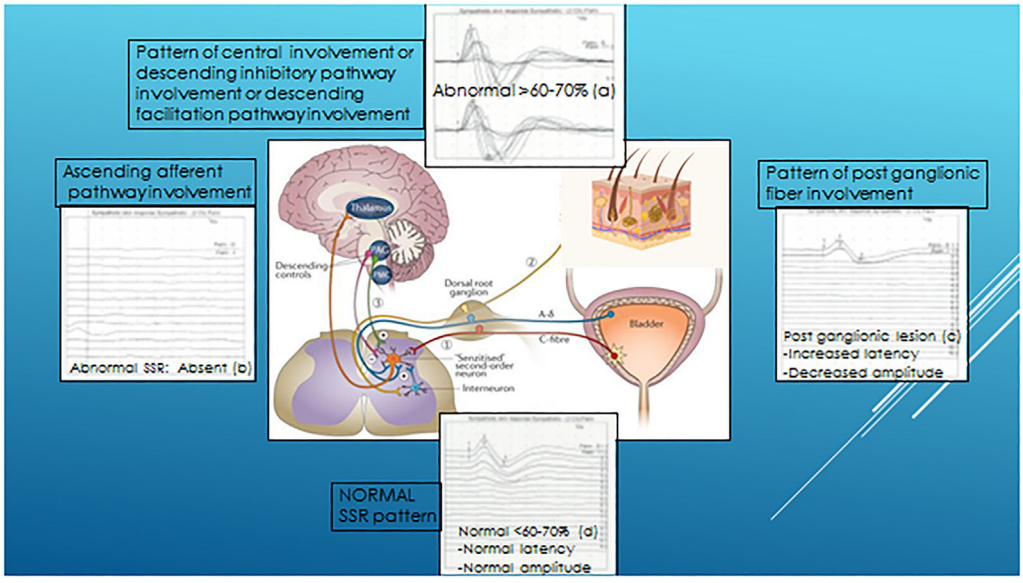


**Fig. 1** Central sensitisation (CS) and sympathetic skin response (SSR) pattern in overactive bladder (OAB), according to involvement to the ascending afferent pathway, central or descending efferent pathway, and postganglionic pathway; and normal SSR. Persistent activation of C-fibres (projected from the bladder [1]) may induce spinal sensitisation (peripheral sensitisation) in (sensitised) second-order neurons. Once peripheral sensitisation is established, this will contribute to OAB, facilitating the ascending transmission of subthreshold impulses (Aδ-fibres). This activation may be observed by measuring the SSR (C-fibres of the sweat glands/skin, which share the efferent anatomical pathway [2]). Furthermore, dysfunction of central processing and of descending fibres may facilitate afferent transmission of signals from the bladder, creating a response of hyperactivity or lack of habituation (SSR > 60%–70% [a] [3]). Involvement of the afferent pathway or at the spinal or central level would manifest as an absent SSR (b). Involvement of the postganglionic efferent fibres (C-fibres) would manifest as a pattern of increased latency and decreased amplitude (c). A normal pattern (without involvement of the afferent, central, efferent, or postganglionic pathways) would manifest as a normal response (< 60%–70% [d]). Modified from Reynolds et al.[3]

## Material and methods

We included 47 patients with clinical and/or urodynamic signs of OAB in our retrospective observational study, which includes an analysis of daily clinical practice. This type of study does not require the approval by an ethics committee but does require the informed consent of patients.

The main inclusion criteria were: *1)* patients older than 18 years; *2)* with clinical symptoms (DUF > 8 and NUF > 2) and/or urodynamic signs of OAB (non-inhibited detrusor contractions); *3)* transferred from the gynaecology or urology department; *4)* who gave written informed consent to receive the treatment; and *5)* with failure of a previous pharmacological treatment.

Exclusion criteria were: *1)* lack of cooperation due to unwillingness to participate in the treatment or due to cognitive impairment; *2)* use of a pacemaker or lumbosacral stimulator; *3)* peripheral nervous system disease (spinal lesion, radiculopathy, neuropathy) or CNS disease (stroke, tumours); and *4)* use of sympatholytic drugs that may alter the SSR.

During the clinical examination and history-taking, we recorded DUF and NUF and measured maximum and mean pelvic floor muscle strength during 1 min of tonic contractions (5-s contraction and 5-s rest) and 1 min of phasic contractions (5 repeated contractions followed by 10 s of rest). For this study, we use the MYOMED 932® biofeedback device (ENRAF-NONIUS) and a vaginal probe. We also recorded existing comorbidities through direct history-taking. In the baseline neurophysiological examination, we recorded baseline values for latency (seconds), amplitude (mV), and habituation (represented by the total number of evoked responses, expressed as a percentage).

The multimodal rehabilitation intervention protocol consisted in pelvic floor muscle exercises assisted by manometric biofeedback, and supervised by a physiotherapist, followed by the application of PTNS in 8 sessions, at a dose of 20 Hz-200 μs for 30 min, with 2 sessions per week.

PTNS was administered with the patient seated; the leg to be treated was elevated. We used 2 surface electrodes, one placed 5 cm proximally to the medial malleolus on the pathway of the posterior tibial nerve and the other on the ipsilateral calcaneus. We used the TENStem eco basic device (CE 0482; Germany). We applied a symmetrical biphasic rectangular current at an intensity of 0–9 mA, frequency of 20 Hz, and pulse width of 200 μs, for 30 min. Current intensity was regulated until patients experienced a tingling sensation on the plantar surface (low intensity <5 mA) or presented plantar flexion of the big toe or fanning of the toes (high intensity >5 mA), depending on the patient's tolerance.[22]

SSR was measured with the patient in the supine decubitus position and in the absence of auditory and visual stimuli for several minutes. After application of a glabellar stimulus, 2 potentials were recorded (one in the right hand and one in the left), using 2 electrodes per hand: one on the palm (active) and the other on the back of the hand (reference) at the level of the second interosseous space. We recorded latencies (seconds), p–p amplitudes (mV), and percentage of persistence (%), ignoring responses with amplitudes lower than 0.2 mV. Glabellar stimuli were applied at 0.1 ms and with a current intensity of 4–10 mA and a sweep speed of 500–1000 ms/div. We applied 20 stimuli at irregular intervals with pauses of several seconds between stimuli (> 30 s) to avoid habituation. We used low-frequency (0.5 Hz) and high-frequency (2000 Hz) filters. The sensitivity of the amplifier was 200–100 mV/div. Body temperature was kept at 28 °C. Response persistence of up to 60%–70% was considered normal, whereas persistence greater than 60%–70% was considered pathological (hyperexcitability, lack of inhibition/habituation, or cortical processing dysfunction), representing a feature of CS. Large decreases in latency and amplitude may indicate postganglionic axonal lesions, whereas a lack of response may indicate afferent pathway lesions (Fig. 2).[16]

The outcome variables assessed were: *a)* clinical variables (DUF and NUF); *b)* physiological variables (latency, amplitude, and SSR habituation percentage); *c)* manometric variables (mean and maximum pelvic floor muscle strength); and *d)* CS-related comorbidities; all measurements were taken at baseline and at the end of treatment (after 8 sessions of PTNS).

Statistical analysis was performed using the SPSS statistics software, version 20.0 (SPSS Inc.; Chicago, USA). We calculated the mean and standard deviation (SD) in the descriptive analysis of quantitative variables and frequencies and percentages in the analysis of qualitative variables. To evaluate the difference in quantitative variables before and after treatment, we used the *t* test for paired samples. The threshold for statistical significance was set at $P < .05$.

## Results

We analysed 47 patients with clinical and/or urodynamic signs of OAB. Mean age was 58.91 (13.27) years.

In terms of clinical variables, PTNS decreased DUF from 10.4 (4.86) to 6.21 (1.87) episodes ($P = .0001$) and NUF from 3.02 (1.66) to 1.17 (1) episodes ($P = .0001$) (Table 1, Fig. 3).

With respect to manometric variables, PTNS decreased maximum pressure from 38.46 mmHg (23.06) to 42.61 mmHg (19.46) ($P = .0001$) and mean pressure from 7.63 mmHg (3.56) to 8.66 mmHg (1) ($P = .0001$) (Table 1, Fig. 4).

Regarding neurophysiological variables, PTNS increased SSR latency from 1.32 (0.32) seconds to 1.38 s (0.32) ($P = .3397$), decreased amplitude from 1.98 mV (1.28) to 1.67 mV (1.44) ($P = .0004$), and decreased habituation from 88.6% (23.5%) to 70% (30.2%) ($P = .0001$) (Table 1, Figs. 5 and 6).

The mean number of CS-related comorbidities was estimated at 1.98 (0.32; range, 1–5) (Table 1). The most frequently reported comorbidities in patients with clinical and/or urodynamic signs of OAB were headache, migraine, depression, and chronic pelvic pain. The least frequently reported were complex regional pain syndrome, anxiety, and autoimmune diseases (hypothyroidism).

## Discussion

To our knowledge, this is the first study to observe that the lack of habituation/persistence (> 70%) is a characteristic

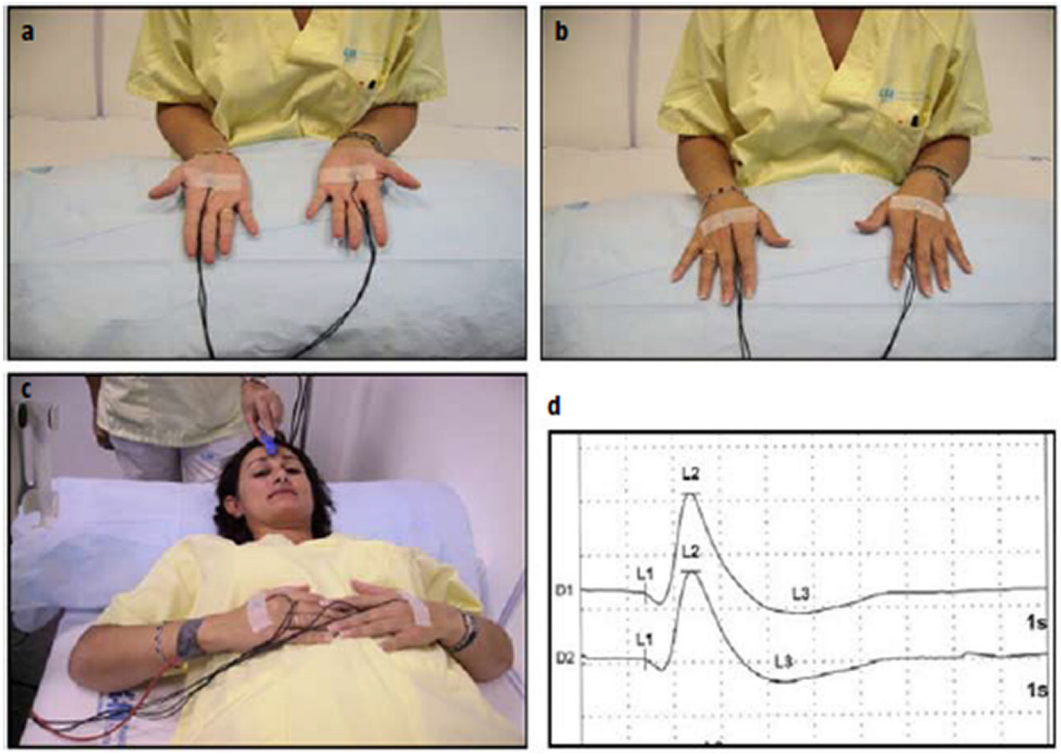


**Fig. 2** Sympathetic skin response (SSR) measurement: *a)* active electrode; *b)* reference electrode; *c)* glabellar stimulation; *d)* bilaterally evoked potentials after a single glabellar stimulus; D1 is SSR in the right hand, D2 is SSR in the left hand (1 s/2 mV).[16]

feature of patients with OAB. Furthermore, PTNS was able to modify or modulate clinical (DUF and NUF), manometric (maximum and mean pressure), and neurophysiological variables (latency, amplitude, and percentage of habituation to SSR) in patients with OAB. We also observed that patients with OAB present 1.98 CS-related comorbidities.

In a preliminary study, we observed that PTNS is able to decrease urinary frequency, to increase the manometric pressure of pelvic floor muscles, and to diminish the lack of habituation in a short series of patients with OAB (n = 10).[20] However, in that study we did not assess the effect of PTNS on latency or amplitude, which are important variables to be considered in the study of SSR.

Our study provides evidence that further corroborates the effectiveness of (transcutaneous) PTNS in improving OAB symptoms, analysed through the assessment of clinical and neurophysiological variables of SSR (latency, amplitude, and lack of habituation), as we only identified 5 studies published to date that support its use.[20,23–26]

Our observations are similar to those made by Okuyucu et al.,[21] who showed that TENS is able to modify the SSR, decreasing its amplitude (right side, 5611.7 to 3627.4 [$P$ = .04]; left side, 6068.9 to 3923.4 [$P$ = .01]).

Recent evidence suggests that C-fibre–mediated hyperactivity of the sympathetic nervous system plays a role in the manifestation of OAB, chronic pain, complex regional pain

**Table 1** Main study variables and the effect of neuromodulation (NM) of the posterior tibial nerve in patients with overactive bladder (n = 47).

| Clinical variables | Before treatment | After treatment | $P$ |
|---|---|---|---|
| DUF, in episodes/day (SD) | 10.42 (4.86) | 6.21 (1.87) | 0.0001* |
| NUF, in episodes/day (SD) | 3.02 (1.66) | 1.16 (1) | 0.0001* |
| Manometric variables | | | |
| Maximum pressure, in mm Hg (SD) | 38.46 (23.06) | 42.61 (19.46) | 0.0964 |
| Mean pressure, in mm Hg (SD) | 7.63 (3.56) | 8.66 (4.76) | 0.1639 |
| Neurophysiological variables | | | |
| Latency, in seconds (SD) (normal range: 1.42 ± 0.03) | 1.32 (0.32) | 1.38 (0.32) | 0.3397 |
| Amplitude, in mV (SD) (normal range: 2.44 ± 1.84) | 1.98 (1.28) | 1.67 (1.44) | 0.0004* |
| Percentage of habituation (SD) (normal range: 67.2 ± 18.9) | 88.6 (23.5) | 70 (30.2) | 0.0001* |
| Comorbidities | | | |
| Number of CS-related comorbidities (SD) | 1.98 (0.32) | NA | NA |

SD: standard deviation; DUF: daytime urinary frequency; NUF: night-time urinary frequency; CS: central sensitisation; NA: not applicable.
*$P$ < .01 ($t$ test).

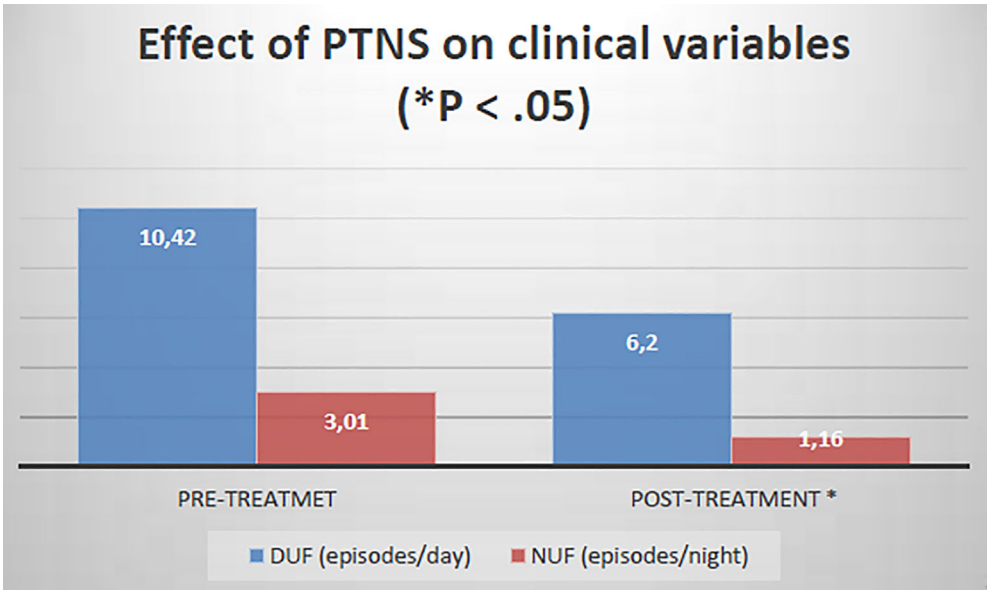


**Fig. 3** Effect of posterior tibial nerve stimulation on clinical variables. DUF: daytime urinary frequency; NUF: night-time urinary frequency. *$P$ < .05.

syndrome, arthrosis, and CS, as C-fibres may modulate the function of sensory nerve fibres.[20]

Megía-García et al.[27] have shown that TENS modulates pain by promoting central descending inhibitory mechanisms and decreasing excitatory signals of the posterior horn of the spinal cord. Furthermore, they observed that a pulse width of 250 μs and treatment sessions longer than 20 min constituted the most effective treatment.[27] This would explain why our neuromodulation protocol (20 Hz, 200 μs, 30 min) improved symptoms and neurophysiological variables (latency, amplitude, and habituation of SSR) in our series of cases with OAB.

Although up to 50 CS-related diseases have been identified, little emphasis has been placed on studying individual associations, especially in patients with OAB and CS-related diseases.[3] In this study, we have observed a mean of 1.98 CS-related comorbidities in patients with OAB (range, 1–5), with the most frequent being headache, migraine, depression, and chronic pelvic pain, whereas the least frequent were complex regional pain syndrome, anxiety, and autoimmune diseases (hypothyroidism). The role of CS in OAB may clearly explain the presence of CS-related comorbidities in this syndrome.[3]

SSR is a neurophysiological measurement seeking to assess the function of unmyelinated C-fibres of the peripheral nervous system. These fibres have recently been associated with OAB and CS-related comorbidities.[3,10] The SSR is a potential generated by the skin as a response to

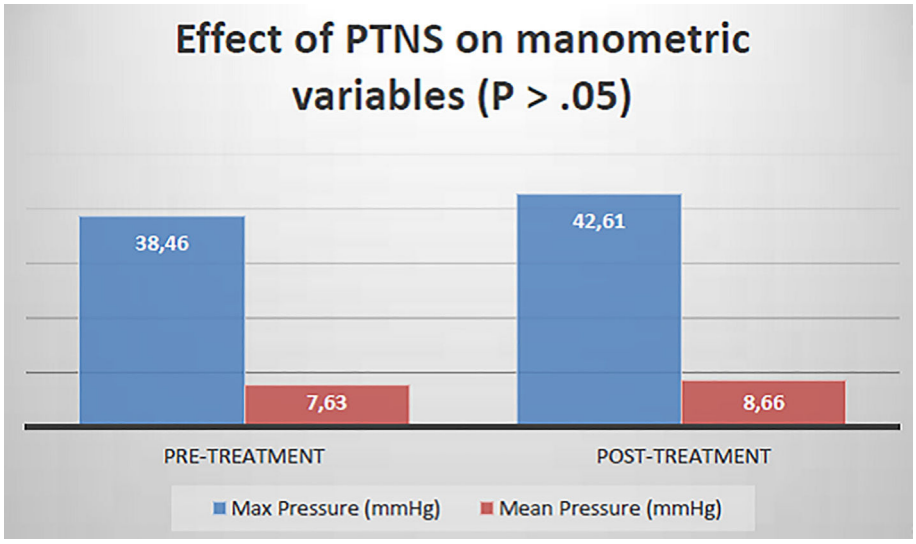


**Fig. 4** Effect of posterior tibial nerve stimulation on manometric variables ($P$ > .05).

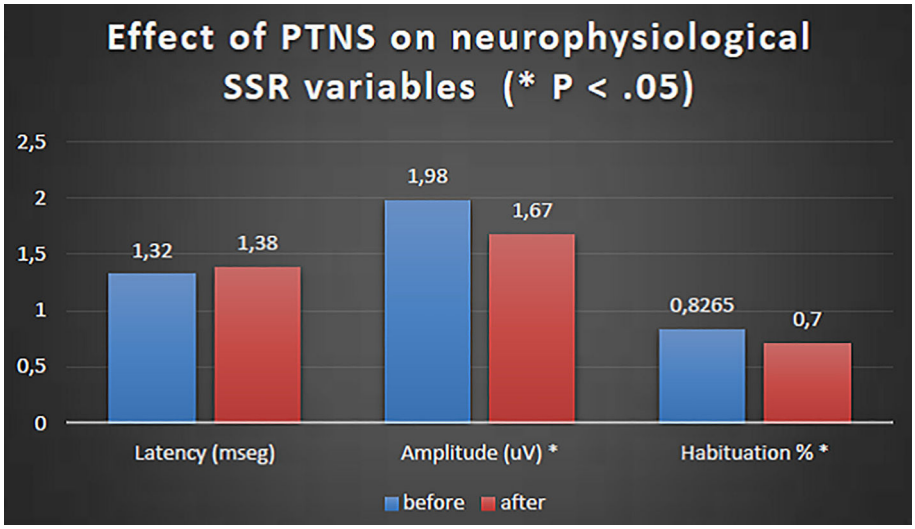


**Fig. 5** Effect of posterior tibial nerve stimulation on neurophysiological variables of the sympathetic skin response: latency, amplitude, and habituation/persistence. *$P$ < .05.

different stimuli (electric, auditory, visual, respiratory, etc) and presents specific characteristics such as latency and amplitude, and particularly habituation.[16] Furthermore, the SSR is a polysynaptic reflex arc that includes: *a)* thick, myelinated, afferent sensory fibres; *b)* a central synapse (posterior hypothalamus, reticular formation in the upper brainstem); *c)* an efferent pathway (spinal cord and preganglionic and postganglionic sympathetic nerve fibres; and *d)* sweat glands (effector).[28]

Habituation is a non-associative learning mechanism characterised by a decrement in the response to repeated stimuli (as observed in the SSR). It is considered a selective attention process that enables individuals to ignore irrelevant stimuli with the aim of freeing space in the limited cognitive storage.[18] In 1970, Graves and Thomson already described habituation and sensitisation as 2 different but antagonistic processes. In 2014, Barry and Steiner reported that the lack of habituation (dishabituation) is caused by sensitisation. Dishabituation is an alteration of the adaptation process, and its scope will be determined by the corresponding level of excitability.[29] We can therefore infer that the lack of habituation corresponds to the phenomenon of central sensitisation.

Thus, in 2008, the International Association for the Study of Pain defined CS as an increased response of CNS nociceptive neurons to a normal or subthreshold stimulus. However, demonstrating increased cerebral activity in the CNS is not sufficient to demonstrate CS. Therefore, demonstrating CS requires documentation of the increased response to a stimulus, as is the case with autonomous responses after quantitative sensory testing (temporal summation, long-term potentiation) or lack of habituation/persistence, as observed in the SSR. The lack of habituation/persistence of the SSR (> 70%) demonstrates the amplification of a stimulus, and therefore CS.[6,10]

The bladder is innervated by 2 types of afferent nerves: *a)* small myelinated Aδ-fibres that are mechanoreceptors that detect emptiness/fullness and wall tension of the bladder; and *b)* unmyelinated C-fibres that detect painful signals and transmit painful (nociceptive) stimuli, as in the case of infection/inflammation, by triggering the micturition reflex and the urge to urinate.[20] As in the pathophysiology of OAB, hyperactivity of the detrusor muscle is C-fibre–mediated; this hyperactivity of the detrusor probably (initially) generates a repeated afferent excitatory stimulus that (subsequently) over time probably causes abnormal processing at the central level or inappropriate activation of the descending inhibitory pathways. This would be reflected in the SSR as activity persistence of 100%, pathological hyperactivity, or lack of inhibition/habituation, which would demonstrate the phenomenon of CS,[20] as we observed in our series of 47 patients with OAB.

Having conducted an exhaustive review of the literature, we suggest that the SSR may present several patterns of response depending on the integrity or impairment of the different pathways that make up the complex reflex arc of SSR. Thus, a SSR with total integrity would show a normal habituation phenomenon (habituation or persistence of response <60%–70%).[16] Involvement of the myelinated sensory pathway would cause an absence of SSR, as shown by Shahani and confirmed in patients with spinal cord injury.[17] An alteration to central information processing or to the descending inhibitory pathway or preganglionic sympathetic fibres would cause a pattern of SSR persistence >60%–70%; this is considered a hyperactive response or lack of habituation/persistence of SSR, compatible with OAB.[20] Finally, a pattern of involvement at the level of postganglionic sensory C-fibres will show a pattern of SSR with increased latencies and decreased amplitudes, as shown in patients with amyotrophic lateral sclerosis,[11] erectile dysfunction,[13] chronic prostatitis,[14] incomplete spinal cord injury syndrome,[17] and carpal tunnel syndrome,[28] among others (Fig. 1).

In our series of 47 patients, we observed the pattern of lack of habituation/persistence of SSR with a habituation percentage of 88.6% (normal range: < 60%–70%). This

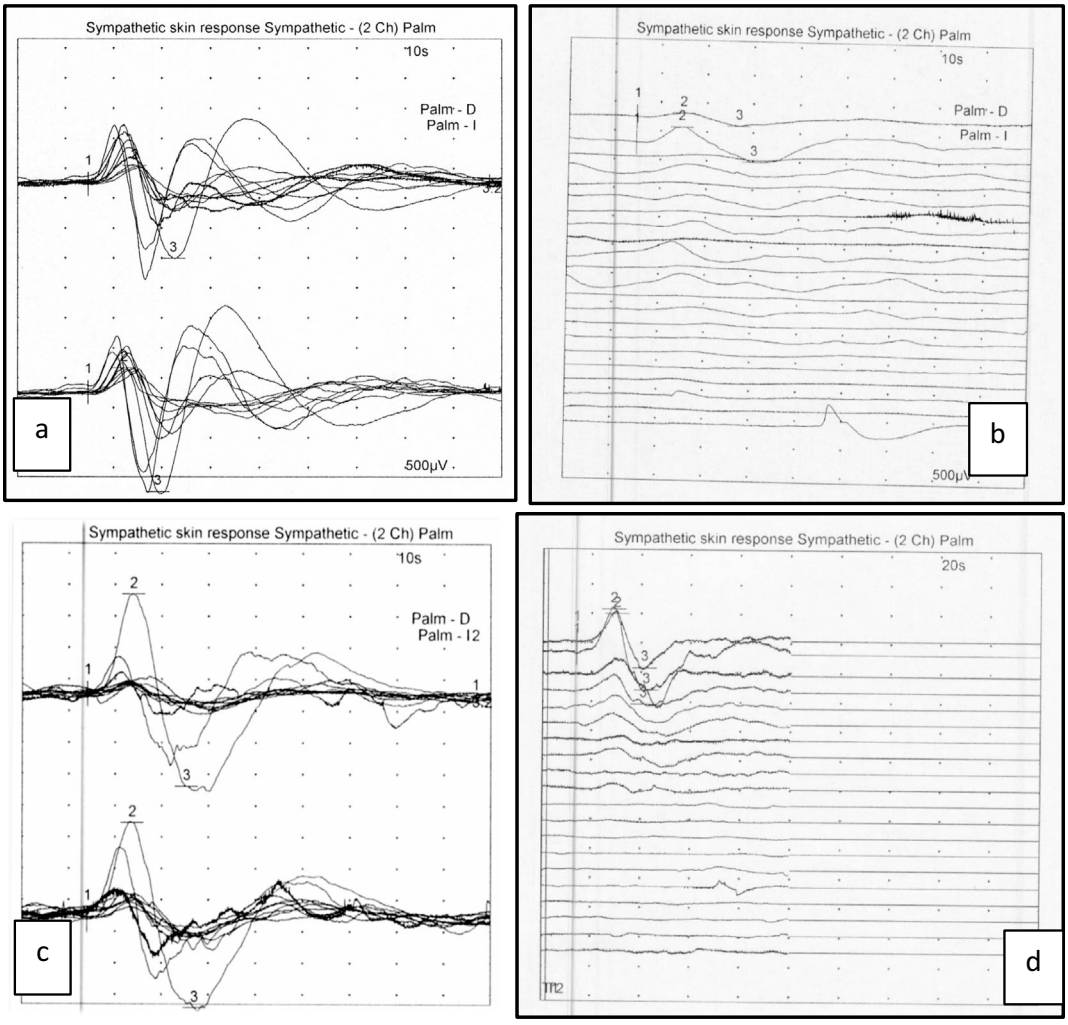


**Fig. 6** **CASE 1:** A 72-year-old woman diagnosed with OAB who, before treatment (a), presented an SSR latency of 1.48 s (right and left), amplitude of 1.55 mV (right side) and 2.07 mV (left side), and lack of habituation/persistence of SSR of 100%. After 8 sessions of posterior tibial nerve stimulation (PTNS) (b), latency remained at 1.48 s (right and left), amplitude decreased to 0.21 mV (right side) and 0.59 mV (left side), and habituation/persistence decreased to 60%. **CASE 2:** A 66-year-old woman diagnosed with OAB who, before PTNS (c), presented a latency of 1.39 s (right and left), amplitude of 1.22 mV (right side) and 1.18 mV (left side), and lack of habituation/persistence of SSR of 100%. After 8 sessions of PTNS (d), latency increased to 1.41 s (right and left), amplitude decreased to 0.37 mV (right side) and 0.28 mV (left side), and habituation/persistence decreased to 50%.

suggests the role of CS as a probable underlying pathophysiological mechanism in patients with OAB.

Once CS has been identified as the probable underlying mechanism in OAB, we would expect treatment approaches to target this sensitisation. Nijs et al.[30] described 3 mechanisms that cause CS: *a)* an ascending peripheral mechanism (increase in afferent excitatory stimulation); *b)* a central mechanism (central processing dysfunction); and *c)* a descending peripheral mechanism (dysfunction with a decrease in the descending inhibitory pathway and stimulation of the descending facilitating pathway) **(**Fig. 1**).**[30]

TENS activates large-calibre afferent fibres (ascending mechanism), which in turn activates descending pain-inhibitory mechanisms by activating the ventrolateral periaqueductal grey matter and the ventrolateral nucleus of the spinal cord (descending mechanism). TENS activates polysegmental inhibitory circuits (acting on $\mu$ and $\delta$ opioid receptors) and spinal GABA receptors, releasing GABA.[30] Therefore, TENS would act on the ascending, central, and peripheral mechanisms, which would explain its inhibitory effects on SSR (increased latency, decreased amplitude, and habituation normalisation).

These observations are in line with Megía-García et al.,[27] who argue that TENS activates the descending inhibitory system, the periaqueductal grey matter, and the rostral ventromedial medulla; in other words, it would act on central and peripheral mechanisms. Okuyucu et al.[21] report that TENS decreases SSR amplitude, with inhibition in the sympathetic nervous system, by blocking/inhibiting/modulating the reflex response within the spinal cord.

Currently, few validated diagnostic tools are available for the diagnosis of sensitisation; the available techniques include *a)* questionnaires (PainDETECT or Chronic Sensitive

Inventory); *b)* psychophysiological tests (Quantitative Sensory Testing [QST]); and *c)* imaging tests (functional magnetic resonance imaging). Our study provides a new objective neurophysiological test that is able to identify CS syndrome in everyday clinical practice, in addition to classifying different patterns of response according to the mechanism involved (ascending afferent mechanism, central mechanism, descending efferent mechanism, or postganglionic afferent mechanism).

In this context, the SSR test may be a useful tool to diagnose CS in patients with OAB, as well as other related diseases, such as interstitial cystitis, painful bladder syndrome, chronic pelvic pain, chronic prostatitis, vulvodynia, vulvar vestibulitis, and painful intercourse, among others. This test may explain the co-presence of CS-related diseases in the same patient. In this series, we observed that patients with OAB present a mean of 1.98 CS-related comorbidities (range: 1–5).

One limitation of our study is the absence of a control group, mainly due to the small sample size (n = 47). However, although this is a retrospective observational study, the analysis of outcome variables followed a pre-post design, using the *t* test to analyse paired samples. Furthermore, patients had given written informed consent to receive the proposed treatment (neuromodulation) after failure of previous pharmacological treatment; therefore, it is not ethical to withhold intervention. Pre-post analysis is a methodology used to avoid the ethical dilemma of not intervening and to solve the issues associated with the absence of a control group. Thus, when analysing pre−/postintervention data in the treatment group, we may assume that the change observed after the intervention is due to the direct effect of neuromodulation.[31] One strength of our study is that, although diagnosis of OAB is fundamentally clinical, it was corroborated in some cases with a urodynamic study. The absence of subgroups of patients with clinical and/or urodynamic OAB does not merit subsequent subanalysis.

## Conclusions

PTNS improves clinical and neurophysiological variables (amplitude and habituation of the SSR) in patients with clinical and/or urodynamic OAB. PTNS reduces DUF and NUF in patients with OAB. PTNS reduces SSR amplitude and decreases the percentage of habituation in OAB.

The lack of habituation/persistence (<70%) is a neurophysiological phenomenon present in patients with OAB.

SSR is a neurophysiological test that can detect the lack of habituation and may also characterise other response patterns depending on the CS mechanism involved (ascending, central, descending, or postganglionic pathway).

## Ethical considerations

The authors observed their centre's protocols for the publication of patient data.

## Informed consent

Patients gave informed consent for the participation and publication of this study.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2023.100112.

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