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ORIGINAL ARTICLE

Site matters: Central neuropathic pain characteristics and somatosensory findings after brain and spinal cord lesions

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Abstract

Background: It is unknown if different etiologies or lesion topographies influence central neuropathic pain (CNP) clinical manifestation.

Methods: We explored the symptom–somatosensory profile relationships in CNP patients with different types of lesions to the central nervous system to gain insight into CNP mechanisms. We compared the CNP profile through pain descriptors, standardized bedside examination, and quantitative sensory test in two different etiologies with segregated lesion locations: the brain, central poststroke pain (CPSP, $n = 39$), and the spinal cord central pain due to spinal cord injury (CPSCI, $n = 40$) in neuromyelitis optica.

Results: Results are expressed as median (25th to 75th percentiles). CPSP presented higher evoked and paroxysmal pain scores compared to CPSCI ($p < 0.001$), and lower cold thermal limen (5.6°C [0.0–12.9]) compared to CPSCI (20.0°C [4.2–22.9]; $p = 0.004$). CPSCI also had higher mechanical pain thresholds (784.5 mN [255.0–1078.0]) compared to CPSP (235.2 mN [81.4–1078.0], $p = 0.006$) and higher mechanical detection threshold compared to control areas (2.7 [1.5–6.2] vs. 1.0 [1.0–3.3], $p = 0.007$). Evoked pain scores negatively correlated with mechanical pain thresholds ($r = -0.38$, $p < 0.001$) and wind-up ratio ($r = -0.57$, $p < 0.001$).

Conclusions: CNP of different etiologies may present different pain descriptors and somatosensory profiles, which is likely due to injury site differences within the neuroaxis. This information may help better design phenotype mechanism correlations and impact trial designs for the main etiologies of CNP, namely stroke and spinal cord lesions. This study provides evidence that topography may influence pain symptoms and sensory profile. The findings suggest that CNP mechanisms might vary according to pain etiology or lesion topography, impacting future mechanism-based treatment choices.

KEYWORDS
central neuropathic pain, central poststroke pain, neuropathic pain after spinal cord injury, neuropathic pain sensory profile, quantitative sensory test

INTRODUCTION

Peripheral neuropathic pain presents symptoms (pain descriptors) and somatosensory profiles (measured by quantitative sensory testing [QST]) that are not dependent on the etiology of the disease associated with somatosensory injury. Different pain phenotypes can emerge following the same disease and the same pattern of peripheral injury [1–5]. Phenotypes are thought to reflect mechanisms of pain generation or maintenance [6]. Subsequently, profiling patients according to specific phenotypes, but not according to the disease related to neuropathic pain, would allow for the design of individualized treatment strategies for each patient and not for each disease [7, 8]. This approach is sound, but some limiting factors still need to be explored in guiding treatment [9]. One of them is that the large majority of studies describing patient profiles in neuropathic pain include exclusively, or essentially, peripheral neuropathic pain [10–17]. This is expected, because most patients with neuropathic pain have peripheral rather than central neuropathic pain (CNP). However, it remains unknown whether the correlations and findings related to sensory findings from QST and sensory symptoms are the same in patients with CNP of different etiologies. Classical studies have reported symptom somatosensory profile correlations of patients with a single etiology of CNP [10–17]. For example, in patients with syringomyelia, higher severity of spinal cord injury (SCI) was associated with more intense deep pain and paresthesia/dysesthesia, whereas patients with evoked pain had more preserved spinothalamic and lemniscal pathways [15]. In patients with central poststroke pain (CPSP), those with preserved tactile sensation had more mechanical allodynia than those with tactile hypoesthesia, whereas cold hypoesthesia was not necessary for developing cold allodynia [17]. A comparison of patients with different and distant lesion sites to the somatosensory system located at different levels of the neuroaxis would allow us to test if these findings occur in a broader range of CNP possibilities, being thus also transetiological in this subgroup of patients with central somatosensory lesions.

Because CNP is particularly refractory to treatment, very few positive randomized trials exist to control pain in these patients [16]. Therefore, expanding our current knowledge on the interactions between symptoms, bedside findings, and somatosensory profiles in CNP would allow us to better understand potential phenotype mechanistic correlations in this patients group, which could be a way to develop mechanism-based approaches for this type of neuropathic pain. For this purpose, here we compared the sensory profile of CNP through pain descriptors, standardized bedside examination, and a comprehensive QST battery in two different etiologies of central nervous system (CNS) lesions related to distant and nosologically different lesion sites, one affecting the brain (stroke) and another mainly affecting the spinal cord (neuromyelitis optica [NMO] under remission).

METHODS

This cross-sectional study, part of the Central Pain Initiative Project, focused on assessing and treating CNP [10, 18, 19]. Here we aimed to compare the pain characteristics and sensory profile of CNP secondary to stroke to CNP secondary to spinal cord lesions in NMO.

Standard protocol approvals and patient consent

Data collection occurred at the Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). The study was approved by the institution's ethics review board (No. 690.455). All participants were volunteers and provided written informed consent before inclusion. Some of the general clinical data of some included patients were reported in publications from this initiative [10, 19].

Patients

Neurologists or primary care physicians consecutively referred patients to the Pain Center of the HC-FMUSP, fulfilling the following criteria: (a) definite neuropathic pain diagnosis according to the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) grading system [20]; (b) occurrence of de novo pain attributed to a central lesion due to stroke or spinal cord injury; (c) pain characteristics not compatible with other etiologies of pain (previous fibromyalgia, migraine, nociceptive pain) [21], (d) pain lasting longer than 3 months and being present most days. Pain classification was made by three researchers (L.M.B., J.R., F.V.d.S.), and cases where no consensus was obtained were discussed with a board (D.C.d.A., M.J.T.).

All participants suffered an ischemic or hemorrhagic stroke confirmed by imaging (computed tomography or magnetic resonance imaging [MRI]) at least 3 months before the evaluation or had previous myelitis secondary to NMO diagnosed by a neuroinflammatory diseases specialist using the current diagnostic criteria [22]. Patients with chronic CNP due to inflammatory spinal cord injury (CPSCI) were confirmed to be in remission of their inflammatory disease with no relapses within the 12 months preceding the evaluation according to clinical assessment, patient report, and a recent MRI performed 2 months before inclusion. Exclusion criteria were significant cognitive or language impairments compromising answering questionnaires or sensory examination and the presence of peripheral neuropathic pain. Also, patients with more than one stroke needed to have deficits related to only one of the strokes, with a normal examination otherwise (i.e., unilateral deficits).

Assessment

Participants were assessed in a single visit, including evaluation of sociodemographic information, medical comorbidity status, medication use, current symptoms and limitations, standardized physical examination focused on sensory and musculoskeletal systems, and quantitative sensory testing (QST). Questionnaires were applied to evaluate pain (Short-Form McGill Pain Questionnaire [SF-MPQ]

[23], Brief Pain Inventory [BPI] [24], and Neuropathic Pain Symptoms Inventory [NPSI] [4]), anxiety and depression (Hospitalar Anxiety and Depression Scale [25]), and disability (functional status: Barthel Index [26]). The NPSI referred to the area of maximum neuropathic pain, and scores were classified according to the previously described five subscores (burning [superficial] spontaneous pain, pressing [deep] spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) [4], and NPSI stratification of patients in three clusters (deep pain, pinpointed pain, and evoked pain) [7]. Spasticity in the upper and lower limbs was quantified according to the modified (m-) Ashworth Spasticity (AS) scale [27]. It was classified into three categories: absent, low to moderate (m-AS scale score 1 or 2 in at least one limb), and moderate to severe (m-AS scale score >2 in at least one limb). Muscle strength was measured according to the Medical Research Council (MRC) Scale for Muscle Strength scoring system, which was grouped into four severity grades: grade 0 (MRC in all limbs = 5), grade 1 (MRC = 4 in at least one limb), grade 2 (MRC = 2 or 3 in at least one limb), and grade 3 (MRC = 0 or 1 in at least one limb) [10].

The sensory assessment employed standardized bedside examination, including touch with graded monofilaments and allodynia with a piece of cotton wool, cold sensitivity and cold allodynia with a metal rod at room temperature, and mechanical pain sensitivity by light prick with a pin. All these modalities were tested in the face, trunk, arms, and legs, and compared with the contralateral side and proximal and distal body regions [10, 19]. The patients were evaluated in a quiet room, at rest, and with eyes closed. They were instructed to compare the sensations between the tested areas and classify their intensity as similar, greater, or lower. When there were doubts, the test was performed again.

Patients underwent QST, through the method of limits, to assess sensory findings at the site of the most severe neuropathic pain area (pain area) compared to a control area (corresponding contralateral site in stroke [28–30] and above the level in SCI). The following QST parameters were tested in both areas by the method of limits according to previously described techniques [18]: cold detection threshold (CDT), warm detection threshold (WDT), mechanical detection threshold (MDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain threshold (MPT), and the numerical pain rating scale for suprathreshold cold (SuThC) pain, suprathreshold heat (SuThH) pain, suprathreshold mechanical (SuThM) pain, and wind-up ratio (WUR). Because warm and cold detection thresholds were the sensory modalities reported to be more altered in CNP [17, 29–35], a cold thermal limen and heat thermal limen was calculated consisting of CDT − CPT and HPT − WDT, respectively [34, 36].

To evaluate the differences between the neuropathic pain and the control area, we used the previously recommended side-by-side comparison parameters [37]. A QST ratio was calculated according to the following formula: value from the pain area / value from the control area for CDT, WDT, MDT, MPT, SuThC, SuThH, SuThM, and WUR [17, 29–35, 37, 38]. For CPT and HPT, the difference between results from test and control areas (pain area − control area) was calculated [37]. Additionally, to assess whether the affected region could influence the QST result, we also performed a subgroup analysis considering only patients evaluated in the upper limbs or cervical dermatomes and the lower limbs or lumbar and sacral dermatomes.

As a supplementary analysis, stroke patients were further classified by a neuroradiologist according to the affected region into cortical, subcortical, brainstem, and cerebellum. Comparative analyses among these groups were performed regarding pain descriptors (NPSI) and somatosensory assessment (bedside examination and QST).

Statistical analyses

This was a convenience sample of patients prospectively assessed for the study. Based on previous studies, we aimed at 40 patients per etiology based on previous data [12, 17, 29, 30, 33, 38–41]. The nonparametric group differences between CPSP versus CPSCI were compared using a Mann-Whitney *U* test. The χ^2 and Fisher exact tests were used to compare the nominal and ordinal qualitative variables between groups. Parametric data are displayed in the text as the mean ± standard deviation, nonparametric data as median and 25th–75th percentile, and categorical as percentages and absolute numbers. A case–control matching analysis was foreseen in case background differences existed between groups, which could influence results (e.g., sex, age).

The Spearman rank correlation coefficient assessed the correlation of QST and bedside examination with pain descriptors (NPSI and SF-MPQ) and pain intensity and interference (BPI). Statistical analyses were performed using the software application IBM SPSS Statistics version 22.0, with a p value of ≤0.05 set as the threshold for statistical significance, and no correction for familywise error was performed for this descriptive and exploratory study [42].

RESULTS

We included 79 patients with CNP (39 with CPSP and 40 with CPSCI). Patients in the CPSP group were older (59.2 ± 11.2 years vs. 48.2 ± 11.1 years, $p < 0.001$), with a higher proportion of males (59% vs. 32.5%, $p = 0.018$), hypertension, and heart disease (Table S1). The mean time (months) elapsed after the central lesion associated with neuropathic pain was similar between CPSP and CPSCI (54.7 ± 58.2 vs. 59.2 ± 46.2, respectively, $p = 0.219$). CPSP comprised 78.9% of ischemic and 21.2% of hemorrhagic strokes, and all 40 CPSCI had lesions due to inflammatory disease. In stroke, the most important frequent lesion locations were subcortical (53.8%), cortical (25.6%), brainstem and cerebellum (20.5%), whereas in SCI they were cervical (55%) and thoracic (45%). More than one injury site was present in 20.5% of CPSP and 57.5% of SCI patients (Table S2).

Pain descriptors were significantly different between groups (Table 1). Paroxysmal and evoked pain were more intense in CPSP, with higher intensity scores for pain evoked by cold, stabbing, and electric shocks, and CPSCI reported more intense squeezing pain.

TABLE 1 Neuropathic Pain Symptoms Inventory.

NPSI items and clusters	CPSP, $N = 39$	CPSCI, $N = 40$	p
NPSI items score, 0–10			
Burning	8.0 (4.0–9.0)	6.0 (3.0–8.0)	0.121
Squeezing	0.0 (0.0–8.0)	6.0 (0.0–8.75)	0.013*
Pressure	3.0 (0.0–8.0)	3.0 (0.0–7.5)	0.955
Electric shocks	5.0 (0.0–8.0)	0.0 (0.0–0.0)	0.002*
Stabbing	0.0 (0.0–7.0)	0.0 (0.0–0.0)	0.006*
Evoked by brushing	0.0 (0.0–7.0)	0.0 (0.0–6.0)	0.241
Evoked by pressure	5.0 (0.0–8.0)	4.0 (0.0–8.0)	0.947
Evoked by cold stimulus	6.0 (0.0–9.0)	0.0 (0.0–5.0)	0.002*
Pins and needles	4.0 (0.0–8.0)	0.0 (0.0–4.7)	0.040*
Tingling	7.0 (0.0–9.0)	3.5 (0.0–8.0)	0.338
NPSI total intensity score, 0–100	40.0 (24.0–59.0)	27.7 (16.2–43.0)	0.040*
NPSI clusters, 0–10			
Burning (superficial) spontaneous pain	8.0 (4.0–9.0)	6.0 (3.0–8.0)	0.121
Pressing (deep) spontaneous pain	3.5 (0.0–6.0)	4.5 (1.7–7.2)	0.131
Paroxysmal pain	3.5 (0.0–6.0)	0.0 (0.0–2.1)	<0.001*
Evoked pain	3.7 (2.0–6.7)	2.6 (0.1–4.7)	0.036*
Paresthesia/dysesthesia	3.0 (1.0–4.5)	4.0 (2.0–7.5)	0.048*
Total NPSI score	23.3 (12.0–29.7)	15.7 (10.7–23.0)	0.046*
NPSI phenotypes, Bouhassira et al.[7]			
Deep pain	14 (35.9%)	29 (72.5%)	0.004*
Provoked pain	15 (38.5%)	7 (17.5%)	
Pinpointed pain	10 (25.6%)	4 (10.0%)	

Note: Categorical variables are expressed in absolute numbers (percentages). Numerical nonparametric data are represented as median (25th–75th percentile).

Abbreviations: CPSCI, central pain in spinal cord injury; CPSP, central poststroke pain; NPSI, Neuropathic Pain Symptoms Inventory.

*$p < 0.05$.

Based on the NPSI cluster stratification [7], deep pain made up 72.5% of the CPSCI group, whereas CPSP was more homogeneously distributed among the three clusters (deep pain, 35.9%; provoked pain, 38.5%; pinpointed pain, 25.6%). Importantly, pain intensity and interference scores from the BPI were similar between groups. CPSP had slightly higher scores in sensory and affective dimensions of pain (Table S3) and depressive symptoms compared to CPSCI (9.0 [5.0–12.0] vs. 4.5 [2.0–9.0], respectively; $p = 0.002$). Regarding the topographical neuropathic pain distribution, although the pain areas in CPSP patients were located more in the deafferented hemibody (especially in the limbs), in patients with CPSCI, the pain was located more in the trunk at the lesion level (Figure 1).

On bedside examination, CPSP had more pinprick hypoalgesia (61.5% vs. 17.5%, $p < 0.001$), dynamic mechanical (61.5% vs. 27.5%, $p = 0.002$), and cold allodynia (61.5% vs. 15%, $p < 0.001$). CPSCI had more cold (100% vs. 61.5%, $p < 0.001$) and tactile hypoesthesia (97.5% vs. 78.9%, $p = 0.013$), pinprick hyperalgesia (80% vs. 38.5%, $p < 0.001$), and hyperpathia (97.5% vs. 71.8%, $p = 0.001$). In addition, CPSCI had more motor impairment (100% vs. 70.3%, $p < 0.001$), spasticity (87.5% vs. 63.8%, $p = 0.003$), and functional impairment (72.3 ± 25.5 vs. 87.0 ± 20.6, $p < 0.001$) compared to CPSP (Table 2).

Sensory assessment through QST showed that CPSP had lower MPT thresholds (235.2 [81.4–1078.0]) and higher cold hyperalgesia (SuThC) (10.0 [0.1–42.0]) compared to CPSCI (784.5 [255.0–1078.0], $p = 0.006$ and 5.0 [0.0–0.33.7], $p = 0.030$, respectively). Additionally, HPT (50.0 [45.7–50.0] vs. 48.4 [44.8–49.8], $p = 0.009$) and WUR (1.0 [1.0–1.4] vs. 0.0 [0.0–1.6], $p = 0.005$) were statistically different between groups but not clinically significant. There was a significantly higher wider cold limen (temperature interval between cold detection and pain thresholds) in CPSCI compared to CPSP (20.0 [4.2–22.9] vs. 5.6 [0.0–12.9], respectively, $p < 0.004$), which was not present for warm/heat limen. Other QST parameters were not significantly different between groups (Table 3). QST assessed areas are described in Table S4.

When comparing QST findings to each patient's control body area, we found that CPSP had lower CPT differences compared to

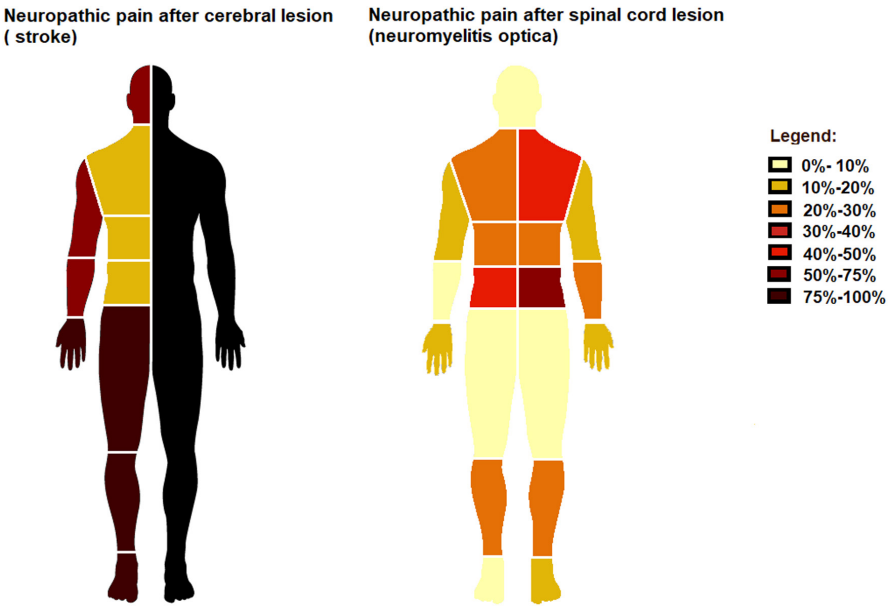

FIGURE 1 Central neuropathic pain distribution in patients with stroke and spinal cord injury in neuromyelitis optica.

CPSCI (−3.5 [−12.5 to 0.2] vs. −13.0 [−19.3 to −6.0], respectively, $p < 0.001$) and lower MDT differences (1.0 [1.0–3.3] vs. 2.7 [1.5–6.2], $p = 0.007$). Furthermore, CPSP had higher cold hyperalgesia (SuThC) (10.0 [0.1–42.0] vs. 5.0 [0.0–33.7], $p = 0.030$) and WUR differences (1.0 [1.0–1.4] vs. 0.0 [0.0–1.9], $p = 0.005$) compared to CPSCI. Other QST variables did not significantly differ between groups (Table S5). Figure 2 summarizes the main differences found between CPSP and CPSCI.

Considering there was a difference in the distribution of sex and age between groups, a case–control matching on sex and age analysis was performed (CPSP = 21 and CPSCI = 21) (Tables S6 and S7). Previously observed differences regarding pain descriptors and bedside examination persisted significantly. Regarding the QST, the main findings, including differences in mechanical pain thresholds, cold pain threshold difference, wind-up, and pain evoked by cold stimulus, remained significant.

A subgroup analysis considering only patients evaluated in the upper limbs or cervical dermatomes (CPSP = 26, CPSCI = 11) and the lower limbs or lumbar and sacral dermatomes (CPSP = 10, CPSCI = 9) was also performed. In the analysis of the upper limbs, we observed that CPSP had lower CDT (18.5 [0.1–27.7] vs. 27.1 [23.2–29.2], $p = 0.033$) and cold limen (6.7 [0.0–13.6] vs. 18.9 [6.5–22.9], $p = 0.004$) and higher HPT (50.0 [44.9–50.0] vs. 45.1 [41.5–49.0], $p = 0.040$) (Table S8), maintaining a significant part of the findings. There was no significant difference in the evaluation of the lower limbs (Table S9) between the CPSP and CPSCI groups.

Additional analysis of stroke patients according to lesion location (cortical, subcortical, brainstem, and cerebellum) showed that the four different stroke locations had similar pain descriptors (NPSI) and somatosensory profile (bedside examination and QST) (Tables S10 and S11). Lesion mapping of stroke location with the affected areas' prevalence is illustrated in Figure S1.

Correlation analysis between pain descriptor scores and QST results revealed negative correlations between MPT and evoked pain (−0.38, $p < 0.001$) and MPT and pain evoked by cold (−0.41, $p < 0.001$). In addition, a negative correlation was also observed between wind-up ratio and evoked pain (−0.57, $p < 0.001$).

DISCUSSION

We evaluated a large sample of patients with CNP with lesion sites located in either the brain or the spinal cord. We have shown that these two groups, despite presenting similar pain intensity and pain interference scores, have significant differences in pain descriptors, standardized bedside examination, and QST findings. CPSP patients had more evoked and paroxysmal pain, whereas CPSCI patients had more paresthetic, squeezing, and deep pain symptoms. In addition, CPSP had more pinprick hypoalgesia and allodynia to thermal and mechanical stimuli, whereas CPSCI had more sensory hypoesthesia (to touch and to cold), more pinprick hyperalgesia, and hyperpathia. Finally, on QST, CPSP patients had lower cold limen, and mechanical and cold pain thresholds. In summary, CPSP presented more evoked and paroxysmal pain and lower cold limen difference, whereas CPSCI showed more deep pain with more signs of impairment of spinothalamic (mechanical pain thresholds) and lemniscal pathways (higher mechanical detection thresholds).

It has been proposed that neuropathic pain is a transetiological entity, where one etiology of the disease is associated with neuropathic pain of diverse clinical presentations and possibly diverse mechanisms. Conversely, different etiologies of neuropathic pain may share similar pain profiles and mechanisms [1–5, 30]. Our data suggest that when assessing patients with CNP with lesion sites that do not primarily intersect, symptoms, clinical examination, and QST findings may differ depending on the etiology of the lesion to the somatosensory system, which probably reflects different sites of CNS injury (spinal cord vs. brain).

Some authors have previously described different CNP clinical manifestations according to the topography [28, 43] and extent of spinothalamic tract injury [14] within the same disease. It was

TABLE 2 Physical examination: Sensory, musculoskeletal, and functional assessment.

Standardized neurological examination	CPSP, $N = 39$	CPSCI, $N = 40$	p, effects between groups
Sensory testing			
Tactile hypoesthesia	30(78.9%)	39 (97.5%)	0.013*
Cold hypoesthesia	24 (61.5%)	40 (100%)	<0.001*
Mechanical hypoalgesia	24 (61.5%)	7 (17.5%)	<0.001*
Mechanical hyperalgesia	15 (38.5%)	32 (80.0%)	<0.001*
Dynamic mechanical allodynia	24 (61.5%)	11 (27.5%)	0.002*
Cold allodynia	24 (61.5%)	6 (15.0%)	<0.001*
Hyperpathia	28 (71.8%)	39 (97.5%)	0.001*
Motor impairment	$N = 37$	$N = 40$	
Paresis grade 0	11 (29.7%)	0 (0%)	0.001*
Paresis grade 1	11 (29.7%)	19 (47.5%)	
Paresis grade 2	11 (29.7%)	15 (37.5%)	
Paresis grade 3	4 (10.8%)	6 (15.0%)	
Ashworth Spasticity scale grade			
Absence	18 (46.2%)	5 (12.5%)	0.003*
Low to moderate, 1, 2	11 (28.2%)	22 (55.0%)	
Moderate to severe, 3–5	10 (25.6%)	13 (32.5%)	
Barthel index	87.0 (20.6)	72.4 (25.5)	<0.001*

Note: Categorical variables are expressed in absolute number (percentage). Paresis grade 0 (MRC = 5), grade 1 (MRC = 4), grade 2 (MRC = 2 or 3), grade 3 (MRC = 1 or 0).

Abbreviations: CPSCI, central pain in spinal cord injury; CPSP, central poststroke pain; MRC, Medical Research Council.

*$p < 0.05$.

observed that patients with thalamic lesions complained more of lacerating pain, had a greater diversity of pain quality, and more severely affected sensitivity to touch, whereas burning was the main descriptor in the other two groups [28]. Additionally, sensory differences in CPSP were observed regarding supratentorial and infratentorial lesions. The former had sharpness and cold deficits, whereas the latter had warm and heat pain deficits [32]. These findings suggest that the CNP lesion site could impact pain and somatosensory findings.

Bowsher compared patients who underwent cordotomy for intractable pain or had strokes to the brainstem or thalamus, and found that all QST modalities were dissociable from one another. He suggested that the representation of somatosensory modalities in pathways ascending from the anterolateral spinal funiculus to the thalamus ends at different levels, with a tendency of dissociation of mechanical pain and cold, and warmth and heat pain as the neuraxis ascends [44]. A small percentage of fibers ascending from the anterolateral funiculus reach the diencephalon directly, and the majority terminates in the infratentorial brainstem [44]. This would explain some sensory differences found between the spinal cord and brain-derived sites of lesion leading to CNP, and understanding these variables would bring insights into mechanisms involved in CNP and possibly improve patient phenotyping and mechanism understanding [7, 8, 45–47]. In our study, we observed that CPSCI had higher mechanical pain thresholds with similar cold detection and pain thresholds and warm detection thresholds compared to CPSP, suggesting dissociation of these spinothalamic pathways, as suggested by Bowsher.

We found that CPSP patients had more evoked pain, cold and mechanical allodynia, and lower cold limen. It was previously suggested that patients with allodynia had reduced thermal deficits [14], and patients with evoked pain had less structural damage and more preserved spinothalamic and lemniscal tracts on QST [15]. Also, it was suggested that mechanical allodynia occurred more frequently in patients with preserved mechanical detection thresholds than in those with hypoesthesia, suggesting mechanical allodynia occurs in disturbances of spinothalamic pathways that spare the tactile-signaling pathways [17]. We also observed a moderate negative correlation between MPT and evoked pain, cold allodynia, and wind-up, suggesting that a relative spearing of the spinothalamic tract could be associated with evoked pain [14].

On physical examination, CPSCI patients presented with more spontaneous deep pain and more signs of deafferentation of the lemniscal, spinothalamic, and corticospinal tracts (more severe cold and tactile hypoesthesia, motor impairment, and spasticity) compared to CPSP patients. It was also previously described that neuropathic pain dimensions, such as deep pain and paresthesia/dysesthesia, correlated with indices of spinal cord structural damage [15]. We found some differences in symptoms and somatosensory assessment when comparing patients with neuropathic pain due to brain injury (CPSP) to those with neuropathic pain due to spinal cord injury (due to neuromyelitis optica). This variability of characteristics may be related to the location of the lesion and, consequently, different proportions of involvement of spinothalamic and lemniscal pathways. We studied, through QST, the area of greatest neuropathic pain and compared it with a contralateral control region in stroke and above the sensory level in SCI, similar to what is performed in clinical practice and according to validation studies [37]. CNP sensory evaluation by QST can be challenging in such instances, because pain areas may be located in diverse body segments [12, 48], not necessarily those areas that were previously mapped in studies aimed at providing normative data for QST [37].

Furthermore, inherent innervation density, innervation quality, and skin thickness differences across body regions may affect the interpretation of QST results [37]. Regarding the comparison with the patients' control areas (QST ratio), it is not possible to affirm that the differences are similar when comparing sides or somatosensory levels. However, most QST ratio modalities were similar between CPSP and CPSCI, except for the WUR ratio, SuThC ratio, MDT ratio, and CPT difference, which were congruent with the different clinical manifestations of neuropathic pain between the two groups, as discussed above.

TABLE 3 Sensory thresholds in the neuropathic pain area.

	CPSP, $N = 39$	CPSCI, $N = 40$	p
Detection thresholds			
CDT, °C	18.8 (1.0–0.26.5)	24.0 (14.1–27.4)	0.180
WDT, °C	42.8 (35.0–50.0)	40.3 (36.0–46.4)	0.365
MDT, mN	0.7 (0.3–3.1)	0.7 (0.4–1.5)	0.695
Pain detection thresholds			
CPT, °C	1.9 (0.1–14.2)	1.4 (0.0–8.1)	0.157
HPT, °C	50.0 (45.7–50.0)	48.4 (44.8–49.8)	0.009*
MPT, mN	235.2 (81.4–1078.0)	784.5 (255.0–1078.0)	0.006*
Thermal limen			
CDT-CPT difference, °C, cold limen	5.6 (0.0–12.9)	20.0 (4.2–22.9)	0.004*
HPT-WDT difference, °C, heat limen	3.4 (0.0–9.4)	5 (2.6–8.2)	0.406
Evoked pain			
SuThC	10.0 (0.1–42.0)	5.0 (0.0–0.33.7)	0.030*
SuThH	3.5 (0.1–49.0)	29.7 (6.6–48.1)	0.257
SuThM	2.0 (0.1–28.0)	10.5 (2.5–29.0)	0.346
WUR	1.0 (1.0–1.4)	0.0 (0.0–1.9)	0.005*

Note: Numerical nonparametric data are represented as median (25th–75th percentile).

Abbreviations: CDT, cold detection threshold; CPSCI, central pain in spinal cord injury; CPSP, central poststroke pain; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; SuThC, suprathreshold cold pain stimuli; SuThH, suprathreshold heat pain stimuli; SuThM, suprathreshold mechanical pain stimuli; WDT, warm detection threshold; WUR, wind-up ratio (temporal summation), numerical rating scale 10° mechanical pain/numerical rating scale mechanical pain.

*$p < 0.05$.

To assess whether the affected region could influence the QST results, we compared the results with the patient's own control body areas. We additionally performed a subgroup analysis considering only patients evaluated in the upper limbs or cervical dermatomes and the lower limbs or lumbar and sacral dermatomes. In the analysis including upper limbs, the main QST differences remained significantly different between groups. However, there was no longer a significant difference in the lower limb comparisons, which is likely related to the limited number of patients in this subgroup and the subsequent decreased power of this comparison. Moreover, although the QST was tested in localized body areas, other assessments such as pain descriptors and somatosensory assessment through bedside examination relate to the whole pain experience and, in the case of bedside examination, including the assessment and comparison of large body areas. These complementary and spatially "broader" assessments corroborated the findings that significant differences exist in pain and somatosensory findings between patients with central pain resulting from brain (stroke) and spinal cord (NMO) injuries.

We also compared standardized bedside examination with a comprehensive battery of QST. Several differences were found between these two approaches, further suggesting that sensory changes in clinical assessments cannot be inferred from QST results. For instance, CPSCI patients had more cold and tactile hypoesthesia and pinprick hyperalgesia, which were not found in the QST. Several technical differences between the procedures may contribute to this divergence, such as the biophysics of the stimulus delivered in each of the scenarios, the body area assessed, and the directions given to patients to obtain the report of their percept. Although intuitive and somehow expected, these findings further support the idea that development and standardization of the clinical assessment and QST findings cannot be directly translated to what care providers will find on physical examination on the first medical encounter with patients with CNP.

Another important point is that in the present study, the CPSP group was older (59.2 ± 11.2 vs. 48.2 ± 11.1 years, $p < 0.001$) and had a higher proportion of males (59% vs. 32.5%, $p = 0.018$) compared to the CPSCI group. These findings reflect the clinical practice and are compatible with the prevalence of the two diseases concerning sex and age. Stroke is more prevalent in males and older people [28, 33, 49], whereas NMO is more prevalent in middle-aged women [50]. Although stimulus-specific changes in pain perception according to sex and age were previously reported [37, 51], most differences remained after case–control matching analysis based on sex and age.

Reflecting the reality in clinical practice, 20.5% of CPSP and 57.5% of CPSCI had more than one CNS lesion. Although signs and symptoms guided us to determine the topography of the most relevant lesion, it is not possible to rule out that other central lesions do not influence the results. Additionally, the generalizability of the

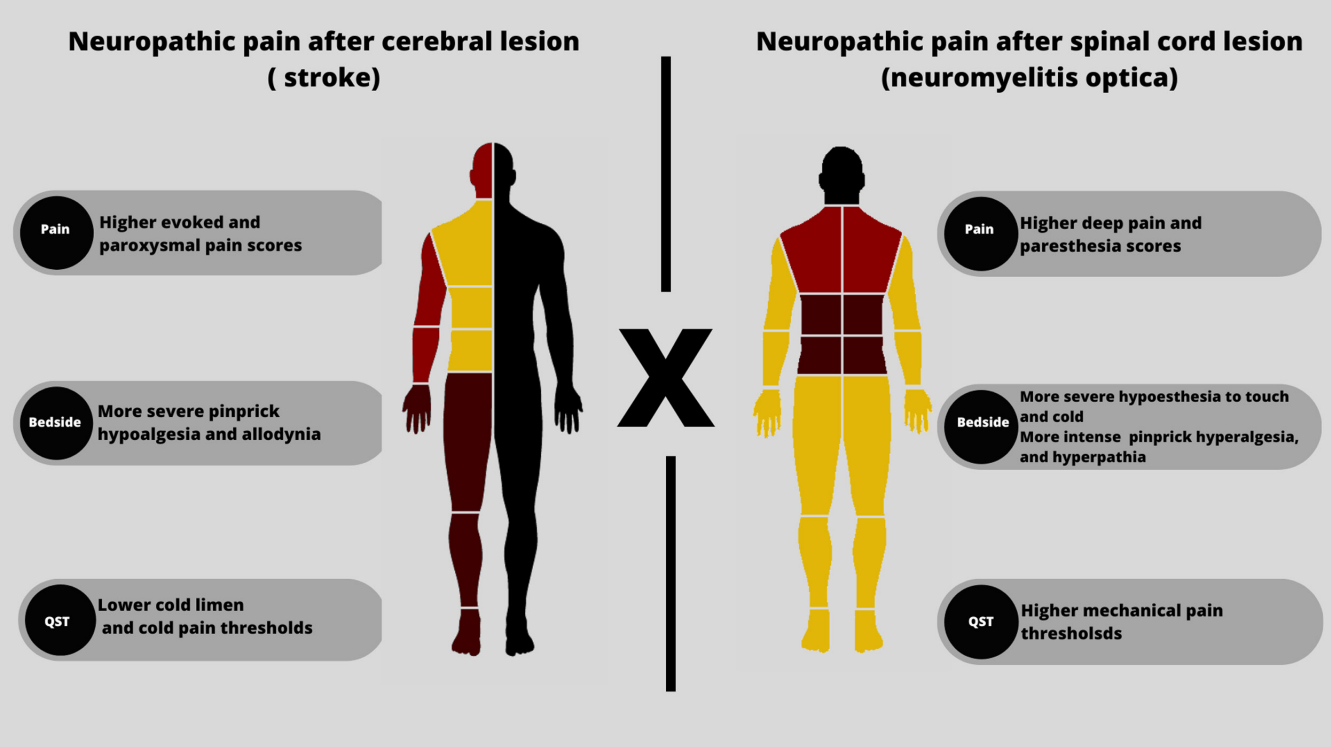

FIGURE 2 Major differences observed between patients with central poststroke pain and central pain after spinal cord injury in neuromyelitis optica. Pain descriptors were evaluated according to the Neuropathic Pain Symptoms Inventory. Bedside refers to somatosensory assessment through physical examination. Areas colored in dark red represent pain areas with higher prevalence, followed by lighter red and yellow. QST, quantitative sensory testing.

present findings to other patients with central pain of distinct etiology remains to be determined. Another important study limitation is that patients with stroke lesions in different areas were considered as a single group, which, although still little explored, may influence the clinical manifestations of central pain [32, 38]. Although our sensitivity analysis did not demonstrate significant differences in pain descriptors and somatosensory profile among the main four stroke locations, the small number of patients in each subgroup may have decreased the power of these assessments. Studies comparing more specific topographies with a larger number of patients could better clarify the influence of topography on central pain.

CONCLUSION

Spinal cord–related CNP patients had more deep pain scores and more intense signs of deafferentation of lemniscal and spinothalamic pathways, whereas cerebral stroke–related neuropathic pain patients had more paroxysmal and evoked pain scores and less marked somatosensory impairment, especially concerning mechanical detection and pain thresholds. Different levels of central nervous system injury (spinal cord/brain) coursing with neuropathic pain seem to influence the clinical manifestations of neuropathic pain with differences in pain descriptors, physical examination, and QST. CNP can manifest with a considerable variety of symptoms and signs, and there are no ubiquitous characteristics among patients. This heterogeneity could be partly explained by different lesion locations and, consequently, different underlying mechanisms involved in the painful process. Trial design and treatment choice should be guided by these differences. Grouping patients with different etiologies of CNP may add an unsought variability to mechanistic and therapeutic studies and may negatively impact the detection of significant effects.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (DCA) upon reasonable request.

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REFERENCES

1. Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. *Pain*. 2014;155(2):367-376. doi:10.1016/j.pain.2013.10.023
2. Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? *Pain*. 2008;138(2):343-353. doi:10.1016/j.pain.2008.01.006
3. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261-272. doi:10.1097/j.pain.0000000000000753
4. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the neuropathic pain symptom inventory. *Pain*. 2004;108(3):248-257. doi:10.1016/j.pain.2003.12.024
5. Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*. 2010;150(3):439-450. doi:10.1016/j.pain.2010.05.002
6. Truini A, Cruccu G. How diagnostic tests help to disentangle the mechanisms underlying neuropathic pain symptoms in painful neuropathies. *Pain*. 2016;157(2):S53-S59.
7. Bouhassira D, Branders S, Attal N, et al. Stratification of patients based on the neuropathic pain symptom inventory: development and validation of a new algorithm. *Pain*. 2021;162(4):1038-1046. doi:10.1097/j.pain.0000000000002130
8. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*. 2002;96(3):375-383. doi:10.1016/S0304-3959(01)00484-5
9. Forstenpointner J, Otto J, Baron R. Individualized neuropathic pain therapy based on phenotyping: are we there yet? *Pain*. 2018;159(3):569-575. doi:10.1097/j.pain.0000000000001088
10. Barbosa LM, da Silva VA, de Lima Rodrigues AL, et al. Dissecting central post-stroke pain: a controlled symptom-psychophysical characterization. *Brain Commun*. 2022;4(3):1-16. doi:10.1093/braincomms/fcac090
11. Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. *Brain*. 2012;135(2):418-430. doi:10.1093/brain/awr270
12. Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. *Brain*. 2003;126(1):57-70. doi:10.1093/brain/awg007
13. Eide PK, Jørum E, Stenehjem AE. Somatosensory findings in patients with spinal cord injury and central dysaesthesia pain. *J Neurol Neurosurg Psychiatry*. 1996;60(4):411-415. doi:10.1136/jnnp.60.4.411
14. Ducreux D, Attal N, Parker F, Bouhassira D. Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia. *Brain*. 2006;129(4):963-976. doi:10.1093/brain/awl016
15. Hatem SM, Attal N, Ducreux D, et al. Clinical, functional and structural determinants of central pain in syringomyelia. *Brain*. 2010;133(11):3409-3422. doi:10.1093/brain/awq244
16. Holmgren H, Leijon G, Boivie J, Johansson I, Ilievska L. Central post-stroke pain – somatosensory evoked potentials in relation to location of the lesion and sensory signs. *Pain*. 1990;40(1):43-52. doi:10.1016/0304-3959(90)91049-O
17. Greenspan JD, Ohara S, Sarlani E, Lenz FA. Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. *Pain*. 2004;109(3):357-366. doi:10.1016/j.pain.2004.02.002
18. Galhardoni R, Da Silva VA, García-Larrea L, et al. Insular and anterior cingulate cortex deep stimulation for central neuropathic pain disassembling the percept of pain. *Neurology*. 2019;92(18):E2165-E2175. doi:10.1212/WNL.0000000000007396
19. Valerio F, Apostolos-Pereira SL, Sato DK, et al. Characterization of pain syndromes in patients with neuromyelitis optica. *Eur J Pain*. 2020;24(8):1548-1568. doi:10.1002/ejp.1608
20. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630-1635. doi:10.1212/01.wnl.0000282763.29778.59
21. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol*. 2009;8(9):857-868. doi:10.1016/S1474-4422(09)70176-0
22. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006;66(10):1485-1489. doi:10.1212/01.wnl.0000216139.44259.74
23. Ferreira KASL, de Andrade DC, Teixeira MJ. Development and validation of a brazilian version of the short-form mcgill pain questionnaire (sf-mpq). *Pain Manag Nurs*. 2013;14(4):210-219. doi:10.1016/j.pmn.2011.04.006
24. Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of brief pain inventory to Brazilian patients with pain. *Support Care Cancer*. 2011;19(4):505-511. doi:10.1007/s00520-010-0844-7
25. Castro MMC, Quarantini L, Batista-Neves S, Kraychete DC, Daltro C, Miranda-Scippa Â. Validade da escala hospitalar de ansiedade e depressão em pacientes com dor crônica. *Rev Bras Anestesiol*. 2006;56(5):470-477. doi:10.1590/s0034-70942006000500005
26. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J*. 1965;14:61-65.
27. Katz R, Rovai G, Brait C, Rymer W. Objective quantification of spastic hypertonia. *Arch Med Rehabil*. 1992;73:339-347.
28. Leijon G, Boivie J, Johansson I. Central post-stroke pain — neurological symptoms and pain characteristics. *Pain*. 1989;36(1):13-25. doi:10.1016/0304-3959(89)90107-3
29. Leijon G, Bowsher D. Somatosensory findings in central post-stroke pain (CPSP) and controls. *Pain*. 1990;41:S468.
30. Krause T, Asseyer S, Geisler F, et al. Chronic sensory stroke with and without central pain is associated with bilaterally distributed sensory abnormalities as detected by quantitative sensory testing. *Pain*. 2016;157(1):194-202. doi:10.1097/j.pain.0000000000000354
31. Fitzek S, Baumgrtner U, Fitzek C, et al. Mechanisms and predictors of chronic facial pain in lateral medullary infarction. *Ann Neurol*. 2001;49(4):493-500. doi:10.1002/ana.99
32. Bowsher D, Leijon G, Thuomas K-A. Central poststroke pain: correlation of MRI with clinical pain characteristics and sensory abnormalities. *Neurology*. 1998;51(5):1352-1358. doi:10.1212/WNL.51.5.1352
33. Bowsher D. Central pain: clinical and physiological characteristics. *J Neurol Neurosurg Psychiatry*. 1996;61(1):62-69. doi:10.1136/jnnp.61.1.62
34. Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. *Pain*. 1995;61(2):177-186. doi:10.1016/0304-3959(94)00140-A

35. Boivie J, Leijon G, Johansson I. Central post-stroke pain – a study of the mechanisms through analyses of the sensory abnormalities. *Pain*. 1989;37(2):173-185. doi:10.1016/0304-3959(89)90128-0
36. Cury RG, Galhardoni R, Teixeira MJ, et al. Subthalamic deep brain stimulation modulates conscious perception of sensory function in Parkinson's disease. *Pain*. 2016;157(12):2758-2765. doi:10.1097/j.pain.0000000000000697
37. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123(3):231-243. doi:10.1016/j.pain.2006.01.041
38. Bowsher D. Allodynia in relation to lesion site in central post-stroke pain. *J Pain*. 2005;6(11):736-740. doi:10.1016/j.jpain.2005.06.009
39. Boivie J. Central pain and the role of quantitative sensory testing (QST) in research and diagnosis. *Eur J Pain*. 2003;7(4):339-343. doi:10.1016/S1090-3801(03)00046-6
40. MacGowan DJL, Janal MN, Clark WC, et al. Central poststroke pain and Wallenberg's lateral medullary infarction: frequency, character, and determinants in 63 patients. *Neurology*. 1997;49(1):120-125. doi:10.1212/WNL.49.1.120
41. Widerström-Noga E, Felix ER, Adcock JP, Escalona M, Tibbett J. Multidimensional neuropathic pain phenotypes after spinal cord injury. *J Neurotrauma*. 2016;33(5):482-492. doi:10.1089/neu.2015.4040
42. Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol*. 2001;54(4):343-349. doi:10.1016/S0895-4356(00)00314-0
43. Misra UK, Kalita J, Kumar B. A study of clinical, magnetic resonance imaging, and somatosensory-evoked potential in central post-stroke pain. *J Pain*. 2008;9(12):1116-1122. doi:10.1016/j.jpain.2008.06.013
44. Bowsher D. Representation of somatosensory modalities in pathways ascending from the spinal anterolateral funiculus to the thalamus demonstrated by lesions in man. *Eur Neurol*. 2005;54(1):14-22. doi:10.1159/000086884
45. Demant DT, Lund K, Finnerup NB, et al. Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. *Pain*. 2015;156:2234-2244.
46. Attal N, de Andrade DC, Adam F, et al. Safety and efficacy of repeated injections of botulinum toxin a in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2016;15(6):555-565. doi:10.1016/S1474-4422(16)00017-X
47. Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain*. 2014;155(11):2263-2273. doi:10.1016/j.pain.2014.08.014
48. de Oliveira RAA, de Andrade DC, Machado AGG, Teixeira MJ. Central poststroke pain: somatosensory abnormalities and the presence of associated myofascial pain syndrome. *BMC Neurol*. 2012;12:12. doi:10.1186/1471-2377-12-89
49. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20(10):1-26. doi:10.1016/S1474-4422(21)00252-0
50. Papp V, Magyari M, Aktas O, et al. Worldwide incidence and prevalence of NMO: a systematic review. *Neurology*. 2020;96(2):59-77. doi:10.1212/WNL.0000000000011153
51. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*. 2005;115(3):410-418. doi:10.1016/j.pain.2005.03.025

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