Universidade de São Paulo

LUCIANA MENDONÇA BARBOSA

Central neuropathic pain: clinical, psychophysical and neurophysiological characterization

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Dor neuropática central: caracterização clínica, psicofísica e neurofisiológica

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutora em Ciências

Programa de Neurologia

Orientador: Prof. Dr. Daniel Ciampi Araújo de Andrade

Coorientatora: Profª. Dra. Adriana Bastos Conforto

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Dedication

To the thousands of ***professors***, ***researchers***, ***teachers***, and ***students*** who contribute to a more dignified and sustainable society through hard work, dedication, and effort, especially in underdeveloped countries.

To chronic pain patients and ***all patients*** who kindly contributed to this study.

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To ***patients*** and their ***families***.

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Summary

Abbreviations

BPI	Brief Pain Inventory
CDT	Cold detection threshold
CE	Cortical excitability
CNP	Central neuropathic pain
CNS	Central nervous system
CPM	Conditioned pain modulation
CPSCI	Central pain secondary to spinal cord injury
CPSP	Central post-stroke pain
CPT	Cold pain threshold
CT	Computerized tomography
DN-4	Douleur Neuropathique Questionnaire-4
HAD	Hospital Anxiety and Depression Scale
HPT	Heat pain threshold
IASP	International Association for the Study of Pain
ICF	Intracortical facilitation
m-AS	Ashworth spasticity scale
MDT	Mechanical detection threshold
MEP	Motor evoked potential
MPT	Mechanical pain threshold
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NeuPSIG/IASP	IASP Special Interest Group on Neuropathic Pain
NMOSD	Neuromyelitis optica spectrum disorder
No-Pain	Post-stroke patients without chronic pain
NPSI	Neuropathic Pain Symptoms Inventory
NRS	Numeric rating scale
PDQ	Pain Disability Questionnaire
PPT	Pressure pain threshold
PSP	Post-stroke pain
PSP-Non	Non-neuropathic post-stroke pain
QST	Quantitative sensory testing
QuickDash	Shortened disabilities of the arm, shoulder, and hand questionnaire
RMT	Resting motor threshold
SCI	Spinal cord injury
SEP	Somatosensory evoked potential
SF-12	The Short Form 12- Health Status Questionnaire
SF-MPQ	Short-form McGill Pain Questionnaire
SICI	Short-interval intracortical inhibition
STCP	Numerical pain rating scale for suprathreshold cold stimuli
STHP	Numerical pain rating scale for suprathreshold heat stimuli

STMP	Numerical pain rating scale suprathreshold mechanical stimuli
STT	Spinothalamic tract
TMS	Transcranial magnetic stimulation
TP	Myofascial trigger points
VDT	Vibration detection threshold
WDR	Wide dynamic range neurons
WDT	Warm detection threshold
WUR	Wind up ratio

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RESUMO

Barbosa LM. Dor neuropática central: caracterização clínica, psicofísica e neurofisiológica [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2022.

Introdução: Os escassos conhecimentos sobre mecanismos envolvidos na dor neuropática central (DNC), a qual impacta a qualidade de vida e reabilitação dos pacientes, são barreiras para otimizar o seu tratamento. Descrever e correlacionar descritores de dor, alterações somatossensoriais e parâmetros neurofisiológicos através de estudo controlado incluindo pacientes com lesões semelhantes, com dor não neuropática e sem dor crônica, contribuiria para diferenciar características típicas da DNC, das relacionadas a outras dores crônicas ou à lesão central. **Métodos:** Para identificar características da DNC pós-AVC (DNC-AVC), compararam-se 39 pacientes com DNC-AVC, através de exame clínico, questionários e teste quantitativo de sensibilidade, com dois grupos de controle pareados por sexo, idade e macrorregião do AVC: 32 pacientes com dor pós-AVC não neuropática e 31 pacientes com AVC sem dor crônica. Para avaliar se diferentes etiologias ou topografias das lesões influenciariam a manifestação da DNC, compararam-se as relações entre os sintomas e alterações somatossensoriais entre pacientes com diferentes tipos de lesões no sistema nervoso central: DNC-AVC (n=39) e lesão medular na neuromielite óptica em remissão (DNC-LM, n=40). Além disso, para descrever alterações neurofisiológicas na DNC, comparou-se a excitabilidade cortical (EC) na DNC-AVC (n=35) e na DNC-LM (n=39) àqueles com lesão central e dor não neuropática (n=43) e sem dor crônica (n=46), pareados por sexo e localização da lesão. **Resultados:** Os pacientes com DNC-AVC apresentaram mais dor em queimação, formigamento e evocada, além de mais alodinia e hiperpatia com maiores níveis de desaferentação ($p<0,012$) e limiares de detecção de frio e quente mais assimétricos em relação aos controles ($p<0,001$). A razão de chances da hipoestesia térmica ao frio foi 12,0 (IC 95%: 3,8–41,6) para dor neuropática. A combinação de hipoestesia térmica ao frio, a pontuação no Inventário de Sintomas de Dor Neuropática e a intensidade da alodinia no exame à beira do leito explicaram 77% da ocorrência de dor neuropática. Quanto à manifestação clínica em topografias diferentes, DNC-AVC apresentou menor diferença entre detecção e dor ao frio (5,6 °C (0,0–12,9)) *vs*. DNC-LM (20,0 °C (4,2–22,9);p =0,004) e maior dor evocada e paroxística, $p<0,001$. DNC-LM apresentou limiares de dor mecânica mais altos (784,5mN (255,0–1078,0)) *vs.* DNC-AVC (235,2 mN (81,4–1078,0)), p=0,006. No estudo de EC, DNC apresentou amplitudes de potencial evocado motor (PEM) menores (366,8±464,1), comparadas a dor não neuropática (478,6±489,4) e sem dor

(765,8±880,0), p<0,001, e inibição intracortical de intervalo curto (ICIC) defeituosa (2,6±11,6) *vs*. grupo sem dor (0,8±0,7), p=0,021. DNC-AVC apresentou PEM reduzido nos dois hemisférios e correlação negativa com alodinia. **Discussão:** Esses achados fornecem relações clínico-psicofísicas na DNC e podem auxiliar na distinção da DNC-AVC da dor não neuropática na prática clínica e em estudos futuros. Adicionalmente, a DNC variou de acordo com a topografia ou etiologia da lesão, podendo afetar futuras escolhas de tratamento baseadas em mecanismos. A EC evidenciou redução do PEM e da ICIC na DNC, fornecendo visão indireta de alterações plásticas globais que ocorrem após lesões centrais e cursam com DNC, sendo uma perspectiva de marcador neurofisiológico.

Descritores: Acidente vascular cerebral; Lesão medular; Neuromielite óptica; Dor crônica; Síndrome de Dejerine-Roussy; Alodinia; Hiperalgesia; Limiar de dor; Excitabilidade cortical.

ABSTRACT

Barbosa LM. Central neuropathic pain: clinical, psychophysical and neurophysiological characterization [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2022.

Introduction: Central neuropathic pain (CNP) impacts life quality, and rehabilitation and its management is challenging. One CNP treatment barrier is the lack of knowledge about its multiple mechanisms. Therefore, describing and correlating pain descriptors, somatosensory abnormalities, and neurophysiological parameters through a controlled study, including patients with similar lesions with non-neuropathic pain and without chronic pain, can help identify characteristics typical of CNP or related to other chronic pain or central lesion. **Methods:** To dissect the characteristics of central neuropathic post-stroke pain (CPSP), we compared 39 CPSP patients, through clinical examination, questionnaires, and quantitative sensory testing, with two control groups matched by sex, age, and stroke macroregion: 32 patients with non-neuropathic post-stroke pain and 31 stroke patients without chronic pain (No pain). To understand if different etiologies or lesions topography might influence CNP manifestation, we explored the symptom-somatosensory profile relationships comparing patients with different types of lesions to the central nervous system: CPSP (n=39) and spinal cord injury in remitted neuromyelitis optica (CPSCI, n=40). Additionally, to describe neurophysiological changes in CNP, we compared cortical excitability (CE) in CPSP (n=35) and CPSCI (n=39) to those with central injury and non-neuropathic pain (n= 43) and without chronic pain (n=46), matched by sex and lesion location. **Results:** Patients with CPSP had more burning, tingling, and evoked pain, in addition to more allodynia and hyperpathia with higher levels of deafferentation ($p<0.012$) and more asymmetrical cold and hot detection thresholds compared to controls ($p <0.001$). The odds ratio of thermal hypoesthesia to cold was 12 (95% CI: 3.8-41.6) for neuropathic pain. The combination of cold thermal hypoesthesia, Neuropathic Pain Symptoms Inventory score, and allodynia intensity on bedside examination explained 77% of the occurrence of neuropathic pain. Regarding the clinical manifestation in different topographies, CPSP presented more evoked and paroxysmal pain compared to CPSCI, $p< 0.001$, and lower thermal limen (5.6 °C (0.0–12.9)) *vs.* CPSCI (20.0 °C (4.2–22.9);$p =0.004$). CPSCI had higher mechanical pain thresholds 784.5mN (255.0 – 1078.0) *vs.* CPSP 235.2 mN (81.4-1078.0),$p=0.006$ and mechanical detection threshold difference compared to control areas 2.7 (1.5 –6.2) vs. 1.0 (1.0 –3.3), $p=0.007$. In the CE study, CNP had lower motor evoked potentials amplitudes (MEP) (366.8±464.1) compared to non-neuropathic (478.6±489.4) and no-pain (765.8± 880.0), $p<0.001$. Short-

interval intracortical inhibition (SICI) was defective in CNP (2.6±11.6) vs. the group without -pain (0.8±0.7), p=0.021. CPSP showed reduced MEP in both hemispheres, which negatively correlated with allodynia. **Discussion**: These findings provide insights into the clinical-psychophysics relationships in CNP and may assist in a more precise distinction of neuropathic from non-neuropathic post-stroke pain in clinical practice and future trials. CNP presents decreased MEP and SICI, which may provide neurophysiological markers of pain development and persistence after injury, as a keyhole view into global cortical excitability plastic changes occurring in people with central lesions leading to CNP. Furthermore, the topography may influence pain symptoms and sensory profile, indicating CNP might vary according to pain etiology or lesion topography, which could impact future mechanisms-based treatment choices.

Descriptors: Stroke; Spinal cord injury; Neuromyelitis optica; Chronic pain; Dejerine Roussy syndrome; Allodynia; Hyperalgesia; Pain threshold; Cortical excitability.

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Introduction

1. Introduction

Chronic pain is a highly disabling condition that significantly interferes with daily activities, relationships, and professional capacity(2–5). Brazil's prevalence ranges from 29.3% to 73.3%(6,7). Based on clinical findings, chronic pain can be classified into the following categories: nociceptive, neuropathic, and nociplastic(8,9). It is a syndromic diagnosis based on clinical features and mechanisms potentially involved in the development of pain. The classification supports the therapeutic approach direction. Pain, in the context of neurological diseases, presents clinical manifestations in different ways and possibly different underlying mechanisms, also associated with the specific expressions of the studied disease in the nervous system. In these cases, rational management of chronic pain requires an analysis of the likely mechanisms of pain generation as a guide to the treatment.

Central neuropathic pain (CNP) occurs following a lesion or disease of the central somatosensory system (CNS)(10) and may manifest in the body area corresponding to CNS injury of any etiology, including stroke, inflammatory, traumatic, and infectious. CNP is not rare among patients with stroke or spinal cord injury (SCI), and its prevalence is up to 18% in stroke(11,12) and 53% in SCI(13). This non-motor symptom can generate disabilities and effects on recovering patients, substantially impacting their future quality of life and limiting their performance and gains during rehabilitation(14,15).

CNP is characterized by pain and somatosensory abnormalities in which other apparent causes of pain, such as nociceptive pain, peripheral neuropathic pain, or nociplastic causes, cannot wholly explain the clinical manifestation. Therefore, the differential diagnosis should be based on the physical examination findings that include sensory evaluations and specific alterations, e.g., musculoskeletal and spasticity assessment(12).

Regardless of its etiology, neuropathic pain manifests through stereotyped symptoms and signs(16). Typically, symptoms and signs related to CNP are those of neuropathic pain in general and comprise a rich semiology(17–22). Pain descriptors include burning, electric shocks, squeezing, pressure, stabbing, tingling, pins and needles, painful cold, and itching, and they can be associated with other symptoms like numbness, paraesthesia, and dysaesthesia(23). Relative to the physical examination, a vast combination of positive and negative signs can be found(1). Positive signs can include hyperpathia, cold allodynia, dynamic mechanical allodynia, static mechanical allodynia, mechanical hyperalgesia, evoked paraesthesia, and dysaesthesia. While negative signs can include cold hypoesthesia, mechanical hypoesthesia, mechanical hypoalgesia, hypopallesthesia, and apallesthesia(17–22). CNP expression varies considerably and encompasses different combinations of pain descriptors and positive and negative sensory signs.

CNP management is a challenge and consists of trial and error. Many patients will need drugs combination, which increases the risk of adverse effects and drug interactions(24). Nevertheless, up to 50% will not respond to any treatment available(16,24). This high number of patients without adequate

treatment may be due to multiple pathophysiological mechanisms implicated in neuropathic pain development, lack of diagnostic accuracy, and relatively ineffective drugs(16)

Extensive efforts have been made to disentangle neuropathic pain mechanisms and improve the therapeutic response. Since neuropathic pain has a wide variety of symptoms and signs, it has been suggested that this significant variability may underlie different pain mechanisms(25,26). On the other hand, central and peripheral neuropathic pain clinical characteristics are similar, which suggests that these different conditions might have an overlapping range of mechanisms(12). Therefore, grouping patients according to their clinical characteristics (pain descriptors or sensory abnormalities), also called pain phenotypes, regardless of the etiology of the nervous system disease, could provide insights into the various mechanisms of neuropathic pain and individualized treatment(27).

It has been widely shown that peripheral neuropathic pain presents with symptoms (pain descriptors) and somatosensory profiles (measured by quantitative sensory test –QST) that are not dependent on the etiology of the disease associated with somatosensory injury but, rather, the different pain phenotypes could occur following the same type of lesion or disease(1,23,25,26,28–31). 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(32–37). Previous clinical trials evaluated a particular drug grouping patients according to the disease, such as diabetic neuropathy or post-

herpetic neuralgia, and not according to phenotypic characteristics. Therefore, this could be an explanation for negative results in several trials in which a single drug was used for different neuropathic pain-related symptoms and signs covering a single etiology(25).

Current attempts to organize a mechanism-based classification rely on pain descriptors scales and QST (Table 1). This approach is sound, but some limiting factors still need to be explored in guiding treatment. Studies integrating individualized and mechanism-based treatments are still lacking, so this concept can be applied in clinical practice(38). The large majority of studies describing patient profile in neuropathic pain included exclusively, or essentially, patients with peripheral neuropathic pain (Table 1). This is expected since most patients with neuropathic pain have peripheral rather than central neuropathic pain (CNP). However, it is not known whether these characteristics can be applied to central neuropathic pain, which seems to have different mechanisms involved and greater refractoriness to treatment (24).

CNP sensory evaluation through the quantitative sensory test (QST) is limited because pain areas may be located in different body parts(18,39), distinct from areas that have normative data(40), and the need to use as comparators body areas that are not necessarily the mirror area (side -by -side). The actual sensory profile based on the QST assessment of CNP remains partially known, and little information exists about the correlation between pain characteristics and sensory findings through clinical examination and QST.

The CNP characterization through its signs and symptoms integrated with psychophysical assessment using QST and neurophysiological assessment

through cortical excitability, as well as the correlation between these findings, can contribute to a better understanding of the pain mechanisms involved in this pain syndrome and, in the future, optimize the design of studies focusing on treatments or individualized preventive actions, based on these findings and mechanisms.

Most studies that characterize CNP do not have a control group or are controlled with healthy individuals or central lesions without pain(18,20–22,41–51). Thus, there are limitations to understanding which alterations are characteristic of CNP or could be attributed to chronic pain in general(14,52–55), and its plastic changes (56,57), central and peripheral sensitization(58), or secondary to the CNS lesion itself(59–62). Also, we still do not know whether the different topographies of the lesions could be associated with different clinical manifestations, as suggested in some studies.

The Central Pain Initiative Project, coordinated by the Pain Center, Division of Neurological Clinic and Division of Neurosurgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, focused on assessing and treating central neuropathic pain(14,63). In one of the spheres of this umbrella project, Valerio-da-Silva, 2019, characterized pain in patients with spinal cord injury (SCI) due to neuromyelitis optica spectrum disorders (NMOSD) through pain descriptors, QST, and cortical excitability(64). Furthermore, patients with CNP were compared to patients with a similar neurological picture with non-neuropathic and without chronic pain. In the current study, part of this umbrella project, we sought to characterize patients with post-stroke central pain (CPSP) through a controlled study design (stroke patients with non-neuropathic pain and

without pain) and also compare the main findings with patients with CNP secondary to SCI due to neuromyelitis optica, which were detailed in the study mentioned above(64).

In order to dissect characteristics that would be characteristic of CNP and whether there would be a topographical relationship, we designed a study with groups of CNP with different injuries and etiologies (stroke and SCI due to NMOSD) compared to control groups with central nervous system injury with chronic non-neuropathic pain or without chronic pain. In the first step of the study, we reported the symptom profile and sensory characteristics of CPSP, compared to stroke patients that developed non-neuropathic pain after the event and without chronic pain, and correlated the pain descriptors to the somatosensory profile. In the second stage, to assess whether changes in symptoms and somatosensory profile are related to topography, we compared patients with distinct lesions: CPSP and CPSCI. CPSCI patients were previously described by Valerio FS, 2019(64). In the third step, we evaluated the neurophysiological parameters of patients with CPSP and CPSCI and compared them to the control groups with non-neuropathic pain and without pain. Later, we performed a pooled analysis with CPSP and CPSCI and their control groups.

The results regarding the controlled clinical characterization of CPSP were previously published, under the open access license in Brain Communication, 2022, with the title “Dissecting central post-stroke pain: a controlled symptom-psychophysical characterization” (65) and are detailed in this thesis.

Table 1 - Studies on neuropathic pain subgroup classification

Study	Patients	Parameters	Results
Bouhassira D *et al,* 2004 (23)	CNP 175 (28%) PNP 453 (72%)	NPSI	Three clusters: pinpointed, provoked, and deep pain
Attal N. *et al.* 2007(30)	CNP 133 (27.6) PNP 349 (72.4%)	NPSI	Strong correlation between -reported pain evoked by brush, pressure, and cold stimuli strongly correlated to allodynia/hyperalgesia to brush, von Frey hairs, and cold stimuli). Few associations between symptoms (or dimensions) and etiologies, types of lesions, or pain localizations.
Lucchetta M. *et al,*2011 (31)	PNP 277 (100%)	NPSI	88.6% presented paresthesia/dysesthesia
Maier C *et al,* 2010 (1)	CNP 51 (4.1%) PNP 1185 (95.9%)	QST	Abnormality occurred in different frequencies, the most common: -Thermal and mechanical hyperalgesias: CRPS complex regional pain syndrome and peripheral nerve injury - Allodynia: PHN - Either mechanical hyperalgesia or mechanical hypoalgesia: CNP and PHN -Thermal/mechanical loss without hyperalgesia: CNP and PHN
Baron R *et al,* 2017(25)	PNP 902 (100%)	QST	Three clusters Cluster 1 (sensory loss, 42%) Cluster 2 (thermal hyperalgesia, 33%) Cluster 3 (mechanical hyperalgesia, 24%)
Vollert J *et al* , 2017 (66)	PNP 583 (100%)	QST	Diabetic polyneuropathy: -sensory loss (83%), Peripheral nerve injury: -mechanical hyperalgesia (59%) PHN:

CN*P*= Central neuropathic pain, PN*P*= Peripheral neuropathic pain NPSI=Neuropathic Pain Symptoms Inventory. QST= Quantitative sensory test. CRPS= complex regional pain syndrome. PHN= post-herpetic neuralgia

-mechanical hyperalgesia (63%)

Table 1- Studies on neuropathic pain subgroup classification (continuation)

Study	Patients	Parameters	Results
Baron R *et al* 2009(26)	PNP 2100 (100%)	PainDETECT Questionnaire and QST	More numbness in diabetic neuropathic More dynamic allodynia and thermal hyperalgesia in PHN
Vollert J *et al,* 2016 (29)	PNP 336 (100%)	PainDETECT Questionnaire and QST	-Loss of thermal sensation, more pain evoked by light touch -Loss of mechanical sensation: more numbness and less burning sensations and pain evoked by light touch.
Freeman R *et al.,* 2014(28)	CNP 217 (18.3%) PNP 967 (81.7%)	NPSI and QST	NPSI –three pain dimensions: -provoked - deep -pinpoint. QST–. two pain dimensions: - evoked by cold -evoked by touch.

CN*P*= Central neuropathic pain, PN*P*= Peripheral neuropathic pain NPSI=Neuropathic Pain Symptoms Inventory. QST= Quantitative sensory test. CRPS= complex regional pain syndrome. PHN= post-herpetic neuralgia

1.1 Central post-stroke pain: a controlled symptom-psychophysical characterization

Annually, 15 million people worldwide have strokes. Of these, 5 million die, and another 5 million are left permanently disabled(67). Along with motor, language, and coordination deficits, stroke may also lead to pain in up to 50% of individuals(4,68–70) Post-stroke pain (PSP) includes several different pain syndromes such as musculoskeletal, spasticity-related, headaches, complex regional pain syndrome, and central neuropathic pain (i.e., central post-stroke pain - CPSP)(12,69).

CPSP occurs in 1%-18% of stroke patients(11,12). Its onset is often reported as insidious, and pain frequently arises during the first three months after a stroke, even though it can emerge in the first days or as long as three years later(4,20,39,71). CPSP can compromise the whole side of the body or be restricted to the face, torso, or part of an extremity like hand or foot(20,39,71). Pain intensity has been classified as moderate to severe (20,39,72) and fluctuates along the day, influenced by emotional factors and external factors such as movements, cold, warmth, and touch (20).CPSP has a significant burden impacting life quality(20,39,72).

Leijon *et al.* described symptoms and signs of 27 CPSP patients regarding the stroke type and location (brain-stem= 8, thalamus= 9, extrathalamic= 6, not determined= 4). Most patients reported more than one pain descriptor; the most frequent was burning, reported by 59%, and the second in frequency were aching (30%) and pricking (30%). Icy cold, piercing, pressing, squeezing, smarting, cramping, and throbbing were less reported. Some frequencies differed

according to stroke location(20). However, until now, there is any particular combination of pain qualities characteristic of a specific topography.

Regarding the physical examination, there are no non-sensory findings associated with CPSP(20,71). Sensory examination reveals a set of positive and negative signs, and abnormalities of cold and pain sensibility appear almost universally (20,21,39,51,69,71).In other modalities, such as touch and vibration, sensory loss is less observed, usually comprehending less than half of the studied individuals(20,21). Respecting the positive signs, including allodynia and hyperpathia, were usually present in more than two-thirds of the patients (20,21). QST analysis from different groups has evidenced that all or almost all patients have reduced or lost sensibility for temperature (cold and/or warmth) and pain sensibility, indicating dysfunction of the spinothalamocortical pathways(21)(21)(21)(51)(73)(1)(47). However, the studies are heterogeneous concerning techniques, areas tested, comparative parameters, and the presence or absence of control groups.

As formerly discussed, mechanism-based profiling could be a direction for improving response to treatment. Another possible route is identifying stroke patients with a higher risk of developing CPSP to program targeted early interventions. A single study evaluated the prophylactic treatment of patients with acute thalamic stroke, and the results were negative(74). Perhaps recognizing predictors factors may change this result. Klit *et al.* indicated that the presence of evoked dysesthesia, allodynia, or hyperalgesia within the first four days of stroke onset increased the odds of central pain at six months by 4.6. Furthermore, the combination of reduced or absent sensation to pinprick or cold and early evoked

pain or dysesthesia at onset increased the odds by 8.0. Evoked dysesthesia or pain had a sensitivity of 16%, a specificity of 96 %, and an accuracy of 85%(75).

CPSP is highly refractory to treatments(11,12). Indeed, a number of medications(24) and neuromodulatory approaches(76,77) that have been shown to relieve pain in peripheral neuropathic pain(78,79) have failed to do so in CPSP(63), the mechanisms of which are poorly understood. Significant insights have been gained from neuroimaging (50,80–85), neurophysiology (86–90), basic studies(91–95), and psychophysics (21,47–51,73,96–100), however the integration of a comprehensive clinical characterization of these patients with the concomitant abnormalities of the somatosensory system in a controlled fashion that includes PSP of non-neuropathic origin, by far the most common PSP subtype is missing.

Studies exploring symptom-psychophysics relationships in CPSP are rare, with either no control groups or one composed of healthy individuals or, less commonly, patients without chronic pain (20,21,39,47,51,71–73,75,101). Consequently, there are limitations in determining if the characteristics described are specific to central neuropathic pain or if they could also be attributed to chronic pain in general and the central sensitization process or even to stroke itself. Therefore, controlled studies, including patients with non-neuropathic post-stroke pain and stroke patients without chronic pain, could contribute to dissecting clinical features typical of CPSP or related to other post-stroke pain syndromes or the stroke.

1.2 Lesion location, pain symptoms, and sensory profile in central neuropathic pain

Lesions of the somatosensory system anywhere or at any level along the neuroaxis can lead to CNP (20,50). However, the affected region determines the manifestation of neurological symptoms and signs and also seems to influence pain characteristics(20). This possible variability of neuropathic pain characteristics according to the affected region may be related to the difference in the proportions of involvement of lemniscal and spinothalamic pathways and might bring insights into mechanisms involved in neuropathic pain. Bowsher demonstrated 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 (81).

Furthermore, it remains unknown whether the correlations and findings relating to sensory abnormalities from QST and sensory symptoms are the same in patients with CNP of different etiologies. Indeed, classical studies have reported symptom-somatosensory profile correlations of patients with a single etiology of CNP(18,22,41,44,49,73). For example, in patients with syringomyelia, higher severity of spinal cord injury was associated with more intense deep pain and paresthesia/dysesthesia, while patients with evoked pain had more preserved spinothalamic and lemniscal pathways (22). Additionally, in patients with post-stroke central 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 (73).

Despite these important results, these studies focused on a single etiology of CNP, and 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. In addition, the relationship between the symptoms of CNP, somatosensory impairment, and topography of the central lesion may provide clues about the underlying neuropathic pain mechanisms, but this has been little explored.

Additionally, healthcare providers have contact with symptoms and bedside examination information. Rarely QST is available to guide decision-making. However, several efforts to phenotype patients used QST alone or along pain descriptors, and the relationship between QST information and findings from a comprehensive and standardized bedside sensory examination remains underexplored in neuropathic pain.

1.3 Corticomotor excitability in central neuropathic pain

Several hypotheses have been put forward to explain CNP, including both bottom-up and top-down processes such as thalamic deafferentation, spinothalamic dysfunction, central sensitization, and disinhibition of nociceptive networks (12,15,46). CNP has recently been proposed as a disorder of brain network reorganization(102). Maladaptive neural plasticity in different brain circuits, including the motor system, would play a role in CNP development(102). After stroke and SCI, circuit reorganization with cortical excitability modifications has been described(62,103,104). Maladaptive neuroplasticity is thought to occur

insidiously after injury and to be responsible for the gradual installation of symptoms and signs that are not present right after the injury but, instead, develop insidiously, such as spasticity, mood disorders, chronic pain, and fatigue. However, it remains unclear why patients with generally similar CNS lesions develop different sets of these symptoms. One way to assess plastic changes in the CNS is through cortical excitability (CE) measurements. CE based on motor evoked potentials (MEP) can provide insights into GABAergic, glutamatergic and general neuronal membrane excitability of motor networks.

CE has brought information related to central nervous system diseases characterized by clinical or subclinical impairment of the first motor neuron, including cervical spondylosis, stroke, and motor neuron disease. It has also been helpful in monitoring motor abnormalities and their recovery(105). Interestingly, corticomotor-based CE is sensitive to excitability changes in neuronal networks beyond motor ones (52,106–109). Cortical and subcortical motor circuits can be modulated through excitatory and inhibitory exchanges with the sensory system(110). This influence has been studied for the last two decades(109–111) and is supported by experimental (109–112) and clinical studies(52).

The pain matrix is a fluid system composed of several interacting networks. Thalamus, insula, and anterior cingulate cortex circuits have connections and intercommunications with the motor cortex(84). Indeed, altered motor CE has been observed in different pain syndromes, such as neuropathic pain of peripheral origin, fibromyalgia, and primary headaches(52). The most commonly described findings suggest motor cortex disinhibition with impaired GABAergic neurotransmission, and these changes were found in both

hemispheres(52,86,113). The motor cortex is also the main target for invasive and non-invasive neuromodulation strategies for pain treatment, and it appears to be superior to deep brain stimulation of the thalamus and midbrain(102). Meta-analyses have shown positive effects of repetitive transcranial stimulation on M1 in neuropathic pain(76,114). On the other hand, stimulation of other targets, including the premotor/dorsolateral prefrontal cortex (77), insular, and anterior cingulate cortex, was ineffective (63) in controlled trials for central pain treatment.

These data suggest motor cortex could serve as an entry gate allowing for modulation of neuronal activity when targeted by neuromodulatory interventions but equally allowing for a read-out of part of the global excitability status of extra-motor areas by means of CE measurements. However, despite the potential to probe the corticomotor system to gain mechanistic insights into the development of CNP, the available data is based on a small number of patients, either lacking a control group or using healthy individuals as comparators(46).

Neuropathic pain is considered transetiological, which means several distinct sensory profiles, pain mechanisms, and potentially different responses to treatment within each etiology(28). Therefore, it has been proposed that neuropathic pain mechanisms investigation and treatment should be based on clinical profile and not on the etiology(25,36,115). Thus, it can be expected that the changes in CE intrinsic to the pain condition are similar among patients with central neuropathic pain, regardless of the etiology.

A variety of factors can influence motor cortex excitability, including learning simple motor tasks(116), medications(117), peripheral afferent nerve stimulation(118), motor impairment(105), experimental(109–111), and chronic

pain in general(52), bringing limitations CE interpretation. For example, studies about central neuropathic pain and CE compared patients with healthy individuals(86,88,90) or did not have a control group(99,119), the larger sample size was 21 patients with CPSP(90), and most of the patients were under treatments that affect CE(86,90,99,119). In addition, except for one study that excluded motor impairment, this variable was not adequately controlled(88). Considering these multiple factors, it is still not possible to conclude that CE abnormalities are specific to neuropathic pain, chronic pain in general, or CNS disease.

CE is an additional tool for understanding neuropathic pain mechanisms. However, studies in this area are still scarce, and several points are to be clarified. A systematic review of cortical excitability and CPSP included four studies, the main limitations in the interpretation of the results were the heterogeneity in the CE parameters, lack of controls with stroke and without pain, and it was not possible to assess the impact of drugs and functional disability(46).

Objectives

2. Objectives

I. In order to dissect CPSP from PSP and stroke in general, we compared a sample of CPSP patients with non-neuropathic PSP patients and stroke patients without chronic pain matched for sex, age, and stroke location. We have evaluated stroke characteristics, neuropathic pain symptoms, bedside examination, and static and dynamic QST across groups to provide a deep-phenotyping of CPSP and describe potential symptom-QST correlations specific to CPSP that could be used in the future in preventive or therapeutic trials;

II. We described and compared the sensory profile of CNP through pain descriptors, standardized bedside examination, and a comprehensive QST battery in two different etiologies of CNS lesions related to distant and nosologically different lesion sites: one affecting the brain (stroke) and another mainly affecting the spinal cord (neuromyelitis optica spectrum disorder, NMOSD, under remission);

III. To describe CE changes attributable to CNP after CNS injury, we compared CNP associated with brain injury after stroke or spinal cord injury (SCI) due to NMOSD to patients presenting similar CNS injury that developed non-neuropathic pain after injury and those without chronic pain, matched by sex and lesion location (for stroke: cortical, subcortical and brainstem, and cerebellum; and SCI: cervical and thoracic), through a battery of CE measurements and a comprehensive pain, neurological, functional, and quality of life assessments. In order to have information on CE abnormalities

on an individual basis, we also classified patients' CE parameters according to normative data from age and sex-matched healthy individuals(106)

Methods

3. Methods

This study had a controlled cross-sectional design, part of the Central Pain Initiative Project, an umbrella project coordinated by the Pain Center, Division of Neurological Clinic and Division of Neurosurgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, focused on assessing and treating central neuropathic pain (14,63). General clinical data of patients with spinal cord injury secondary to NMOSD were previously reported in publications from this initiative(14,64).

Standard protocol approvals and patient consent

Data collection occurred at the Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). It was approved by the Institution's Ethics Review Board (No. 690.455) (Annexe A). All patients were volunteers, informed about the procedures, and provided written informed consent before inclusion in the study (Annexe B). No financial compensation was offered for study participation. Neuroimaging findings from part of these patients have been reported elsewhere(120).

3.1 Central post-stroke pain: a controlled symptom-psychophysical characterization

In this part of the study, we aimed to compare pain characteristics and sensory profile of central post-stroke pain patients (CPSP) with two control groups: i. patients with non-neuropathic post-stroke pain (PSP-Non), and ii. stroke patients without chronic pain (No-pain). The three groups were matched

according to sex, age, and stroke area (divided according to the most symptomatic stroke area: cortical, subcortical, and brainstem and cerebellum).

3.1.1 Patients

According to clinical evaluation and imaging information, two neurologists trained in pain management and one neuroradiologist (LMB, JRJr, and LTL) classified each patient's pain syndrome. All cases were confirmed by a board (DCA, MJT), and only cases where all evaluators agreed upon the pain classification were included (10,12). All participants had suffered an ischemic or hemorrhagic stroke at least three months before the evaluation, confirmed by imaging (CT or MRI). Annexes C and D. Exclusion criteria were major cognitive or language impairments that would compromise filling in questionnaires or sensory examination (Figure 1). 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). This granted that mirror areas had no sensory deficits due to previous strokes.

CPSP group

The CPSP sample was composed of patients consecutively referred to the pain center by neurologists or primary care physicians and fulfilling the following criteria: a. definite diagnosis of neuropathic pain according to the NeuPSIG/IASP (IASP Special Interest Group on Neuropathic Pain) grading system for neuropathic pain (10); b. occurrence of *de novo* pain attributed to a central lesion due to stroke; c. pain characteristics not compatible with other etiologies of pain (previous fibromyalgia, migraine, nociceptive pain)(12).

Control groups

CPSP patients were compared to two control groups: i. post-stroke pain that was non-neuropathic in nature (PSP-Non), and ii. stroke patients without chronic pain (No-Pain). These groups were recruited from the cerebrovascular diseases outpatient clinic of the Department of Neurology, University of São Paulo. They were matched according to sex, age, and stroke location (i.e., divided into three macro-regions: cortical, subcortical, and brainstem/cerebellum, by a blinded neuroradiologist)(121).

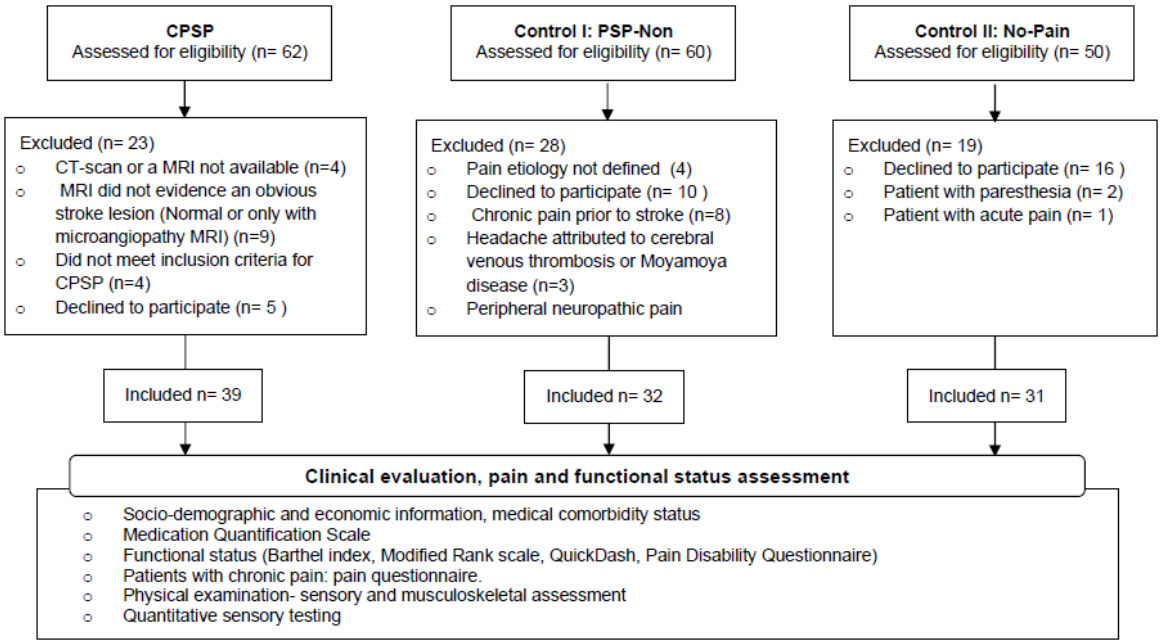
The PSP-Non group

Post-stroke painful symptoms present most days for longer than three months) with a clear non-neuropathic etiology (i.e., muscle spasms, spasticity, headache, musculoskeletal pain / myofascial pain syndrome, frozen shoulder), in the absence of concomitant neuropathic pain according to the IASP/NeuPSIG grading system. In addition, the presence of chronic pain before the stroke was an exclusion criterion for the PSP-Non group(12).

The No-Pain group

Included patients without chronic pain before or after stroke and no episode of acute pain (e.g., episodic headaches) within the seven days preceding the clinical evaluation.

Figure 1 - STROBE flow diagram of stroke patients recruitment according to pain characteristics



CPSP: Central post-stroke pain. PSP-Non: Non-neuropathic post-stroke pain. No-Pain: stroke patients without chronic pain. CT: computerized tomography. MRI: magnetic resonance imaging.

3.1.2 Assessments

Participants were assessed in a single visit. They underwent a clinical evaluation, which included an analysis of current symptoms and limitations, and a physical examination focused on sensory musculoskeletal systems. Sociodemographic information, medical comorbidity status, and medication use were registered (Annexe E). Concomitantly, functional scores, and questionnaires to evaluate pain, incapacity, mood, and catastrophization, all validated in Brazilian Portuguese language, were also filled out as detailed below.

3.1.2.1 Functional assessment

The subsequent scales were employed to assess functional status (Annexe F).

a. Barthel index(122),(123): quantifies the level of independence, which varies from 0 to 100 (100 is totally independent, and 0 is entirely dependent on daily activities);
b. Modified Rankin scale (mRS)(123),(124) : seven-point scale for functional outcome after stroke anchored at 0 =asymptomatic and 6 = death;
c. Shortened disabilities of the arm, shoulder, and hand questionnaire (QuickDash)(125): assess disability, limitations for social activities and work, the severity of pain, and the interference with sleep, related to arm, shoulder, and hand symptoms (i.e., a 100-point scale; the higher the score, the worse the upper limb disability(126);
d. Pain Disability Questionnaire (PDQ)(127),(128): it is composed of two factors: i- functional status component (maximum score of 90) and ii- psychosocial component (maximum score of 60). The total PDQ score consists of all items sum (maximum score of 150, with higher scores indicating more severe disability).

3.1.2.2 Pain scales and questionnaires

The following questionnaires were used to assess pain in the CPSP and PSP-non groups (Annexe F):

a. Short-form McGill Pain Questionnaire (SF-MPQ): pain descriptors are divided into three dimensions: sensory (eight items), affective (five items),

and evaluative (two items)(129). Sensory, affective, evaluative, and total descriptors are obtained by counting the words chosen by the patient(129),(130);

b. Brief Pain Inventory (BPI): measures pain intensity (least, average, now, and worst pain in the last 24 hours, each ranging from 0- no pain to 10- maximal pain imaginable); and interference scores (general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life, with a total score ranging from 0 to 70, where higher scores mean higher inference of pain in daily activities)(131),(132);
c. Douleur Neuropathique Questionnaire-4 (DN-4): a screening test for neuropathic pain composed of ten items. It ranges from 0 to 10 and is positive when ≥ 4(133),(134);
d. Neuropathic Pain Symptoms Inventory (NPSI): a qualitative and quantitative inventory of different neuropathic pain descriptors that enables the evaluation of different phenotypes through discrimination and quantification of five distinct clinically relevant dimensions of neuropathic pain: burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. Its total score ranges from 0-100, and each dimension's score ranges from 0-10, with higher scores indicating more intense symptoms(23),(135). Recently, a new cluster has been proposed, classifying patients into three groups according to an artificial intelligence algorithm applied to the scores of each item: pinpointed, deep, and provoked pain (136). In addition, ROC curve analysis assessed the cut-off point of the NPSI total score differentiating neuropathic from non-neuropathic pain.

3.1.2.3 Quality of life, mood, and catastrophization assessment

a. The Short Form 12- Health Status Questionnaire (SF-12): measures health-related quality of life and is composed of 12 items that generate two scores related to physical health (PCS) and mental health (MCS). Each score ranges from 0 to 100; the higher the score, the greater the health-related quality of life(137);
b. Hospital Anxiety and Depression Scale (HAD): evaluates symptoms of anxiety and depression; Higher scores mean more severe symptoms. Scores of eight for anxiety and nine for depression were used as cut-off values(138),(139);
c. The Pain Catastrophizing Scale: assesses catastrophic thoughts or feelings accompanying the experience of pain. This scale consists of thirteen items on a Likert scale. The total scale score ranges from 0 to 52; higher scores represent greater catastrophic thinking(140).

3.1.2.4 Physical examination

Physical examination –musculoskeletal assessment

Spasticity in the upper and lower limbs was quantified according to the modified (m-) Ashworth spasticity scale (AS), in which higher values indicate more severe spasticity(141). It was classified into three categories –absent, low to moderate (m-AS 1 or 2 in at least one limb), and moderate to severe (m-AS score above 2 in at least one limb)(142). Muscle strength was measured according to the Medical Research Council (MRC) scoring system. Motor

impairment degree was grouped into four severity grades–grade 0 (MRC in all limb=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)(143). Myofascial trigger points (TP) were evaluated bilaterally in standardized regions, including temporal, masseter, scalene, trapezius, pectoralis major, levator scapulae, rhomboid, supraspinatus, biceps brachii, triceps brachii, wrist, and finger extensors, first dorsal interosseous, quadratus lumborum, gluteus maximus, piriformis, vastus lateralis, and gastrocnemius muscles(144). Briefly, TP was looked for with 4 kg/cm^2 of pressure using the thumb (just enough to blanch the examiner's nailbed)(145). Active TP was considered present when digital pressure evoked pain in a corresponding referred pain pattern and resembled at least 50% of the patients' clinical pain(14,146) (Annexe E).

Sensory assessment –bedside examination

The sensory assessment employed standardized bedside examination, including the evaluation of superficial touch 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. Regions of the face, trunk, arms, and legs were tested, comparing them with the contralateral side and proximal and distal body regions(14). Hyperpathia was assessed with a pin: patients were asked to quantify the evoked pain during examination using the numeric rating scale (NRS: 0-10, where 0 means no pain and 10 maximal pain imaginable) after one stimulus and after a train of 10 stimuli delivered at 1Hz(147). Allodynia intensity (NRS) differentiating neuropathic from non-

neuropathic pain patients was assessed through ROC curve analysis (Annexe E).

3.1.2.5 Static and dynamic quantitative sensory testing

CPSP patients underwent a static QST battery to assess sensory findings at the site of the most severe neuropathic pain area (pain area) and the corresponding contralateral site (mirror area) (20,47,48). PSP-Non and No-Pain groups were tested over the area of most severe motor/sensory abnormalities (contralateral to stroke) and their respective asymptomatic mirror area. If the patient presented bilateral symptoms, the worse area was tested, and the contralateral mirror area was used as the control side. In all areas, the following QST parameters were tested according to previously described techniques: briefly, cold detection threshold (CDT), warm detection threshold (WDT), mechanical detection threshold (MDT), vibration detection threshold (VDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain threshold (MPT), and the numerical pain rating scale for suprathreshold cold (STCP), suprathreshold heat pain (STHP), suprathreshold mechanical pain (STMP) and wind up ratio (WUR) were evaluated. The tests were assessed by the method of limits(63),(148) (Annexe G).

Results were analyzed in three outputs according to specific research questions:

i. Side-to-side differences: comparisons were made within-subjects (pain or affected area vs. mirror area (21,47,48,50,51,73,149–151)), and a QST index of asymmetry was obtained to assess differences between groups so

that threshold or hyperalgesia indices for each QST parameter was calculated according to the formula: $\text{value from the test area}$/value from the mirror area;

ii. Single-patient classification: single QST results from each parameter were classified as normal or abnormal according to Rolke *et* al., 2006 recommendations for side-to-side comparisons(40), so that a ratio (values from tested area/ values from the mirror area) was calculated and considered abnormal if it was above or below the following lower and upper cut-off values for CDT (0.41–2.42), WDT (0.42–2.39), MDT (0.38–2.62), MPT (0.4–2.53), WUR (0.52–1.94) (40). For CPT and HPT, the difference between results from test and mirror areas ($\text{test area} - \text{mirror area}$) was calculated and considered abnormal if it was above or below the following lower and upper cut-off values: CPT (-10.3°C–10.3°C) and for HPT (- 4.2°C – 4.2 °C)(40). For VDT, STCP, STHP, and STMP, abnormal values were considered for indices below 0.4 or above 2.5. Secondly, patients were classified according to the presence of loss or gain of somatosensory function, as previous Maier C. et al. 2010 classification (1): L: loss, G: gain. Normal values were coded as L0.L1: loss of thermal detection (cold or warm detection threshold).L2: loss of mechanical detection (mechanical or vibratory detection threshold). L3: loss of thermal and mechanical detection. G0: normal values. G1: gain of function in heat or cold pain threshold. G2:gain of function in mechanical pain detection threshold or dynamic mechanical allodynia. G3: gain of function in thermal and mechanical stimuli;

iii. Thermal limen assessment: since warm and cold detection thresholds were the sensory modalities reported to be more starkly altered in CPSP (21,47,48,50,51,73,149,150), a "thermal ratio" was created consisting of $\text{CDT pain area x WDT mirror}/\text{CDT mirror x WDT pain area}$ .This CDT/WDT thermal ratio is analogous to the "sensory limen" (148) or the sensitivity index proposed by Jansen et al., 1991(152) and used by Vestergaard et al., 1995(149)). It was intended to illustrate unbalance between cold and warm detection thresholds (which has been associated with experimental allodynia under the thermal grill illusion of pain) in spinal cord injury patients(153,154).

Pressure pain threshold (PPT) was assessed with an algometer (Pain Diagnostics & Thermograph Inc, Great Neck, NY) in patients with chronic pain in the same muscles tested in the myofascial pain investigation, as described above. The rubber tip of the algometer was vertically positioned on the point to be examined. The pressure was continuously increased at approximately 1kg/second until the subject reported the triggering of pain or discomfort. PPT was considered the lowest pressure value-generating pain at each point (155). Furthermore, the deep pressure hyperalgesia [i.e., the intensity of the pain (0-10 NRS) generated by a three second-stimulation at the PPT+ 2 Kg/cm² was also measured for each muscle site(156).

Dynamic QST was assessed by conditioned pain modulation (CPM) and was evaluated by measuring the pain intensity of a stimulus (test-stimulus-suprathreshold heat pain stimulus over the thigh not affected by stroke) which was then repeated after a painful tonic stimulus (conditioning cold pressor test –

immersion of the contralateral hand)(55),(157). CPM was reported as the evoked pain intensity difference between the conditioned and unconditioned test stimuli (Annexe H).

3.1.3 Statistical analysis

Categorical variables were represented by frequencies, percentages, and absolute numbers. Quantitative variables were tested for normal distribution using Kolmogorov-Smirnoff tests, Q-Q plots, and histograms. The Kruskal-Wallis test was employed for comparisons of non-parametric quantitative variables between the three groups. The Mann-Whitney test was applied for comparisons of non-parametric quantitative variables between two groups, and the Bonferroni correction was used for multiple comparisons. The Chi-square and Fisher's exact test were used to compare the nominal and ordinal qualitative variables between groups. The odds ratio and 95% confidence intervals (CI) were calculated to assess the relationship between neuropathic pain and somatosensory abnormalities assessed through physical examination and QST. Spearman coefficients were used to assess the correlation between variables found to be significantly different. Correlations with a correlation coefficient >= ± 0.4 were included in logistic regression analyses. Basic assumptions were checked before the test, including independence of errors, linearity in the logit for continuous variables, absence of multicollinearity, and lack of strongly influential outliers.

The study size was estimated based on the proportion of the most prominent finding on QST in CPSP (mechanical allodynia) according to one of the largest studies to date (151). This convenience sample with 31 patients in the

smallest group allowed us to detect a difference in the proportion of around 23% between chronic pain groups with a power of 80% and a type I error set at 5% bilaterally. The estimated sample size was also in line with the CPSP sample size of previous studies (20,21,39,47,51,71–73,75). The level of significance considered was 5%.

Since it was an exploratory study, adjusting for multiple testing was not mandatory. However, we opted to evaluate the subgroup analysis with a pairwise correction to distill the more robust findings that could be inputted into the regression model(158), so Bonferroni correction for multiple testing was performed when indicated.

3.2 Lesion location, pain symptoms, and sensory profile in central neuropathic pain: comparison between central neuropathic pain secondary to stroke and central neuropathic pain secondary to spinal cord injury due to NMOSD

Here we aimed to compare pain characteristics and sensory profile of CNP secondary to stroke (CPSP) to central pain secondary to spinal cord injury in NMOSD (CPSCI).

3.2.1 Patients

Patients from the CPSP group were the same mentioned in the section “2.1.1 Patients – CPSP patients”. CPSCI patients were previously studied in another sphere of the umbrella project on central pain (14,64). They were consecutively referred to the Pain Center of the HC-FMUSP by neurologists or primary care physicians, fulfilling the following criteria: a. definite diagnosis of neuropathic pain according to the NeuPSIG/IASP (IASP Special Interest Group

on Neuropathic Pain) grading system for neuropathic pain (10); b. occurrence of de novo pain attributed to a central lesion due to spinal cord injury; c. pain characteristics not compatible with other etiologies of pain (previous fibromyalgia, migraine, nociceptive pain)(12). Pain classification was made by two researchers (FVS and DCA). Had previous myelitis secondary to NMOSD diagnosed by a neuroinflammatory diseases specialist (SLAP) using the revised diagnostic criteria(159). CPSCI patients needed to be in remission of their inflammatory disease with no relapses within the 12 months preceding the evaluation, according to clinical assessment and patient report to avoid evaluation during its acute, inflammatory phase, which could be a confounding factor. Exclusion criteria were significant cognitive or language impairments that compromised answering questionnaires or undergoing sensory examination.

3.2.2. Assessments

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 also applied to evaluate pain (Short-form McGill Pain Questionnaire –SF-MPQ(129), Brief Pain Inventory–BPI(131),, and Neuropathic Pain Symptoms Inventory – NPSI(23)), anxiety and depression (Hospitalar Anxiety and Depression Scale- HAD(138)) and disability (Functional status: Barthel index(122)).NPSI 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](23), and NPSI stratification of patients in three clusters (deep pain, pinpointed pain and evoked pain)(32). Physical examination included spasticity, motor impairment, and sensory assessment as described in the section “2.1.2.4 Physical examination. “

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 (20,47,48) 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(63,148): 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 (STCP), suprathreshold heat pain (STHP), suprathreshold mechanical pain (STMP) and wind up ratio (WUR). Since warm and cold detection thresholds were the sensory modalities reported to be more altered in CNP(21,47,48,50,51,73,149,150), a “cold thermal limen” and “heat thermal limen” was calculated consisting of $CDT - CPT$ and $HPT - WDT$ respectively(148,149).

To evaluate differences between the neuropathic pain and the control area, a QST ratio was calculated according to the formula: $\text{value from the pain area}$/value from the control area) for CDT, WDT, MDT, MPT, STCP, STHP, STMP, and WUR(21,40,47,48,50,51,73,149–151). For CPT and

HPT, the difference between the results from the tested and control areas ($\text{pain area} - \text{control area}$) was calculated(40).

3.2.3 Statistical analysis

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(18,21,45,47,48,73,97,151,160). The non-parametric group differences between CPSP vs. CPSCI were compared using a Mann-Whitney *U* test. The Chi-square and Fisher's exact test were used to compare the nominal and ordinal qualitative variables between groups. Parametric data are displayed in the text as the mean ± standard deviation, non-parametric data as median, percentile 25 and 75, 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.

3.3 Corticomotor excitability in central neuropathic pain compared with non-neuropathic pain or pain-free patients

This part of the study compared the cortical excitability profile of CNP secondary to stroke (CPSP) or spinal cord lesion in NMOSD (CPSCI) with two

control groups: i. patients with non-neuropathic pain after stroke or spinal cord lesion due to NMOSD (Non-neuropathic pain) and ii. stroke and spinal cord lesion in NMOSD patients without chronic pain (No-pain).

3.3.1. Patients

According to clinical evaluation and imaging information, three neurologists trained in pain management (Stroke patients: LMB and JRJr, SCI patients: FVS) and one neuroradiologist (LTL) classified each patient's pain syndrome. All cases were confirmed by a board (DCA, MJT), and only patients with consensual pain classifications were included. Stroke patients' general inclusion and exclusion criteria were mentioned in the section "2.1.1 Patients". Patients with SCI secondary to NMOSD were diagnosed by a neuroinflammatory diseases specialist (SLAP) using the revised diagnostic criteria(159). They needed 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 two months before inclusion. Exclusion criteria were significant cognitive or language impairments that compromised answering questionnaires or undergoing sensory examination, the presence of conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head or within 30 cm of the transcranial magnetic coil, presence of seizures within the previous six months, and undetectable motor evoked potential due to an extensive CNS lesion even in stimulation intensities at 100% of maximal stimulator output.

The neuropathic pain group was composed of patients consecutively referred to the pain center by neurologists or primary care physicians and fulfilling the following criteria: a. definite diagnosis of neuropathic pain according to the NeuPSIG/IASP (IASP Special Interest Group on Neuropathic Pain) grading system for neuropathic pain (10); 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)(12).

Control groups

Controls were recruited from the cerebrovascular diseases outpatient clinic and the neuroimmunology outpatient clinic from the Department of Neurology, University of São Paulo. i. Non-Neuropathic pain group: post-stroke and post-spinal cord injury painful symptoms present most of the days for longer than three months) with a clear non-neuropathic etiology (i.e., muscle spasms, spasticity, headache, musculoskeletal pain / myofascial pain syndrome, frozen shoulder), in the absence of concomitant neuropathic pain according to the IASP/NeuPSIG grading system(12). II. No-pain group: patients without chronic pain before or after stroke or spinal cord lesion and no episode of acute pain (e.g., episodic headaches) within the seven days preceding the clinical evaluation.

3.3.2Assessments

In this part of the study, we included sociodemographic information, medical comorbidity status, medication use, standardized physical examination focused on sensory and musculoskeletal systems (as mentioned in the section “2.1.2.4

Physical examination “), functional status (Barthel index(122))questionnaires to evaluate pain (Pain scales and questionnaires: Short-form McGill Pain Questionnaire (SF-MPQ)(129), Brief Pain Inventory (BPI)(131), Douleur Neuropathique Questionnaire-4 (DN-4) (133) and Neuropathic Pain Symptoms Inventory (NPSI) (136)·, mood (Hospital Anxiety and Depression Scale (138)), and catastrophization (The Pain Catastrophizing Scale: (140)·).

Cortical excitability

Cortical excitability evaluation was carried out with transcranial magnetic stimulation (TMS) to obtain measures of resting motor threshold (RMT), motor evoked potentials (MEP), short interval intracortical inhibition (SICI), and intracortical facilitation (ICF) in both hemispheres. A circular coil (MC-125) was placed in the anteroposterior direction, tangential to the scalp region corresponding to the motor area M1. An amplifier module (Magventure Tonika Elektronic, Denmark) and surface electrodes (Alpine Biom, Skovlunde, Denmark) were used to record motor evoked potentials in the first interosseous of the contralateral hand on the side stimulated. Patients were seated in a quiet room and kept their hands relaxed. Three surface electrodes were placed in the first interosseous contralateral to the side to be stimulated — one on the muscle belly, another on its tendon, and the third on a site far from the other two for grounding. The hotspot localization was made by performing a stimulus every two seconds to find the area of stimulation that evoked the largest MEP. Once the hotspot was found, its location was marked on a cap. The rest motor threshold was considered the lowest output intensity capable of eliciting a 50 μv motor evoked potential in

five out of ten trials and is represented as a percentage of maximal generator output.

MEP amplitude was measured from peak to peak at two intensities, 120% and 140% of RMT, two-time points where MEPs are more variable in the input-output curves. A proxy of the stimulus-response curve was provided by the ratio of MEPs obtained at 140% and 120% of RMT (MEP 140/120) (63,161). In each hemisphere, we performed four pulses for each MEP and averaged responses. Short-interval intracortical inhibition (SICI) was conducted through paired pulses with conditioning intensities set at 80% RMT, followed by a test stimulus at 120% RMT. Interstimulus intervals of 2 and 4 ms were used to investigate short intracortical inhibition and 10 and 15 ms to investigate intracortical facilitation. The mean result of the four trials was considered. Short intracortical inhibition was calculated as a ratio of the conditioned and unconditioned MEPs delivered in an interstimulus interval (ISI) of 2ms and 4ms. A similar ratio was calculated for intracortical facilitation, but after measurements performed at 10ms and 15ms ISI (106,107,161) (Annexe I).

We classified individual parameters of RMT, MEP 120, MEP 140, SIC, and FIC according to previous published normative data of cortical excitability from healthy subjects, adjusted according to age (above or below 50 years) in“low,” “normal,” or “high” for each parameter(106).

3.3.3 Statistical analyses

We compared results according to the pain groups (neuropathic pain, non-neuropathic pain, and no-pain) and CNS lesion type (stroke or SCI). For stroke

patients, we also compared the affected with the unaffected hemispheres. Following these analyses, we grouped patients with both etiologies of CNS injury for the following comparisons. First, we considered CE parameters from the hemisphere affected by the CNS injury in stroke patients and averaged results from both hemispheres for SCI patients. Additionally, we compared individual results to normative data of cortical excitability from healthy subjects and classified patients' results as low, normal, or high(106) for each parameter.

For patients with brain injury (stroke), we considered analysis of the affected and unaffected hemisphere, while for patients with SCI, since the parameters were statistically similar between the hemispheres, we considered the mean of both sides. According to previously published normative data, cortical excitability parameters were evaluated as a categorical variable and as a numeric variable.

Categorical variables were represented by absolute numbers and percentages. The Chi-square test and Fisher's exact test were used to compare the nominal variables between the three groups. Quantitative variables were represented by mean and standard deviation. They were tested for normal distribution using Kolmogorov-Smirnoff tests, Q-Q plots, and histograms. The Kruskal-Wallis test was employed to compare non-parametric variables between the three groups. The Mann-Whitney test was applied to compare non-parametric quantitative variables between two groups. The Bonferroni correction was used for multiple comparisons for pairwise evaluation. Spearman coefficients were used to assess the correlation between variables found to be significantly different. The level of significance considered was 5%. This was a convenience sample with 43 patients in the smallest group allowing the detection of a

difference in the proportion of around 20% between chronic pain groups with a power of 80% and a type I error set at 5% bilaterally. The estimated sample size was in line with the CNP sample size of the previous studies in CE(162).

Results

4. Results

4.1 Central post-stroke pain: a controlled symptom-psychophysical characterization

4.1.1 Sample characteristics

A total of 102 stroke patients were evaluated; 39 had central neuropathic pain due to stroke (CPSP group), 32 patients had chronic pain of non-neuropathic origin with onset post-stroke - (PSP-Non group), and 31 were pain-free (No-pain) (Figure 1). The mean age was 59.4 (±11.9) years, with no significant differences among groups (p= 0.28). Male patients made up 64.7% of the total sample, and most medical comorbidities were similar between groups (Table 2 and Table 3).

Table 2- Sociodemographic characteristics and comparative analysis between stroke patients grouped according to pain syndrome

	Group according to pain classification							
	CPSP n =39	PSP-Non n =32	No-Pain n =31	Total n =102	P between groups	CPSP x PSP-Non	CPSP x No-Pain	PSP-Non x No-Pain
Age (years)	59.2(11.2)	61.9 (11.1)	57.1 (13.3)	59.4 (11.9)	0.281			
Sex (Male)	23 (59.0%)	19 (59.4%)	24 (77.4%)	66 (64.7%)	0.207			
Educational level								
Low[a]	14 (35.9%)	19 (59.4%)	15 (48.4%)	48 (47.1%)	0.055			
Medium[b]	19 (48.7%)	10 (31.3%)	7 (22.6%)	36 (35.3%)				
High [c]	6 (15.4%)	3 (9.4%)	9 (29.0%)	18 (17.6%)				
Working	2 (5.1%)	6 (18.8%)	11 (35.5%)	19 (18.6%)	0.005*	0.071	0.001†	0.135

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. *$p<0.05$, † $p<0.0167$ (pairwise comparisons Bonferroni correction for multiple comparisons).[a]Low: middle, elementary school, or no education. [b]Medium: high school. [c]High: bachelor's degree or higher. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain.

Table 3 -Medical comorbidity and Body Mass Index characteristics and comparative analysis between stroke patients grouped according to pain syndrome

	Group according to pain classification							
	CPSP n=39	PSP-Non n =32	NO-Pain n=31	Total n =102	P between groups	CPSP x PSP-Non	CPSP x No-Pain	PSP-Non x No-Pain
Medical history								
Diabetes	10 (25.6%)	13 (40.6%)	8 (25.8%)	31 (30.4%)	0.315			
Hypertension	33 (84.6%)	28 (87.5%)	24 (77.4%)	85 (83.3%)	0.542			
Heart disease	8 (20.5%)	16 (50.0%)	14 (45.2%)	38 (37.3%)	0.021*	0.009†	0.027	0.701
CKD	1 (2.6%)	7 (21.9%)	2 (6.5%)	10 (9.8%)	0.025 *	0.019	0.580	0.148
Depression	10 (25.6%)	6 (18.8%)	4 (12.9%)	20 (19.6%)	0.407			
Currently smoking:	7 (17.9%)	4 (12.5%)	3 (9.7%)	14 (13.7%)	0.674			
Body Mass Index(Kg/m²)	28.0 (4.6)	26.1 (3.7)	27.0 (4.4)	27.1 (4.3)	0.136			

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation *$p<0.05$, † $p<0.0167$ (pairwise comparisons Bonferroni correction for multiple comparisons).CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. CKD: Chronic kidney disease.

4.1.2 Stroke characteristics

The stroke location (cortical, 38.2%, subcortical, 37.3%, brain stem/cerebellum, 24.5%), the time elapsed since stroke (47.7±44.3 months), the event type (ischemic 86.1%, hemorrhagic 13.9%), and the number of lesions (20.6% had more than one) were distributed similarly in the three groups, with no significant differences among them (Table 4).

Table 4 - Stroke characteristics regarding the event type, location, and symptomatic side, and comparative analysis between stroke patients grouped according to the pain syndrome

	Group according to pain classification				
	CPSP	PSP-Non	No-Pain	Total	p
Time elapsed after stroke	n= 38 55.1(58.0)	n =32 51.0 (38.9)	n= 31 35.2(24.0)	n =101 47.7 (44.3)	0.268
Event type	N= 38	N =32	N =31	N =101	
Hemorrhagic Ischemic	8 (21.1%) 30 (78.9%)	2 (6.3%) 30 (93.8%)	4 (12.9%) 27 (87.1%)	14 (13.9%) 87 (86.1%)	0.179
Stroke side	N=39	N=32	N=31	N=102	
Right Left Bilateral	22 (56.4%) 11 (28.2%) 6 (15.4%)	14 (43.8%) 12 (37.5%) 6 (18.8%)	10 (32.3%) 17 (54.8%) 4 (12.9%)	46 (45.1%) 40 (39.2%) 16 (15.7%)	0.229
Symptomatic side					
Right Left	14 (35.9%) 22 (56.4%)	13 (40.6%) 14 (43.8%)	14 (45.2%) 8 (25.8%)	41 (40.2%) 44 (43.1%)	0.064
Stroke location					
Cortical Subcortical Brainstem and cerebellum	11 (28.2%) 20 (51.3%) 8 (20.5%)	13 (40.6%) 11 (34.4%) 8 (25.0%)	15 (48.4%) 7 (22.6%) 9 (29.0%)	39 (38.2%) 38 (37.3%) 25 (24.5%)	0.178
More than one lesion	8 (20.5%)	9 (28.1%)	4 (12.9%)	21 (20.6%)	0.342

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. NO-Pain: Stroke without pain

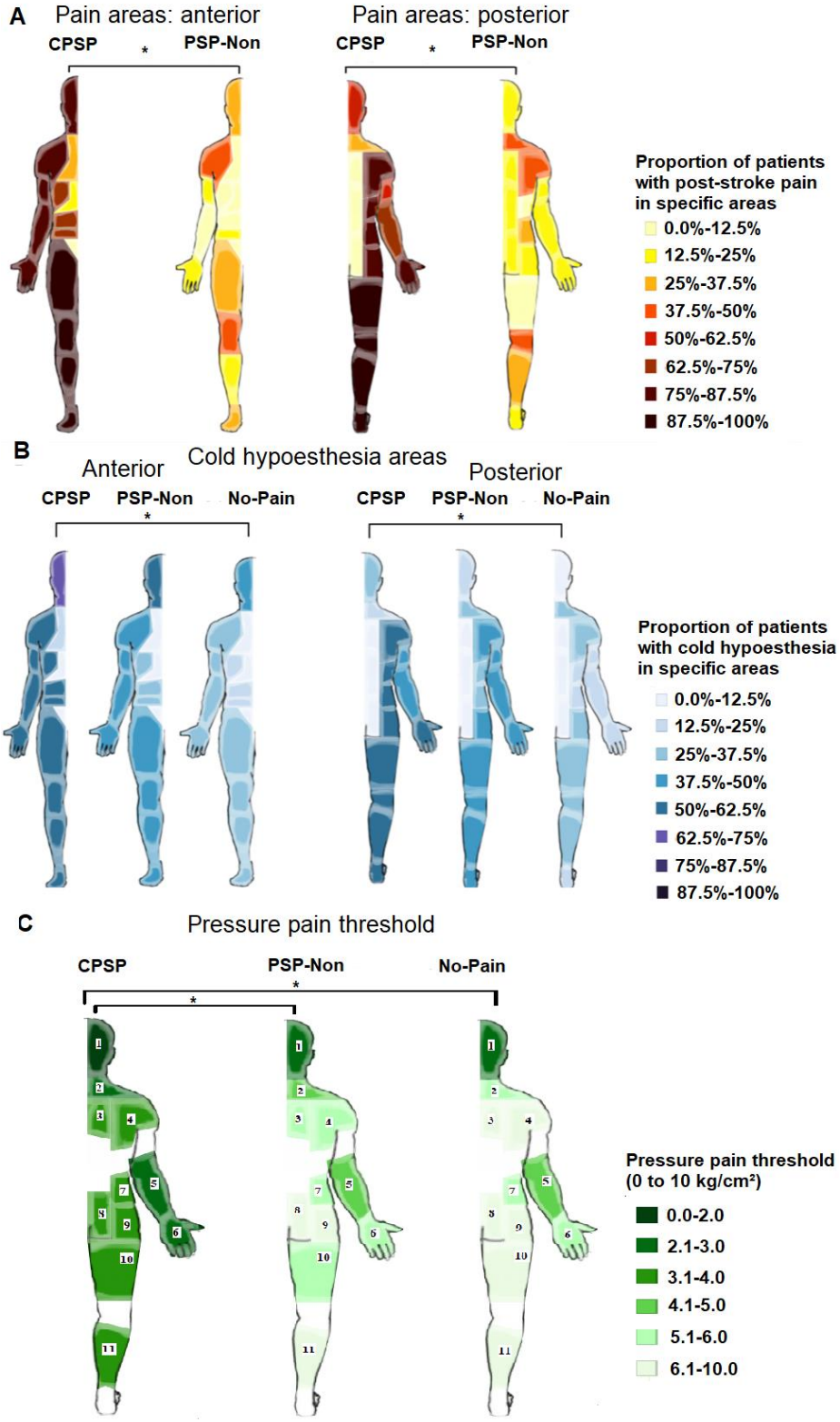
4.1.3 Pain characteristics

The mean duration of pain was 47.3 (±47.2) months without difference between groups (p=0.949). CPSP pain was mainly located in the face, upper and lower limbs (Figure 2), 79.5% of CPSP patients (n=31) considered their pain as continuous compared to 40.6% in the PSP-Non group (n=13), p= 0.001. Pain in the PSP-Non pain

group was mainly axially located: in the neck, shoulders, and knees (Figure 2). Pain occurred within body areas presenting sensory abnormalities confirmed on physical examination in 100% of CPSP patients and 37.5% of PSP-Non patients (p<0.001). The spatial distribution pattern of pain areas in this subgroup of PSP-non patients was similar to the rest of the PSP-Non group (Figure 3). In all cases, these patients had a clear etiology for their pain as a non-neuropathic origin (i.e., osteoarthritis, spasticity, tendinitis, or bursitis) and a negative DN-4. The most common pain type in the non-neuropathic pain group was musculoskeletal pain. Exclusive musculoskeletal pain made up 68.8% (n=22), chronic headache (more than 15 days per month for three months), 12.5% (n=4), and headache associated with musculoskeletal pain 18.8% (n=6) of this group.

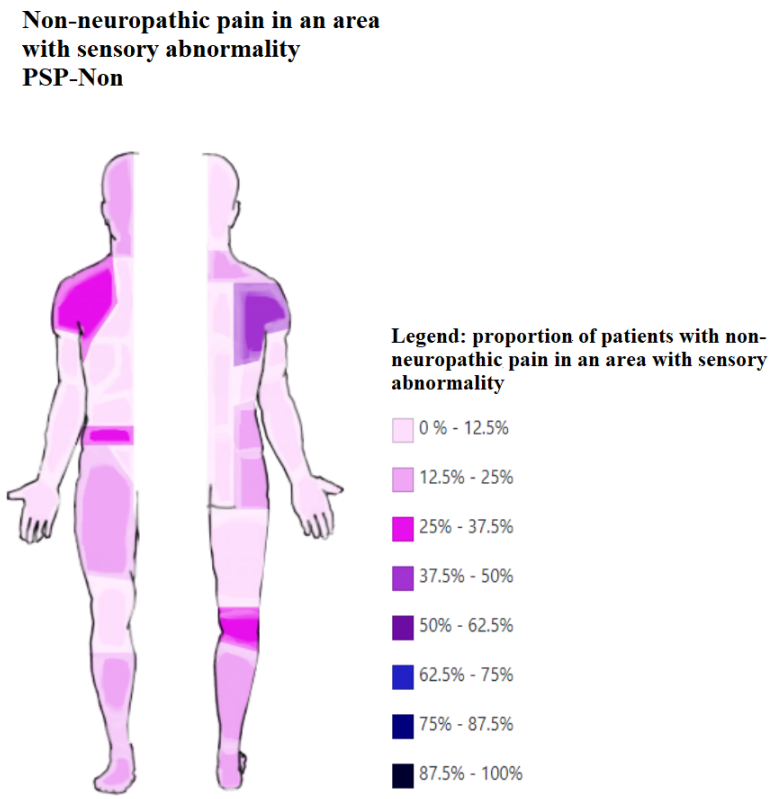
Except for one CPSP patient, all others had previously been diagnosed with neuropathic pain and received pain treatment since they were recruited from the Central Pain outpatient clinic. This contrasts with 46.9% (n=15) of patients in the non-neuropathic pain group recruited from the Cerebrovascular outpatient clinic, who had not been given a diagnosis concerning their pain symptoms until the first evaluation for this research. Furthermore, 25% (n=8) were not undergoing any pain treatment. The median time of treatment was lower in the PSP-Non, 12 months, ranging from 0 to 120, compared to CPSP, median of 36 months, ranging from 0 to 276.

Figure 2- Pain area, cold hypoesthesia, and pressure pain threshold distribution according to pain groups frequency



Pain area distribution according to pain groups.* p was <0.05 for all areas except pelvic and lumbar regions. B– Cold hypoesthesia distribution. *p<0.0167 (with Bonferroni correction for multiple comparisons). C- Pressure pain threshold *p<0.0167 (with Bonferroni correction for multiple comparisons). Tested areas 1= temporal and masseter,2=trapezius, 3= rhomboid, 4= levator scapulae, supraspinatus, 5= wrist, and finger extensors, 6= first dorsal interosseous, 7=quadratus lumborum, 8=gluteus maximus, 9= piriformis,10= vastus lateralis, 11=gastrocnemius. CPSP: Central post-stroke pain. PSP-Non: Non-neuropathic post-stroke pain. No-Pain: Stroke without pain.

Figure 3 – The proportion of patients with Post-Stroke non-neuropathic pain in an area with sensory abnormality



Number of evaluated patients= 12 PSP-Non: Post-Stroke non-neuropathic pain.

4.1.4 Pain assessment

CPSP patients had significantly higher scores for the intensity of both sensory (5.7±1.7 *vs*.3.5±2.0, $p<0.001$) and affective dimensions of pain (3.9±1.4 *vs*. 2.9±1.4, $p=0.003$) (Tables 5 and 6).

Table 5 - Results of The Brief Pain Inventory scores

The Brief Pain Inventory				
	Group according to pain classification			
	CPSP n= 39	PSP-Non n= 32	Total n=71	P effects between groups
Severity items (pain)				
Least (0-10)	5.1 (2.2)	2.9 (1.8)	4.1 (2.3)	<0.001*
Average (0-10)	6.5 (1.6)	4.8 (2.6)	5.7 (2.2)	0.003*
Now (0-10)	6.6 (1.8)	3.2 (3.1)	5.1 (3.0)	<0.001*
Worst (0-10)	7.5 (1.7)	6.5 (3.3)	7.1 (2.6)	0.493
Interference items				
General activity (0-10)	5.4 (3.5)	3.8 (3.4)	4.7 (3.6)	0.055
Mood (0-10)	4.9 (3.9)	3.8 (3.7)	4.4 (3.8)	0.265
Walking ability (0-10)	4.9 (4.0)	4.4 (3.8)	4.7 (3.9)	0.531
Normal work (0-10)	3.9 (3.8)	4.2 (3.2)	4.0 (3.5)	0.771
Relationships with others (0-10)	3.9 (4.2)	2.5 (3.3)	3.3 (3.9)	0.185
Sleep (0-10)	4.1 (4.3)	3.7 (3.9)	3.9 (4.1)	0.708
Enjoyment of life (0-10)	5.3 (4.1)	4.1 (3.8)	4.72 (4.0)	0.225
Percentage of relief provided by pain treatment (0-100%)	41.3 (25.8)	52.9 (38.1)	46.1 (31.8)	0.141

Numerical variables are represented by mean and standard deviation. *p<0.05. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain.

Table 6 - Short-Form of the McGill pain questionnaire.

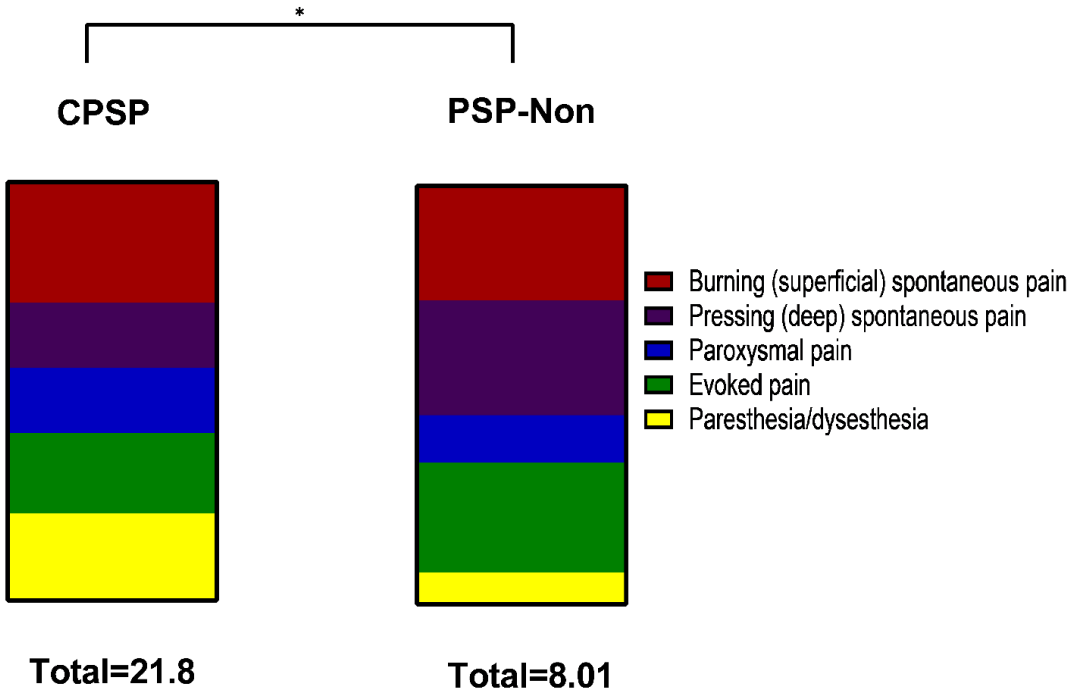
Short-form McGill				
	Group according to pain classification			
	CPSP n= 39	PSP-Non n= 32	Total n=71	P
Total score (0-15)	11.2 (2.8)	7.8 (3.3)	9.6 (3.5)	<0.001*
Sensory (0-8)	5.7 (1.7)	3.5 (2.0)	4.7 (2.1)	<0.001*
Affective (0-5)	3.9 (1.4)	2.9 (1.4)	3.4 (1.4)	0.003*
Evaluative (0-2)	1.6 (0.5)	1.4 (0.6)	1.5 (0.6)	0.075

Numerical variables are represented by mean and standard deviation. *p<0.05

The specific pain symptoms most frequently reported in the CPSP group were burning (82.1%, n=32, p<0.001), tingling (66.7%, n= 26, p<0.001), and pain evoked by

cold stimulus (64.1%, n=25, p<0.001). PSP-Non patients never described their pain as tingling or as electric shocks. The pain descriptors were clustered in the five distinct dimensions of neuropathic pain, and the burning (superficial) spontaneous pain dimension corresponded to the highest scores in the CPSP. All scores, except the pressing (deep) spontaneous pain, were significantly higher in the CPSP group compared to the PSP-Non (Figure 4 and Table 7). Similar findings were found when cluster symptoms were classified according to Bouhassira et al., 2021(32), where "provoked pain" was more common in CPSP patients, "pinpointed pain" occurred exclusively in CPSP, whereas "deep pain" was more common in the non-neuropathic PSP-Non group. The NPSI total score cut-off point for neuropathic pain was 20/100, with a sensitivity of 87% and a specificity of 28% (Figure 5).

Figure 4 - The Neuropathic Pain Symptoms Inventory (NPSI) presented in five clusters



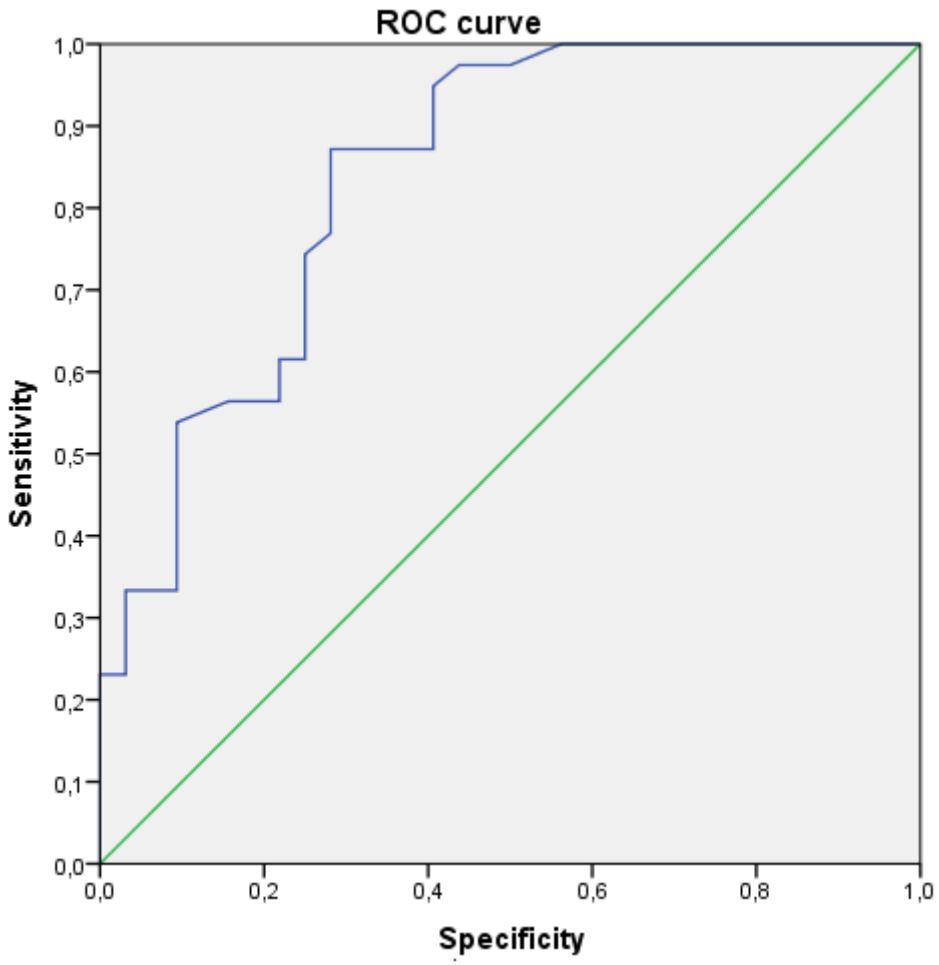
* p<0.005, the NPSI score varied from 0 to 50 and is represented as the mean. Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain.

Table 7 - Results of the neuropathic pain symptoms inventory

	CPSP n=39	PSP-Non n=32	Total n=71	P
Pain Descriptor (items) Number and Percentage of patients who reported a score > 0				
Burning	32 (82.1%)	10 (31.3%)	42 (59.2%)	<0.001*
Squeezing	15 (38.5%)	8 (25.0%)	23 (32.4%)	0.228
Pressure	20 (51.3%)	11 (34.4%)	31 (43.7%)	0.153
Electric shocks	23 (59.0%)	0 (0.0%)	23 (32.4%)	<0.001*ß
Stabbing	17 (43.6%)	7 (21.%)	24 (33.8%)	0.054
Evoked by brushing	18 (46.2%)	4 (12.5%)	22 (31.0%)	0.002 *
Evoked by pressure	24 (61.5%)	21 (65.6%)	45 (63.4%)	0.722
Evoked by cold stimulus	25 (64.1%)	2 (6.3%)	27 (38.0%)	<0.001*ß
Pins and needles	22 (56.4%)	5 (15.6%)	27 (38.0%)	<0.001*ß
Tingling	26 (66.7%)	0 (0.0%)	26 (36.6%)	<0.001*ß
Spontaneous pain during the last 24h				0.003*
Permanently	26 (66.7%)	9 (28.1%)	35 (49.3%)	
Between 8 and 12 h	3 (7.7%)	6 (18.8%)	9 (12.7%)	
Between 4 and 7 h	5 (12.8%)	9 (28.1%)	14 (19.7%)	
Between 1 and 3h	2 (5.1%)	1 (3.1%)	3 (4.2%)	
Less than 1 h	3 (7.7%)	7 (21.9%)	10 (14.1%)	
Pain attacks during the last 24h				<0.001*
More than 20	9 (23.1%)	0 (0.0%)	9 (12.7%)	
Between 11 and 20	3 (7.7%)	0 (0.0%)	3 (4.2%)	
Between 6 and 10	5 (12.8%)	2 (6.3%)	7 (9.9%)	
Between 1 and 5	10 (25.6%)	3 (9.4%)	13 (18.3%)	
No pain attack	12 (30.8%)	27 (84.4%)	39 (54.9%)	
NPSI scores (0-10)				
Burning	6.28 (3.58)	2.22 (3.54)	4.45 (4.08)	<0.001*
Squeezing	2.87 (3.97)	1.97 (3.49)	2.46 (3.76)	0.344
Pressure	3.87 (4.17)	2.59 (3.82)	3.30 (4.03)	0.162
Electric shocks	4.08 (3.76)	0.00 (0.00)	2.24 (3.44)	<0.001*
Stabbing	2.72 (3.47)	2.06 (3.741)	2.42 (3.58)	0.345
Evoked by brushing	3.28 (3.80)	1.00 (2.82)	2.25 (3.56)	0.005*
Evoked by pressure	4.26 (3.77)	5.03 (4.08)	4.61 (3.90)	0.351
Evoked by cold stimulus	5.05 (4.22)	0.47 (1.88)	2.99 (4.062)	<0.001*
Pins and needles	3.8 (3.8)	1.4 (3.0)	2.7 (3.7)	0.003*
Tingling	5.1 (4.1)	0.00 (0.00)	2.8 (4.0)	<0.001*
NPSI total intensity score (0-100)	41.3 (20.7)	16.1 (17.1)	29.9 (22.9)	<0.001*
NPSI five clusters (0-10)				
Burning (superficial) spontaneous pain	6.3 (3.6)	2.2 (3.5)	4.4 (4.1)	<0.001*
Pressing (deep) spontaneous pain	3.4 (3.4)	2.2 (2.9)	2.8 (3.2)	0.145β
Paroxysmal pain	3.4 (3.0)	0.9 (1.8)	2.7 (2.8)	<0.001*
Evoked pain	4.2 (2.9)	2.1 (2.0)	3.3 (2.7)	0.002*
Paresthesia/dysesthesia	4.5 (3.1)	0.6 (1.5)	2.7 (3.2)	<0.001*
Sum of subscores score (0-50)	21.7 (10.4)	8.1 (8.8)	15.6 (11.8)	<0.001*
NPSI three clusters (Bouhassira D. *et al.* 2021)				
Deep pain	14 (35.9%)	26 (81.3%)	40 (56.3%)	
Provoked pain	15 (38.5%)	6(18.8%)	21(29.6%)	<0.001 *
Pinpointed pain	10 (25.6%)	0	10(14.1%)	

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. *p<0.05

Figure 5 - Neuropathic pain symptom inventory (NPSI) cut-off for detecting neuropathic pain



ROC curve analysis. Diagonal segments are produced by ties

4.1.5 Quality of life, mood, and function

Quality of life, mood, and catastrophization ratings were worse in patients with chronic pain (both CPSP and PSP-non) compared to No-Pain. (Table 8). The Barthel index revealed lower scores in CPSP groups, followed by PSP- Non, and No-Pain, p=0.013. The mRS followed the same trend, with a higher concentration in mRS 3 and 5 in the CPSP (CPSP 35.8%, n= 14 *vs*. PSP-Non 15.6%, n=5, and *vs*. No-Pain 16.1%, n=5), p= 0.013. Comparisons between groups evidenced a difference when comparing CPSP versus No-Pain for the Barthel index (p=0.004) and the mRS (p=0.005) –Table 9. Upper limb disability was most prevalent in the CPSP group, followed by PSP-Non

and No-Pain, $p < 0.001$. Pairwise comparisons confirmed differences between all pairs.

A similar trend was observed for the Pain Disability Questionnaire (Table 9).

Table 8 - The Hospital Anxiety and Depression Scale, the Pain Catastrophizing Scale, and the: Short Form Health Status Questionnaire (SF-12)

The Hospital Anxiety and Depression Scale, the Pain Catastrophizing Scale, and the SF-12								
	Group according to pain classification							
	CPSP n=37	PSP-Non n =32	NO-Pain n=31	Total n =102	P between groups	CPSP x PSP-Non	CPSP x No-Pain	PSP-Non x No-Pain
(HAD_A) ≥ 8	22 (59.5%)	15 (46.9%)	5 (16.1%)$_b$	42 (42.0%)	0.001*	0.296	<0.001†	0.009 †
(HAD_D) ≥ 9	19 (51.4%)	12 (38.7%)	4 (13.3%)$_b$	35 (35.7%)	0.005*	0.297	0.001†	0.024
PCS	26.3 (13.9)	23.3 (12.0)		24.9 (13.0)	0.273			
SF-12 PCS	31.4 (8.7)	34.9 (9.4)	51.2 (6.6)	38.5 (11.9)	<0.001*	0.099	<0.001 †	<0.001 †
SF-12 MCS	38.9 (14.5)	46.0 (13.0)	50.8 (10.1)	44.8 (13.6)	0.001 *	0.023	<0.001†	0.169

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. *p<0.05, † p<0.0167 (pairwise comparisons Bonferroni correction for multiple comparisons).CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain.HAD_A: Hospital Anxiety Depression Scale subscore for anxiety. HAD_D: Hospital Anxiety Depression Scale subscore for anxiety. PCS: The Pain Catastrophizing Scale. SF-12: Short Form Health Status Questionnaire. SF-12- PCS: Physical component score. SF-12- MCS: Mental component score

Table 9 - Functional assessment: Barthel index, Modified Rankin Scale, QuickDash, and Pain Disability Questionnaire

Functional Assessment								
	Group according to pain classification							
	CPSP n=39	PSP-Non n= 32	No-Pain n= 31	Total n (%) 102	P effects between groups	CPSP x PSP-Non	CPSP x No-Pain	PSP-Non x No-Pain
Barthel index	87.1 (20.6)	91.7 (14.6)	98.1 (4.4)	91.9 (15.9)	0.013 *	0.438	0.004 †	0.028
Modified Rankin Scale					0.013 †*	0.44	0.005 †	0.028
0 No symptoms	0 (0%)	0 (0%)	5 (16.1%)	5 (4.9%)				
2-Mild disability	17 (43.6%)	13 (40.6%)	16 (51.6%)	46 (45.1%)				
2: Slight disability	8 (20.5%)	14 (43.8%)	5 (16.1%)	27 (26.5%)				
3: Moderate disability	7 (17.9%)	3 (9.4%)	5 (16.1%)	15 (14.7%)				
4: Moderate to severe disability	7 (17.9%)	2 (6.3%)	0 (0.0%)	9 (8.8%)				
Quick dash	60.1 (26.5)	38.1 (25.4)	10.6 (11.6)	38.1 (30.3)	<0.001 *	0.001†	<0.001†	<0.001†
The Pain Disability Questionnaire								
Functional Status (0-90)	54.9 (21.8)	42.4 (18.9)		49.3 (21.3)	0.018*			
Psychosocial (0-60)	32.4 (13.4)	24.1 (14.5)		28.7 (14.4)	0.02*			
Total PDQ score (0-150)	87.3 (31.1)	66.5 (29.3)		77.9 (31.8)	0.007*			

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. *p<0.05, † p<0.0167 (pairwise comparisons Bonferroni correction for multiple comparisons). CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain

4.1.6 Physical examination

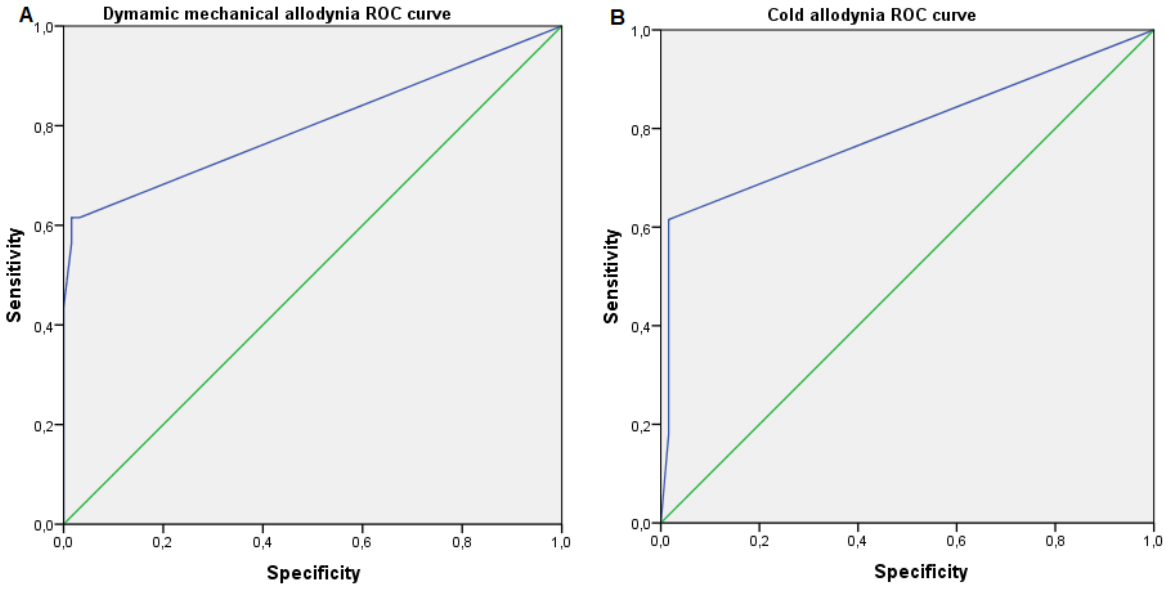
Thermal and dynamic mechanical allodynia were observed more frequently in CPSP [61.5% (*n*=24) for both types] (Table 10), and both types of allodynia occurred concomitantly in 48.7% of CPSP patients. The allodynia NRS cut-off point for neuropathic pain was 2/10, with a sensitivity of 61% and specificity of 1.6% (Figure 6). Cold hypoesthesia was more commonly located in the face, upper and lower limbs in CPSP and its spatial profile was significantly different from No-pain (Figure 2). Mechanical hypoalgesia was more frequently detected in CPSP (61.5%) and PSP-Non (62.5%) than in No-Pain (35.5%), *p*=0.047. Hyperpathia was more frequently detected in CPSP (71.8%, *n*=28) than in PSP-Non (34.4%, *n*=11) and in No-Pain (35.5%, *n*=11), *p*= 0.001 (Table 10).

Table 10 - Sensory assessment

Physical examination −Sensory testing					
	Group according to pain classification				
	CPSP n=39	PSP-Non n=32	No-Pain n=31	Total n=102	P effects between groups
Tactile hypoesthesia	30 (78.9%)a	19 (59.4%)a,b	13(41.9%)b	62 (61.4%)	0.007*, †
Cold hypoesthesia	24 (61.5%)	19 (59.4%)	13 (41.9%)	56 (54.9%)	0.217
Mechanical hypoalgesia	24 (61.5%)a	20 (62.5%)a	11 (35.5%)a	55 (53.9%)	0.047*,
Mechanical hyperalgesia	15 (38.5%)	6 (18.8%)	5 (16.1%)	26 (25.5%)	0.059
Dynamic mechanical allodynia	24 (61.5%)a	2 (6.3%)b	0 (0.0%)b	24 (23.5%)	<0.001*, †
Cold allodynia	24 (61.5%)a	1 (3.1%)b	0 (0.0%)b	24 (23.5%)	<0.001*, †
Hyperpathia /Temporal summation	28 (71.8%)a	11 (34.4%)b	11(35.5%)b	50 (49.0%)	0.001*, †

Categorical variables are expressed in absolute numbers and percentages. *p<0.05, † p<0.0167 Pairwise comparisons Bonferroni correction for multiple comparisons; the groups with different letters are statistically different. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain

Figure 6 - Dynamic mechanical allodynia and cold allodynia cut-off point for neuropathic pain



A: Numerical Rating Pain Scale reported for dynamic mechanical allodynia ROC curve analysis for Neuropathic pain. B: Numerical Rating Pain Scale reported for cold allodynia ROC curve analysis for Neuropathic pain. Diagonal segments are produced by ties

Spasticity was present in 53.8% CPSP (*n*=21) *vs*. 25% (*n*=8) PSP-Non and 9.7% (*n*=3) *p*<0.001, and motor weakness was present in 70.3% (*n*=26) of CPSP, 75% (*n*=24) PSP-Non and 54.8% (*n*=17) No-Pain *p*=0.030, evidencing a tendency of higher impairment in CPSP *vs*. No-Pain (Table 11). Furthermore, active myofascial trigger points were more frequently observed in the PSP- Non group (75%, *n*=24), whereas they were present in 13.2% *(n*=5) of the CPSP group, *p*<0.001 (Tables 11 and 12).

Table 11 - Musculoskeletal assessment Ashworth Spasticity grade, Medical Council Research and myofascial trigger points evaluation

Musculoskeletal assessment								
	Group according to pain classification							
	CPSP n= 39	PSP-Non n= 32	No-Pain n= 31	Total n=102	p effects between groups	CPSP x PSP-Non[2]	CPSP x No-Pain[2]	PSP-Non x No-Pain[2]
Ashworth Spasticity grade								
Absence	18 (46.2%)	24 (75%)	28(90.3%)	70 (68.6%)				
Low to moderate (1-2)	11 (28.2%)	7 (21.9%)	2 (6.5%)	20 (19.6%)	<0.001 *	0.777	<0.001†	0.012†
Moderate to severe (3-5)	10 (25.6%)	1 (3.1%)	1 (3.2%)	12 (11.8%)				
Paresis	n= 37	n=32	n=31	n= 100				
Paresis grade 0	29.7% (11)	25% (8)	45.2% (14)	33% (33)				
Paresis grade 1	29.7% (11)	65.6% (21)	45.2% (14)	46% (46)				
Paresis grade 2	29.7% (11)	3.1% (1)	9.7% (3)	15% (15)	0.030 *	0.181	0.017	0.151
Paresis grade 3	10.8% (4)	6.3% (2)	0% (0)	6 (6%)				
Active myofascial trigger points	5 (13.2%)	24 (75.0%)	-	29 (41.4%)	<0.001*			

Categorical variables are expressed in absolute numbers and percentages. *p<0.05, † p<0.0167 (pairwise comparisons Bonferroni correction for multiple comparisons. Paresis grade 0 (MRC=5) , grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). CPSP: Central Post-Stroke PainPSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. MRC Medical Council Research

Table 12 - Myofascial Trigger Points Evaluation

Myofascial Trigger Points Evaluation				
	Group according to pain classification			
	CPSP n=38	PSP-Non n= 32	Total n= 70	P effects between groups
Active myofascial trigger points	5 (13.2%)	24 (75.0%)	29 (41.4%)	<0.001*
Temporal	2 (5.3%)	9 (28.1%)	11 (15.7%)	0.009 *
Masseter	3 (7.9%)	13 (40.6%)	16 (22.9%)	0.001 *
Scalenes	3 (7.9%)	15 (46.9%)	18 (25.7%)	<0.001*
Trapezius	1 (2.6%)	16 (50.0%)	17 (24.3%)	<0.001*
Levator scapulae	2 (5.3%)	12 (37.5%)	14 (20.0%)	0.001 *
Rhomboids	0 (0.0%)	11 (34.4%)	11 (15.7%)	<0.001*
Supraspinatus	1 (2.6%)	10 (31.3%)	11 (15.7%)	0.001 *
Pectoralis major	0 (0.0%)	11 (34.4%)	11 (15.7%)	<0.00*ß
Wrist and finger extensors	1 (2.6%)	10 (31.3%)	11 (15.7%)	0.001 *
First dorsal interosseous	1 (2.6%)	13 (40.6%)	14 (20.0%)	<0.001*
Quadratus lumborum	0 (0.0%)	15 (46.9%)	15 (21.4%)	<0.001*
Gluteus maximus	1 (2.6%)	7 (21.9%)	8 (11.4%)	0.02 *
Piriformis	1 (2.6%)	9 (28.1%)	10 (14.3%)	0.004 *
Vastus lateralis	1 (2.6%)	13 (40.6%)	14 (20.0%)	<0.001*
Gastrocnemius	1 (2.6%)	10 (31.3%)	11 (15.7%)	0.001 *

Categorical variables are expressed in absolute numbers and percentages. *p<0.05. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain

4.1.7 Quantitative sensory testing

i. Side-to-side differences were measured via the affected area *vs*. mirror area and QST index of asymmetry. CPSP had higher CDT and WDT asymmetry than PSP-Non ($p<0.001$ and $p=0.003$) and No-Pain ($p<0.001$ and $p=0.012$, respectively), indicating a higher degree of sensory deafferentation. Conversely, mechanical hyperalgesia (STHP) was higher in the PSP-Non group than in CPSP ($p=0.007$). All QST findings are reported in Tables 13 and 14. None of the other asymmetry scores significantly differed between CPSP and control groups (Figure 7)

Table 13 - Quantitative sensory testing evaluation of affected and mirror area according to pain groups

	Group according to pain classification								
	CPSP n =39			PSP-Non n=32			No-Pain n=31		
Modality	Affected area	Mirror area	Affected x Mirror p	Affected area	Mirror area	Affected x Mirror p	Affected area	Mirror area	Affected x Mirror p
CDT (ºC)	18.8 (0.1-26.5)	29.2 (27.2-29.7)	<0.001*	26.6 (24.3-29.3)	27.7 (25.7-29.9)	0.056	27.7(25.0-29.0)	29.2 (28.7-30.3)	<0.001*
WDT (°C)	42.8 (35.6-50.0)	34.9 (34.5-36.0)	<0.001*	36.4 (34.9-38.8)	35.6 (34.4-36.7)	0.134	35.2 (34.3-36.5)	34.0 (33.6-34.7)	0.003*
CPT (ºC)	1.9 (0.1-14.2)	12.5 (2.8-19.0)	0.003*	9.6 (0.1-21.1)	14.4 (5.2-22.0)	0.150	10.5 (3.7-20.2)	16.3 (8.7-20.7)	0.124
HPT (ºC)	50.0 (45.7-50.0)	45.0 (41.1-48.1)	<0.001*	45.9 (41.3 48.1)	44.0 (41.7-46.0)	0.102	47.6 (43.4-49.3)	45.8 (41.1-48.2)	0.023*
MDT (mN)	0.7 (0.2-3.1)	0.2 (0.2- 0.7)	0.041*	0.2 (0.2-0.3)	0.2 (0.2-0.2)	0.327	0.2(0.2-0.2)	0.2 (0.2-0.2)	0.207
MPT (mN)	235.2 (81.4-1078.0)	490.3 (81.4-1078.0)	0.777	333.3 (235.2-1078.0)	333.3 (235.2-1078.0)	1.0	490.3 (308.8-1078.0)	1078.0 (333.3-1078.0)	0.084
VDT (mm-64Hz)	7.0 (2.9-31.0)	4.9 (2.2-8.6)	0.048*	1.9 (1.2-7.5)	1.9 (1.4-4.0)	0.189	1.1 (0.6-1.9)	1.9 (0.7-1.7)	0.658
STCP (NRS)	10.0 (0.1-42.0)	23.5 (6.0-41.5)	0.197	11.0 (0.1-34.5)	15.7 (0.1-41.7)	0.451	15.5 (2.5-50.0)	21.5 (9.5-67.5)	0.070
STHP (NRS)	3.5 (0.1-49.0)	26.0 (13.5-51.5)	0.031*	20.5 (6.5-37.6)	27.0 (6.2-51.6)	0.375	20.0 (8.0-35.0)	18.0 (9.0-55.5)	0.153
STMP (NRS)	2.0 (0.1-28.0)	2.0 (0.1-17.0)	0.851	10.0 (2.2-24.5)	8.5 (1.3-22.2)	0.284	5.0 (0.1-14.0)	5.0 (0.10-15.0)	0.484
WUR	1.0 (1.0-1.4)	1.0 (1.0-1.2)	0.458	1.0 (1.0- 1.0)	1.0 (1.0- 1.0)	0.330	1.0 (1.0-1.2)	1.0 (1.0-1.0)	0.767
Allodynia	0.1 (0.1- 6.0)								

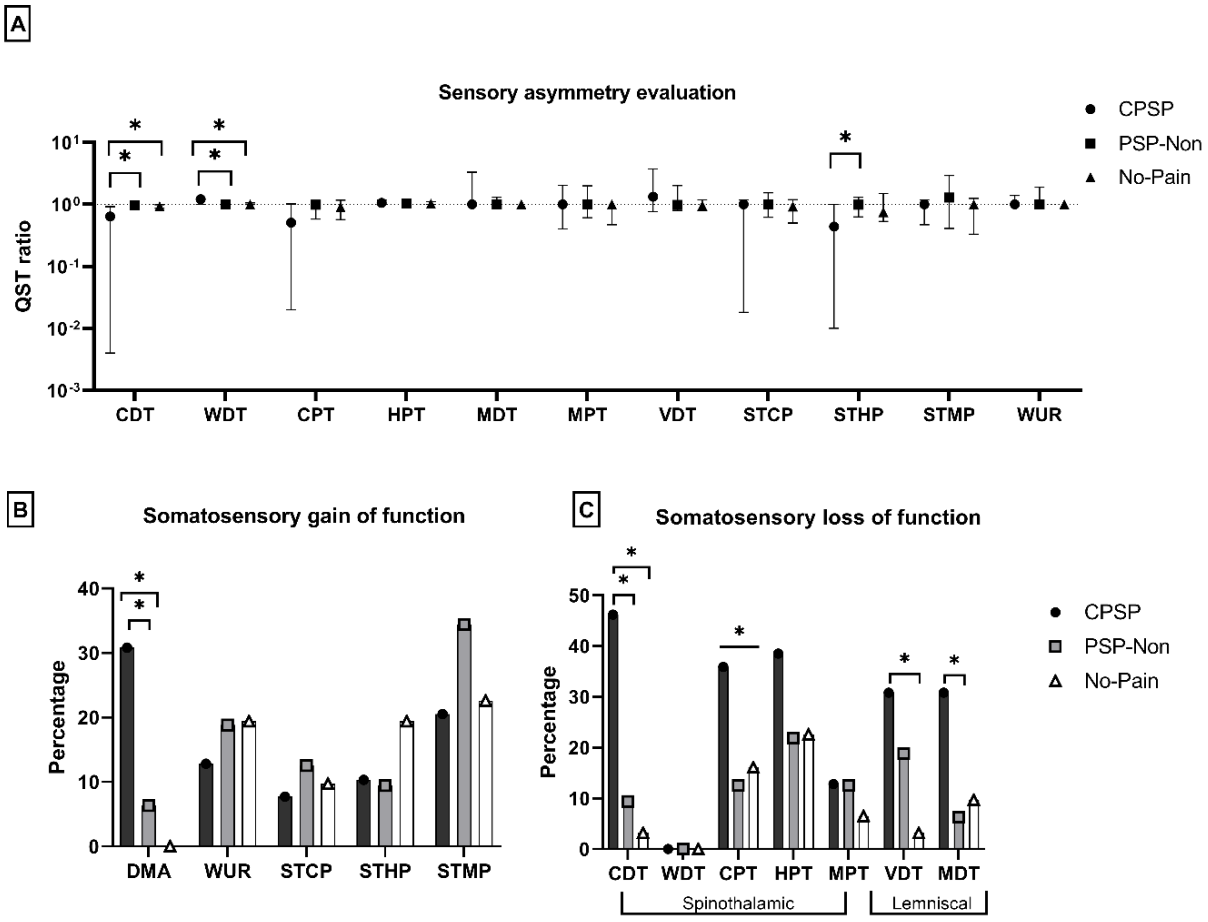
Numerical variables are represented by median and p 25 and p75 *p<0.05. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain.CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. WUR: wind-up ratio (temporal summation): NRS 10º mechanical pain/ NRS mechanical pain.NRS: numerical rating scale

Table 14 - Quantitative Sensory Testing side-to-side comparison between groups

Modality	CPSP n =39 Side-to-side (index) ϭ	PSP-Non n=32 Side-to-side (index) ϭ	No- pain n=31 Side-to-side (index) ϭ	Index comparison between groups P	CPSP x PSP-Non p	CPSP x No-Pain p	PSP-Non x No-Pain p
CDT	0.6 (0.0- 0.9)	1.0 (0.9-1.0)	0.9 (0.9-1.0)	<0.001 *	<0.001*†	<0.001*†	0.329
WDT	1.2 (1.0-1.4)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	0.004 *	0.003* †	0.012* †	0.379
CPT	0.5 (0.0-1.0)	1.0 (0.6-1.1)	0.9 (0.6-1.2)	0.118			
HPT	1.0 (0.8- 1.3)	1.0 (1.1- 1.1)	1.0 (1.0-1.1)	0.181			
MDT	1.0 (1.0- 3.3)	1.0 (1.0-1.3)	1.0 (1.0-1.0)	0.239			
MPT	1.0 (0.4-2.0)	1.0 (0.6-2.0)	1.0 (0.5-1.0)	0.732			
VDT	1.3 (0.3-120)	1.0 (0.8-2.0)	0.9 (0.8- 1.2)	0.195			
STCP	1.0 (0.0-1.2)	1.0 (0.6-1.5)	0.9 (0.5-1.2)	0.332			
STHP	0.4 (0.0-1.0)	1.0 (0.6-1.3)	0.7 (0.5-1.5)	0.012 *	0.007* †	0.022 *	0.601
STMP	1.0 (0.5-1.2)	1.3 (0.4-2.9)	1.0 (0.3-1.2)	0.421			
WUR	1.0 (1.0-1.4)	1.0 (1.0-1.2)	1.0 (1.0-1.0)	0.608			

Numerical variables are represented by median and p25, and p75. Index was calculated according to the formula: affected /mirror. *$p<0.05$, † $p<0.0167$ (pairwise comparisons Bonferroni correction for multiple comparisons). CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. WUR: wind-up ratio (temporal summation): NRS 10º mechanical pain/ NRS mechanical pain. NRS: numerical rating scale

Figure 7 - Quantitative sensory testing assessment with sensory asymmetry evaluation and somatosensory gain and loss of function



A– Asymmetry evaluation through the ratio of affected side per unaffected side. The QST ratio is represented as median and interquartile ranges in a log10 scale. Kruskal-Wallis followed by pairwise comparisons were performed using Mann Whitney for two independent samples with a Bonferroni correction for multiple comparisons. Statistical significance was accepted at the $p<$ 0.0167 level.*$p<0.05$ for analyses between groups and $p<0.0167$ for pairwise comparisons. B Chi-square and Fisher tests were performed, followed by pairwise comparisons with Bonferroni correction for multiple comparisons. Statistical significance was accepted at $p<$ 0.0167. B1–Percentage of patients with a somatosensory gain of function. B2– Percentage of patients with a somatosensory loss of function. *$p<0.05$ for analyses between groups and $p<0.0167$ for pairwise comparisons. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. CDT: Cold detection threshold. WDT: Warm detection threshold. MDT: Mechanical detection threshold. CPT: Cold pain threshold. HPT: Heat pain threshold. MPT: Mechanical pain threshold. VDT: Vibration detection threshold. STCP: suprathreshold cold pain– pain referred according to the Numeric Pain Rating Scale (NRS) after suprathreshold cold pain stimulus. STHP: suprathreshold heat pain–NRS after suprathreshold heat pain stimulus. STMP: NRS after suprathreshold mechanical pain stimulus. WUR wind-up ratio

ii. Single-patient classification: CPSP presented higher percentages of loss of function for spinothalamic tract- STT (CDT and CPT) and for dorsal column lemniscal-

dependent inputs (VDT and MDT) – Figure 7 and Table 15. The sensory profiles evaluation (1) showed that 41.5% of all CPSP patients had somatosensory loss without gain of function, 23% had a combination of loss and gain of function, 25.5% had no loss with some gain, and 10% had no loss and no gain of function. While 69% of the PSP-Non group and 77.7% of the No-Pain group presented loss of function or any loss without gain (Table 16 and Figure 8). Cold hypoesthesia presented an odds ratio of 12 (95% CI: 3.8-41.6) for neuropathic pain (Table 17 for the additional odds ratio of the other QST modalities).

Table 15 - Somatosensory gain and loss of function according to quantitative sensory testing

	Group according to pain classification			
	CPSP n=38	PSP-Non n= 32	Total n= 70	P effects between groups
Somatosensory gain of function				
DMA	24 (61.5%)a	2 (6.3%)b	0 (0.0%)b	<0.001*
WUR	5 (12.8%)	6 (18.8%)	6 (19.4%)	0.754
STCP	3 (7.7%)	4 (12.5%)	3 (9.7%)	0.914
STHP	4 (10.3%)	3 (9.4%)	6 (19.4%)	0.464
STMP	8 (20.5%)	11 (34.4%)	7 (22.6%)	0.429
Somatosensory loss of function				
CDT	18 (46.2%)a	3 (9.4%)b	1 (3.2%)b	<0.001*
WDT	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
CPT	14 (35.9%)a	4 (12.5%)a	5 (16.1%)a	0.026*
HPT	15 (38.5%)	7 (21.9%)	7 (22.6%)	0.508
MPT	5 (12.8%)	4 (12.5%)	2 (6.5%)	0.725
VDT	12 (30.8%)a	6 (18.8%)a,b	1 (3.2%)b	0.005*
MDT	12 (30.8%)a	2 (6.3%)a	3 (9.7%)a,b	0.030*

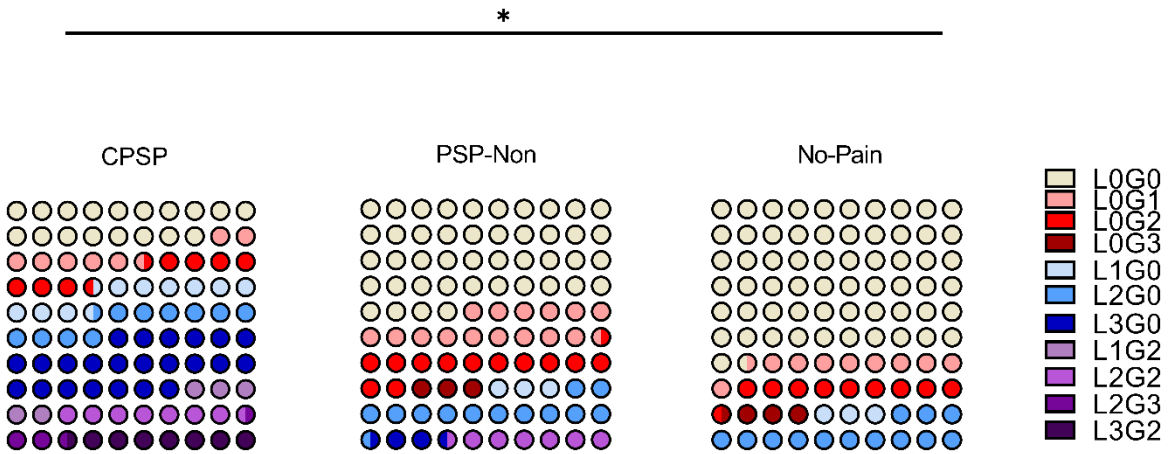
Patients were classified with normal or abnormal parameters on quantitative sensory evaluation according to values proposed by Roke *et al*., 2006[89]. Categorical variables are expressed in absolute numbers and percentages. **p*<0.05. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (*p*<0.0167) CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. CDT: Cold detection threshold. WDT: Warm detection threshold. MDT: Mechanical detection threshold. CPT: Cold pain threshold. HPT: Heat pain threshold. MPT: Mechanical pain threshold. VDT: Vibration detection threshold. STCP: suprathreshold cold pain–pain referred according to the Numeric Pain Rating Scale (NRS) after suprathreshold cold pain stimulus. STHP: suprathreshold heat pain– NRS after suprathreshold heat pain stimulus. STMP: NRS after suprathreshold mechanical pain stimulus. WUR wind-up ratio:

Table 16 - Quantitative sensory testing evaluation according to sensory loss and gain adapted from Maier C. *et al.* 2010(1)

Group according to pain classification			Gain				
			G0	G1	G2	G3	Total
CPSP	Loss	L0	4 (10.0%)	0(0.0%)	2 (5.0%)	8 (20.5%)	14 (35.9%)
		L1	2 (5.0%)	0(0.0%)	0(0.0%)	4 (10.0%)	6 (15.3%)
		L2	0(0.0%)	1 (2.5%)	1 (2.5%)	5 (12.8%)	7 (18.0%)
		L3	3 (7.7%)	2 (5.0%)	2 (5.0%)	5 (12.8%)	12 (30.8%)
	Total		9 (23.0%)	3 (7.7%)	5 (12.8%)	22 (56.4%)	39 (100.0%)
PSP-Non	Loss	L0	16 (50%)	2 (6.0%)	5 (15.6%)	1 (3.0%)	24 (75.0%)
		L1	1 (3.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1 (3.0%)
		L2	3 (9.0%)	0(0.0%)	2 (6.0%)	0(0.0%)	5 (15.6%)
		L3	2 (6.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2 (6.0%)
	Total		22 (68.7%)	2 (6.0%)	7 (21.8%)	1 (3.0%)	32 (100%)
No-Pain	Loss	L0	20 (62.5%)	2 (6.4%)	4 (12.9%)	1 (3.2%)	27 (87.0%)
		L1	1 (3.2%)	0(0.0%)	0(0.0%)	0(0.0%)	1 (3.2%)
		L2	3(9.6%)	0(0.0%)	0(0.0%)	0(0.0%)	3 (9.6%)
	Total		24 (77.4%)	2 (6.4%)	4(12.9%)	1 (3.2%)	31 (100%)

L: loss, G: gain. Normal values were coded as L0.L1: loss of thermal detection (cold or warm detection threshold).L2: loss of mechanical detection (mechanical or vibratory detection threshold). L3: loss of thermal and mechanical detection. G0: normal values. G1: gain of function in heat or cold pain threshold. G2:gain of function in mechanical pain detection threshold or dynamic mechanical allodynia. G3: gain of function in thermal and mechanical stimuli. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain

Figure 8 Somatosensory loss and gain classification adapted from Maier C. *et al.* 2010(1)



L: loss, G: gain. Normal values were coded as L0.L1: loss of thermal detection (cold or warm detection threshold).L2: loss of mechanical detection (mechanical or vibratory detection threshold). L3: loss of thermal and mechanical detection. G0: normal values. G1: gain of function in heat or cold pain threshold. G2:gain of function in mechanical pain detection threshold or dynamic mechanical allodynia. G3: gain of function in thermal and mechanical stimuli. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain. Post-Stroke Pain. No-Pain: Stroke without pain. *p<0.05

Table 17 – The odds ratio of neuropathic pain in quantitative sensory testing modalities

QST modality	Odds ratio	IC 95% inf	IC95% sup	P
Temporal summation	4.4	1.9	10.5	0.001
Cold hypoesthesia	12	3.8	41.6	<0.001
Cold hypoalgesia	3.4	1.28	8.8	0.011
Mechanical hypoesthesia	5.2	1.6	16.1	0.03
Hypopallesthesia	3.6	1.3	10.0	0.013
STT	9.1	3.1	26.5	<0.001
LMN	5.0	2.1	12	<0.001

QST: Quantitative sensory testing. STT spinothalamic tract impairment (cold detection, cold pain, warm detection, heat pain, or mechanical pain thresholds impairment. LMN lemniscal tract impairment (mechanical or vibratory thresholds) The other QST modalities did not evidence statistical significance.

iii. Thermal limen assessment: patients with CPSP showed values more distant from 1.0 (greater dissociation between cold and warm thermal channels) when compared to the PSP-Non and No-Pain groups (median 0.57 *vs*. 0.95 *vs.* 0.91; $p<0.001$). Additionally, there was a correlation between this CDT/WDT thermal ratio limen and the presence of neuropathic pain ($\rho=-0.4$, $p< 0.001$) and also with pain intensity ($\rho=-0.3$, $p< 0.001$).

Conditioned pain modulation differed between groups ($p=0.047$), with patients with chronic pain (CPSP and PSP-Non) showing lower values, meaning a defective CPM, but these findings did not persist after multiple comparison adjustments (Table

18). Pressure pain threshold (PPT) over the reference site (glabella) was similar between groups (2.3±1.24 *vs*. 2.25±0.70 *vs*. 2.58 ±1.33, *p*= 0.947) though CPSP had lower PPT in all muscles tested compared to PSP-Non and No- Pain (Figure 2).

Table 18 - Conditioned Pain Modulation (CPM) according to pain groups

	CPSP n=24	PSP-Non n=30	No-pain n=30	Comparisons between groups	CPSP x PSP-Non	CPSP x No-Pain	PSP-Non x No-Pain
Unconditioned stimuli	74.5 (56.7-92.7)	80.0 (63.7-92.0)	80.0 (58.5-91.2)				
Conditioned stimuli	70.0 (42.2-86.0)	72.0 (47.5-92.0)	53.0 (27.2-81.2)				
CPM	1.5 (-2.7-22.5)	0.0 (-5.0-16.0)	10.0 (0-40)	0.047 *	0.669	0.093	0.016 †

Unconditioned and conditioned stimuli were measured through the numerical rating pain scale. Numerical variables are represented by median and p25, and p75. Level. *p<0.05, † p<0.0167 (pairwise comparisons Bonferroni correction for multiple comparisons. CPSP: Central Post-Stroke Pain. PSP-Non: Non-neuropathic post-stroke pain

Correlations were found between a number of neuropathic pain symptom clusters and QST modalities in the CPSP group, as follows:

i. Paroxysmal pain and CPT (ρ=-0.4, p=0.008) and HPT (ρ=0.5, p=0.003);

ii. Burning pain and MDT (ρ= -0.4, p<0.015) and MPT (ρ=-0.4, p<0.013).

iii. Evoked pain and MPT (ρ= -0.3, p=0.047) and STMP (ρ= -0.3, p=0.032).

There was no correlation between the other two clusters (pressing pain and paresthesia/dysesthesia) and QST modalities (Table 19).

Table 19 - Correlations between Neuropathic Pain Symptom Inventory (NPSI) phenotypes and quantitative sensory testing (QST)

Correlations between NPSI phenotypes and QST modalities		ρ	p
Paroxysmal	CPT	0.420	0.008
	HPT	0.460	0.003
Evoked	MPT	-0.320	0.047
	STMP	0.345	0.032
Burning	MDT	-0.387	0.015
	MPT	-0.395	0.013

Correlations were included when ρ≥ 0.3 and *p*< 0.05.CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. For asymmetry index calculation: a ratio (values from tested area/ values from the mirror area) for CDT, WDT, MDT, MPT, VDT, STCP, STHP, STMP.For CPT and HPT evaluation, the difference between values of tested and mirror area ($tested\ area - mirror\ area$). There was no correlation between pressing and paresthesia phenotypes and QST

4.1.8 Multivariate analyses

We performed a binomial logistic regression including variables found to be different between groups from pain descriptors (NPSI), from clinical bedside examination (allodynia), and from QST (CDT in painful-side vs. mirror area < 41%) and the likelihood these patients would have been classified as being from the CPSP group. The model was statistically significant ($\chi^2(3)= 85.1$, $p<0.001$) and explained 77% (Nagelkerke R2) of the variance in CPSP. Of the variables, were statistically significant: cold hypoesthesia OR = 8.1, 95% CI = 1.6 - 42.5; NPSI OR = 1.1, 95% IC = 1.0 - 1.1; NRS allodynia OR = 2.1; 95% IC = 1.3 - 3.7.

Employing dichotomous variables on the model NPSI (≥20) and NRS allodynia (≥2), the model was statistically significant ($\chi^2(3) = 51.3$, $p<0.001$) and explained 69% (Nagelkerke R^2) of the variance in CPSP. Of the variables, all were statistically

significant: cold hypoesthesia *OR* = 7.4 95% *CI* 1.3-43.6, NPSI *OR*= 11.3 95% *CI* 2.4-53.4, allodynia *OR*= 36.9 95% *CI* 3.7 -370.6.

4.2 Results – Lesion location, pain symptoms, and sensory profile in central neuropathic pain

4.2.1 Patients

We included 79 patients with CNP (39 with CPSP and 40 with CPSCI). CPSP group was older (59.2 ± 11.2 vs. 48.2 ±11.1, $p<0.001$), with a higher proportion of males (59% vs. 32.5%, $p=0.018$), hypertension, and heart disease(Table 20). 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 stroke, 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%), while in SCI, 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 21).

Table 20 - Sociodemographic characteristics and comorbidities, comparative analysis between central post-stroke and central pain in spinal cord injury

	CPSP N =39	CPSCI N =40	p between groups
Age (years)	59.2 (11.2)	48.2 (11.1)	<0.001*
Sex (female)	16 (41.0%)	27 (67.5%)	0.018 *
Educational level β			
Low	14 (35.9%)	19 (47.5%)	0.579
Medium	19 (48.7%)	16 (40.0%)	
High	6 (15.4%)	5 (12.5%)	
Working	2 (5.1%)	9 (22.5%)	0.026*
Medical history			
Diabetes	10(25.6%)	6 (15.0%)	0.239
Hypertension	33 (84.6%)	13 (32.5%)	<0.001*
Heart disease	8 (20.5%)	2 (5.0%)	0.048 *
CKD	1 (2.6%)	0 (0.0%)	0.494
Depression	10 (25.6%)	10 (25%)	0.948
Currently smoking:	7 (17.9%)	8 (20%)	0.816

Categorical variables are expressed in absolute numbers and percentages. **p<0.05* βLow: middle, elementary school or no education; medium: high school, high: bachelor's degree or higher. CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury CKD: Chronic kidney disease.

Table 21 - Lesion characteristics regarding the event type, location, and symptomatic side or level, and comparative analysis between stroke patients and spinal cord injury

	CPSP N=39	CPSCI N =40	p between groups
Time elapsed lesion (months)	54.7 (58.2)	59.3 (46.2)	0.219
Event type	Ischemic 30 (78.9%) Hemorrhagic 8 (21.1%)	Inflammatory 40 (100%)	<0.001 *
Most important lesion location			<0.001*
Cortical	10 (25.6%)	0 (0%)	
Subcortical	21 (53.8%)	0 (0%)	
Brainstem and cerebellum	8 (20.5%)	0 (0%)	
Cervical	0 (0%)	22 (55.0%)	
Thoracic	0 (0%)	18(45%)	
More than one lesion	8 (20.5%)	23 (57.5%)	0.001*

Categorical variables are expressed in absolute numbers and percentages. Numerical non-parametric data are represented as median and percentile 25 and 75. **p<0.05* CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury.

4.2.2 Pain characteristics

Pain descriptors were significantly different between groups (Table 22). Paroxysmal and evoked pain were more intense in CPSP, with higher intensity scores for pain evoked by cold, stabbing, and electric shocks, and CPSCI patients reported more intense squeezing pain. Based on the NPSI cluster stratification(136), deep pain made up 72.5% of the CPSCI group, while 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 23) and depressive symptoms compared to CPSCI: 9.0 (5.0–12.0) vs. 4.5 (2.0–9.0), respectively, *p*= 0.002.

Table 22 – The Neuropathic Pain Symptoms Inventory (NPSI)

NPSI	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 five clusters (0-10) Bouhassira *et al.,* 2014			
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,* 2021			
Deep pain	14 (35.9%)	29 (72.5%)	
Provoked pain	15 (38.5%)	7 (17.5%)	0.004 *
Pinpointed pain	10 (25.6%)	4 (10.0%)	

Categorical variables are expressed in absolute numbers and percentages. Numerical non-parametric data are represented as median and 25-75 percentile. *p<0.05 CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury.

Table 23 - Short-Form McGill, Brief Pain Inventory and Hospitalar Anxiety and Depression Scale evaluation according to pain etiology

	CPSP N 38	CPSCI N =40	p
Short-Form McGill			
Total score (0-15)	11.5 (9.0–14.0)	9.0 (8–11)	0.002 *
Sensory (0-8)	6.0 (4.0–7.0)	4.5 (3.0–6.0)	0.003 *
Affective (0-5)	4.0 (3.0–5.0)	3.0 (3.0–14.0)	0.012 *
Evaluative (0-2)	2.0 (1.0–2.0)	1.5 (1.0–2.0)	0.201
Brief Pain Inventory			
Severity pain items			
Least (0-10)	6.0 (4.0–7.0)	3.0 (2.0–4.7)	<0.001*
Average (0-10)	7.0 (5.0–8.0)	7.0 (5.0–8.0)	0.873
Now (0-10)	7.0 (5.0–8.0)	6.0 (3.0–8.0)	0.128
Worst (0-10)	8.0 (6.0–9.0)	8.0 (6.2–9.0)	0.783
Interference items			
General activity (0-10)	6.0 (3.0–8.0)	6.0 (2.2–8.0)	0.886
Mood (0-10)	5.0 (0.0–8.0)	5.0 (1.5–8.0)	0.929
Walking ability (0-10)	5.0 (0.0–9.0)	4.0 (0.0–8.0)	0.397
Normal work (0-10)	3.0 (0.0–8.0)	6.0 (0.5–9.0)	0.105
Relationships with others (0-10)	1.0 (0.0–8.0)	3.0 (0.0–6.7)	0.891
Sleep (0-10)	3.0 (0.0–8.0)	4.5 (0.0–7.7)	0.875
Enjoyment of life (0-10)	6.0 (0.0–10.0)	5.0 (1.2–8.0)	0.514
Hopsitalar and Anxiety Depression Scale (HAD)			
HAD- Depression	9.0 (5.0–12.0)	4.5 (2.0–9.0)	0.002*
HAD- Anxiety	9.0 (4.5–13.0)	7.0 (4.0–10.0)	0.269
HAD total score	18.0 (9.5–25.5)	13.5 (7.0–19)	0.022*

.Numerical non-parametric data are represented as median and percentile 25 and 75. CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury. *p<0.05

4.2.3 Physical examination

On bedside examination, CPSP patients 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). On the other hand, CPSCI patients 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, according to musculoskeletal assessment, CPSCI patients 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 patients (Table 24) Active myofascial trigger points were similarly present in both groups (CPSCI 24.3% vs. CPSP 10.8%, *p*=0.127).

Table 24 - 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 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%)	
Active myofascial trigger points	4 (10.8%)	9 (24.3%)	0.127
Barthel index	87.0 (20.6)	72.4 (25.5)	<0.001*

Categorical variables are expressed in absolute numbers and percentages.Paresis grade 0 (MRC=5) , grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury. **p<0.05.*

4.2.4 Quantitative sensory testing

Sensory assessment through QST evidenced CPSP patients had lower MPT thresholds [235.2 (81.4-1078.0)] and higher cold hyperalgesia - STCP (10.0 (0.1–

42.0)] compared to CPSCI 784.5 (255.0 – 1078.0) *p*=0.006 and 5.0 (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 patients, 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 25). The QST assessed areas are described in Table 26.

Table 25 - Sensory thresholds in the neuropathic pain area

	CPSP N 39	CPSCI N =40	p
Detection thresholds			
CDT (ºC)	18.8 (1.0 –.26.5)	24.0 (14.1 – 27.4)	0.180
WDT (ºC)	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 (ºC)	1.9 (0.1–14.2)	1.4 (0.0 –8.1)	0.157
HPT (ºC)	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 (ºC) Cold limen	5.6 (0.0–12.9)	20.0 (4.2–22.9)	0.004*
HPT-WDT difference (ºC) Heat limen	3.4 (0.0–9.4)	5 (2.6–8.2)	0.406
Evoked pain			
STCP	10.0 (0.1–42.0)	5.0 (0.0–.33.7)	0.030*
STHP	3.5 (0.1–49.0)	29.7 (6.6–48.1)	0.257
STMP	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*

Numerical non-parametric data are represented as median and percentile 25 and 75. CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury. CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. WUR: wind-up ratio (temporal summation): NRS 10º mechanical pain/ NRS mechanical pain.NRS: numerical rating scale. *p<0.05.

Table 26 - Quantitative sensory testing areas assessed, including affected area and control area

Quantitative sensory testing areas		
Quantitative sensory testing area in CPSP (n=39)		
	Tested area (worse neuropathic pain area)	Control area (contralateral side)
Face	3 (7.7%)	3 (7.7%)
Arm	16 (41.0%)	16 (41.0%)
Hand	10 (25.6%)	10 (25.6%)
Leg	4 (10.3%)	4 (10.3%)
Feet	6 (15.4%)	6 (15.4%)
Quantitative sensory testing area in CPSCI (n=40)		
	Tested area (worse neuropathic pain area)	Control area (above the level)
Cervical dermatome	11 (27.5%)	37 (92.5%)
Thoracic dermatome	20 (50.0%)	3 (7.5%)
Lumbar dermatome	7 (17.5%)	0 (0.0%)
Sacral dermatome	2 (5.0%)	0 (0.0%)

Categorical variables are expressed in absolute numbers and percentages. CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury.

When comparing QST findings to each patient´s control body area, we found that CPSP had lower CPT differences compared to CPSCI -3.5 (-12.5 – 0.-2) vs. -13.0 (-19.3 – -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 (STCP), 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 27.

Table 27 - Sensory thresholds and experimental pain relative to changes from the control area

	CPSP N 39	CPSCI N =40	p
CDT ratio	0.6 (0.0 – 0.9)	0.81 (0.5 – 1.3)	0.385
CPT difference	-3.5 (-12.5 – 0.-2)	-13.0 (-19.3 – -6.0)	<0.001*
WDT ratio	1.2 (1.1 –.13)	1.2 (1.0 – 1.3)	0.879
HPT difference	2.8 (0.7 – 7.0)	4.6 (3.1 – 8.3)	0.073
MDT ratio	1.0 (1.0 –3.3)	2.7 (1.5 –6.2)	0.007*
MPT ratio	1.0 (0.40 –2.0)	1.0 (0.5 – 1.8)	0.565
Evoked pain			
STCP ratio	1.0 (0.0 –1.2)	0.23 (0.0 –8.4)	0.001*
STHP ratio	0.4 (0.1 –1.0)	0.74 (0.21 – 1,0)	0.474
STMP ratio	1.0 (0.5 –1.2)	0.9 (0.1 –1.2)	0.054
WUR ratio	1.0 (1–1.4.)	0 (0.0– 1.6)	0.002*

QST ratio was calculated as the ratio of the affected side values divided by the unaffected side values. CPT and HPT are expressed as the difference between the affected and unaffected sides. Numerical non-parametric data are represented as median and percentile 25 and 75.CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury. CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. WUR: wind-up ratio (temporal summation): NRS 10º mechanical pain/ NRS mechanical pain.NRS: numerical rating scale. *p<0.05

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 (CPS*P*=21 and CPSCI=21)– Tables 28 and 29. 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.

Correlation analysis between pain descriptors (from the NPSI) and QST results evidenced 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 the wind-up ratio and the evoked pain intensity -0.57, p<0.001.

Table 28 - Comparative analysis between central post-stroke and central pain in spinal cord injury matched by age and sex

	CPSP N =21	CPSCI N =21	p between groups
Age (years)	54.6 (8.5)	55.1 (8.4)	0.772
Sex (female)	12 (57.1%)	12 (57.1%)	0.622
NPSI five clusters			
Paroxysmal	4.0 (0.7-6.0)	0 (0.0-3.7)	0.010*
Evoked	5.3 (1.8-6.7)	2.7 (0.0-3.5)	0.006*
Paresthesia	4.5 (2.2-8.2)	2.5 (0.0-4.0)	0.027*
Pressing	3.5 (0.0-6.5)	4.5 (2.0-6.5)	0.357
Burning	8.0 (2.5-9.5)	5.0 (1.5-8.0)	0.186
NPSI three clusters			
Pinpointed pain	5 (23.8%)	2 (9.5%)	0.031*
Provoked pain	9 (42.9%)	3 (14.3%)	
Deep pain	7 (33.3%)	16 (76.2%)	
Bed-side examination			
Tactile hypoesthesia	17 (81.0%)	20 (95.2%)	0.153
Cold hypoesthesia	13 (61.9%)	21 (100%)	0.002*
Mechanical hypoalgesia	14 (66.7%)	6 (28.6%)	0.029*
Mechanical hyperalgesia	8 (38.1%)	16 (76.2%)	0.013*
Dynamic mechanical allodynia	11(54.2%)	4 (19%)	0.024*
Cold allodynia	13 (61.9%)	3 (14.3%)	0.001*
Hyperpathia	13 (61.9%)	20 (95.2%)	0.008*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. [β]Low: middle, elementary school or no education; medium: high school; high: bachelor's degree or higher. CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury CKD: Chronic kidney disease. **p<0.05*

Table 29 - Sensory thresholds and experimental pain relative to changes from the control area: a comparative analysis between central post-stroke and central pain in spinal cord injury matched by age and sex

	CPSP N 21	CPSCI N =21	p
CDT (°C)	17.0 (1.3 – 26.6)	22.9 (10.6 – 25.9)	0.650
CPT (°C)	2.1 (1.0 – 13.4)	0.6 (0.0 – 4.8)	0.097
CDT-CPT (°C)	5.6 (0.0-12.8)	18.2 (2.2-22.4)	0.118
WDT (°C)	44.9 (36.1 –.50.0)	43.9 (37.0 – 48.1)	0.630
HPT (°C)	50 (47.6 – 50.0)	49.2 (47.0 – 50.0)	0.119
MDT(mN)	0.7 (0.2 –7.0)	0.4 (0.2 –1.7)	0.827
MPT (mN)	490.3 (166.6 –1078.0)	980.7 (588.4 – 1079.0)	0.021*
Evoked pain			
STCP	5.5 (0.1 –41.7)	5.0 (0.0 –34.5)	0.172
STHP	3.0 (1.0 –48.5)	21.5 (0.0 – 47.2)	0.879
STMP	2.0 (0.1 –16.5)	5.0 (0.0 –26.5)	0.970
WUR	1.0 (1–1.4.)	0 (0.0– 0.8)	0.001*
Quantitative sensory ratio (comparison between pain area and control area)			
CDT ratio	0.6 (0.6–0.9)	0.8 (0.3–0.9)	0.831
CPT difference	-3.7 (-12.7 – -0.1)	-14.4 (-19.1 – -7.0)	0.015*
WDT ratio	1.3 (1.0–1.4)	1.2 (1.1 –1.4)	0.782
HPT difference	4.4 (1.5 –8.2)	5.3 (3.8 – 9.2)	0.204
MDT ratio	1.2 (1.0 –23.9)	1.5 (1.0–6.1)	0.483
MPT ratio	1.0 (1.0–2.0)	1.0 (0.5 –4.0)	0.538
Evoked pain			
STCP ratio	0.6 (0.2–1.0)	0.2 (0.0–0.8)	0.012*
STHP ratio	2.8 (0.0–1.0)	0.6 (0.0–0.9)	0.870
STMP ratio	1.0 (0.5 –1.0)	0.9 (0.0–1.6)	0.286
WUR ratio	1.0 (1.0–1.4)	0.0 (0.0–0.8)	0.001*

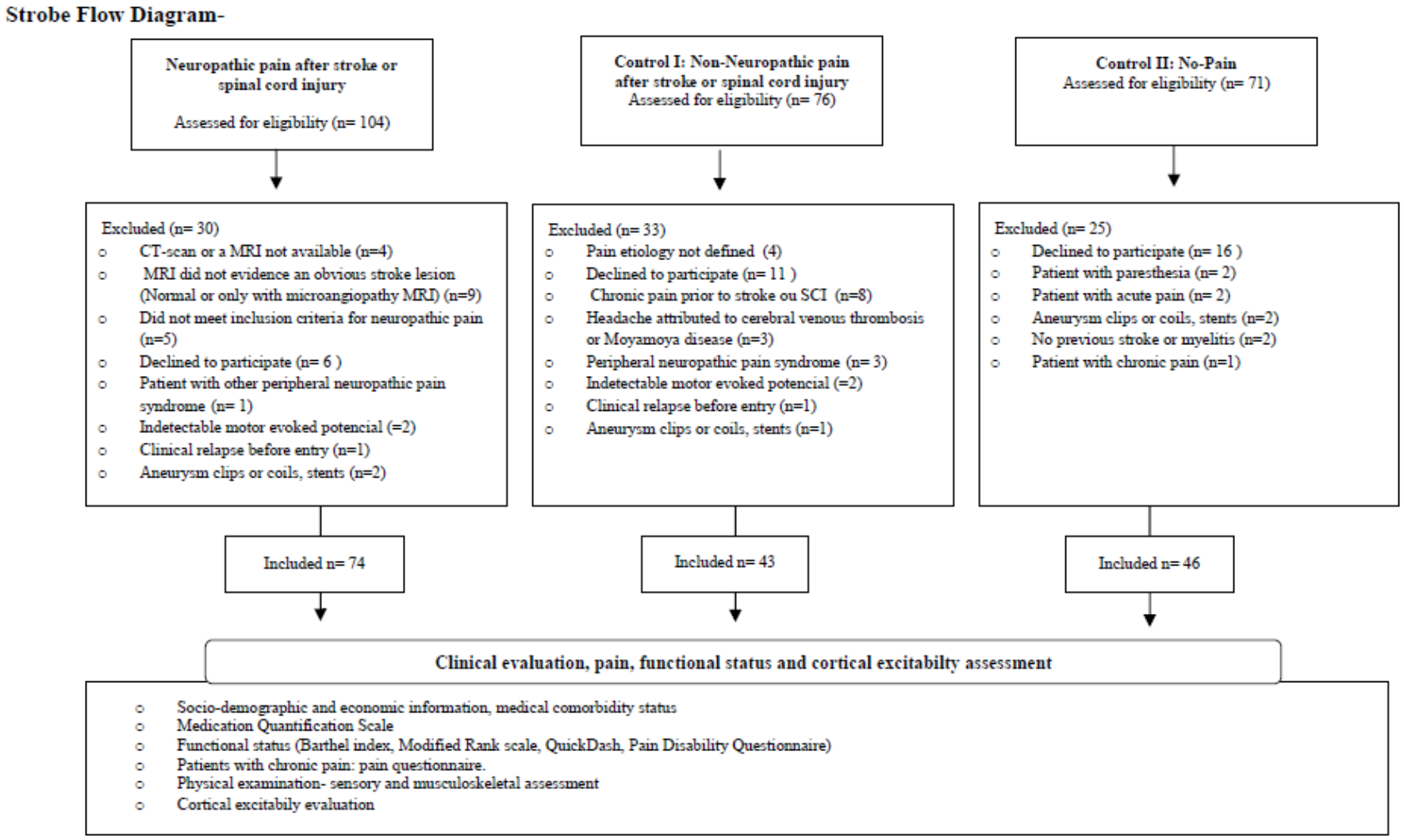
QST ratio was calculated as the ratio of the affected side values divided by the unaffected side values. CPT and HPT are expressed as the difference between the affected and unaffected sides. Numerical non-parametric data are represented as media, percentile 25 and 75.CPSP: central post-stroke pain. CPSCI: central pain in spinal cord injury. CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. STCP: suprathreshold cold pain stimuli. STHP: suprathreshold heat pain stimuli. STMP: suprathreshold mechanical pain stimuli. WUR: wind-up ratio (temporal summation): NRS 10º mechanical pain/ NRS mechanical pain.NRS: numerical rating scale. *p<0.05

4.3 Results – Corticomotor excitability in central neuropathic pain

4.3.1 Patients

We screened 251 patients for participation, and a total of 163 patients (50.3% female) were included (stroke n=93, SCI n=70): 74 had central neuropathic pain, 43 had chronic pain of non-neuropathic origin, and 46 were pain-free (Figure 9). Demographic data are available in Tables 30 (A, B, and C) and 31 (A, B, and C). For most variables, there were no significant differences (i.e., sex, educational level, and medical comorbidities), except for the mean age, which was slightly higher in non-neuropathic pain patients (53.0±12.6 in Neuropathic pain vs. 57.6 ±12.3 in the Non-neuropathic pain and 47.2± 18.1 in the No-Pain, p = 0.021) with pairwise comparisons differences only between the control groups (Non-neuropathic pain vs. No-pain). Time elapsed from the appearance of symptomatic CNS lesion (52.9 ± 44.1 months), type of CNS injury (ischemic or hemorrhagic stroke or inflammatory SCI), and location of lesions were similarly distributed between neuropathic, non-neuropathic, and no pain groups (Table 32).

Figure 9 - Strobe Flow Diagram



CPSP: Central post-stroke pain. CPSCI: central pain secondary to spinal cord injury

Table 30 A - Sociodemographic characteristics and comparative analysis between groups according to their pain syndrome in stroke patients

	Neuropathic pain n= 35	Non-neuropathic pain n =30	No-Pain n =28	p between groups
Age (years)	59.3 (11.6)	62.4 (10.6)	57.3 (13.6)	0.391
Sex (female)	14 (40%)	12 (40%)	6 (21.4%)	0.236
Educational level β				
Low	14 (40%)	18 (60%)	13 (46.4%)	0.115
Medium	15 (42.9%)	9 (30.0%)	6 (21.4%)	
High	6 (17.1%)	3 (10.0%)	9 (32.1%)	
Working	2 (5.7%)a	6 (20.0%)a,b	9 (32.1%)b	0.020*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) β Low: middle, elementary school or no education; medium: high school, high: bachelor's degree or higher. *p< 0.05

Table 30 B- Sociodemographic characteristics and comparative analysis between groups according to their pain syndrome in patients with spinal cord injury

	Neuropathic pain n= 39	Non-neuropathic pain n =13	No-Pain n =18	p between groups
Age (years)	47.9 (11.1)a	46.5 (8.3)a	31.7 (12.0)b	<0.001*
Sex (female)	26 (66.7%)	10 (76.9%)	14 (77.8%)	0.717
Educational level β				
Low	19 (48.7%)	9 (69.2%)	7 (38.9%)	0.397
Medium	15 (38.5%)	3 (23.1%)	6 (33.3%)	
High	5 (12.8%)	1 (7.7%)	5 (27.8%)	
Working	9 (23.1%)	4 (30.8%)	6 (33.3%)	0.709

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) β Low: middle, elementary school or no education; medium: high school, high: bachelor's degree or higher. *p< 0.05

Table 30 C- Sociodemographic characteristics and comparative analysis between groups according to their pain syndrome in stroke and spinal cord injury patients

	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p between groups
Age (years)	53.0 (12.6)a	57.6 (12.3)ab	47.2 (18.1)b	0.021*
Sex (female)	40 (54.1%)	22 (51.2%)	20 (43.5%)	0.543
Educational level [β]				
Low	33 (44.6%)a	27 (62.8%)a	20 (43.5%)a	0.029*
Medium	30 (40.5%)a	12 (27.9%)a	12 (26.1%)a	
High	11 (14.9%)a	4 (9.3%)a	14(30.4%)a	
Working	11 (14.9%)	10 (23.3%)	15 (32.6%)	0.074

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) [β] Low: middle, elementary school or no education; medium: high school, high: bachelor's degree or higher. p< 0.05

Table 31 A - Medical comorbidity characteristics and comparative analysis groups according to their pain syndrome in stroke patients

	Neuropathic pain n= 35	Non-neuropathic pain n =30	No-Pain n =28	p between groups
Medical history				
Diabetes	9 (25.7%)	12 (40.0%)	7 (25.0%)	0.366
Hypertension	29 (82.9%)	27 (90.0%)	21 (75.0%)	0.327
Heart disease	7 (20.0%)a	16 (53.3%)b	13 (46.4%)a,b	0.014*
CKD	1 (2.9%)	6 (20.0%)	2 (7.1%)	0.090
Depression	8 (22.9%)	5 (16.7%)	4 (14.3%)	0.710
Currently smoking:	5 (14.3%)	4 (13.3%)	3 (10.7%)	0.929

Categorical variables are expressed in absolute numbers and percentages. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) CKD: Chronic kidney disease. *p< 0.05

Table 31 B - Medical comorbidity characteristics and comparative analysis groups according to their pain syndrome in spinal cord injury patients

	Neuropathic pain n= 39	Non-neuropathic pain n =13	No-Pain n =18	p between groups
Medical history				
Diabetes	6 (15.4%)	2 (15.4%)	2 (11.1%)	0.908
Hypertension	13 (33.3%)a	1 (7.7%)a	1 (5.6%)a	0.030*
Heart disease	2 (5.1%)	1 (7.7%)	1 (5.6%)	0.942
CKD	0 (0.0%))	0 (0.0%)	0 (0.0%)	
Depression	9 (23.1%)	4 (30.8%)	2 (11.1%)	0.419
Currently smoking:	8 (20.5%)	2 (15.4%)	4 (22.2%)	0.926

Categorical variables are expressed in absolute numbers and percentages. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) CKD: Chronic kidney disease. *p< 0.05

Table 31 C - Medical comorbidity characteristics and comparative analysis groups according to their pain syndrome in stroke and spinal cord injury patients

	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p between groups
Medical history				
Diabetes	15 (20.3%)	14 (32.6%)	9 (19.6%)	0.260
Hypertension	42 (56.8%)	28 (65.1%)	22 (47.8%)	0.270
Heart disease	9 (12,2%)a	17 (39.5%)b	14 (30.4%)b	0.002*
CKD	1 (1.4%)a	6 (14.0%)b	2 (4.3%)a,b	0.012*
Depression	17 (23.0%)	9 (20.9%)	6 (13.0%)	0.409
Currently smoking:	13 (17.6%)	6 (14.0%)	7 (15.2%)	0.891

Categorical variables are expressed in absolute numbers and percentages. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) CKD: Chronic kidney disease. *p< 0.05

Table 32- Lesion characteristics regarding the event type, location, and symptomatic side or level, and comparative analysis groups according to their pain syndrome in stroke and spinal cord injury patients

	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p between groups
Time elapsed lesion (months)	58.8 (53.3)	56.0 (38.6)	40.6 (28.6)	0.137
Lesion type				0.051
Stroke	35 (47.3%)	30 (69.8%)	28 (60.9%)	
Spinal cord injury	39 (52.7%)	13 (30.2%)	18 (39.1%)	
Event type				0.590
Ischemic	27 (37.0%)	28 (65.1%)	24 (52.2%)	
Hemorrhagic	7 (9.6%)	2 (4.7%)	4 (8.7%)	
Inflammatory	39 (53.4%)	13 (30.2%)	18 (39.1%)	
Most important lesion location				0.071
Cortical	9 (12.2%)	11 (25.6%)	14 (30.4%)	
Subcortical	18 (24.3%)	11 (25.6%)	6 (13.0%)	
Brainstem and cerebellum	8 (10.8%)	8 (19.6%)	8 (17.4%)	
Cervical	21 (28.4%)	4 (9.3%)	11 (23.9%)	
Thoracic	18 (24.3%)	9 (20.9%)	7 (15.2%)	
More than one lesion	26 (40%)	19 (45.2%)	14 (34.1%)	0.592

Categorical variables are expressed in absolute numbers and percentages.

4.3.2 Physical examination, functional status, pain scales, and questionnaires

CNP was more functionally impaired (Barthel index = 81±23.9 vs. 90.8 ± 15.7 in the non-neuropathic pain group vs. 88.8± 20.0 in the no-pain group, p= 0.009), had more spasticity (68.9% vs. 39.6% in the non-neuropathic pain group vs. 32.6% in the no-pain group p<0.001) and had more severe motor impairment compared to both control groups (84.7% vs. 81.4% in the non-neuropathic pain group vs.73.9% in the no-pain p=0.010). In addition, active myofascial trigger points were more frequent in the non-neuropathic pain group (67.4% vs. 17.4% in the neuropathic pain group vs.

19.6% in the no-pain group, $p<0.001$) – Table 33A. CPSP had more spasticity and motor impairment than control groups with stroke (Table 33B). While in the spinal cord, spasticity and motor impairment were similar between groups (Table 33C).

Table 33 A - Functional and musculoskeletal assessment–Barthel index, Ashworth Spasticity grade, Medical Council Research, and myofascial trigger points groups according to their pain syndrome in stroke patients and spinal cord injury

Functional and Musculoskeletal assessment				
	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p effects between groups
Barthel index	81.0 (23.9)a	90.8 (15.7)b	88.8 (20.0)b	0.009*
Ashworth Spasticity grade				
Absence	23 (31.1%)a	26 (60.5%)b	31 (67.4%)b	<0.001*
Low to moderate (1-2)	31 (41.9%)a	15 (34.9%)a	11 (23.9%)a	
Moderate to severe (3-5)	20 (27.0%)a	2 (4.7%)b	4 (8.7%)b	
Motor impairment [β]				
Paresis grade 0	11 (15.3%)a	8 (18.6%)a	12 (26.1%)a	0.010*
Paresis grade 1	30 (41.7%)a	30 (69.8%)b	23 (50.0%)a,b	
Paresis grade 2	24 (33.3%)a	5 (11.6%)b	8 (17.4%)a,b	
Paresis grade 3	7 (9.7%)a	0 (0.0%)a	3 (6.5%)a	
Active myofascial trigger points	12 (17.4%)a	29 (67.4%)b	9 (19.6%)a	<0.001*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction [β] Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). *$p<0.05$

Table 33 B - Functional and musculoskeletal assessment–Barthel index, Ashworth Spasticity grade, Medical Council Research, and myofascial trigger points groups according to their pain syndrome in stroke patients

Functional and Musculoskeletal assessment				
	Neuropathic pain n= 35	Non-neuropathic pain n =30	No-Pain n =28	p effects between groups
Barthel index	89.4 (18.3)	94.5 (9.2)	97.9 (4.6)	0.081
Ashworth Spasticity grade				
Absence	18 (5.4%)a	24 (80.0%)b	25 (89.3%)b	0.002*
Low to moderate (1-2)	9 (25.7%)a	6 (20.0%)a	2 (7.1%)a	
Moderate to severe (3-5)	8 (22.9%)a	0 (0.0%)b	1 (3.6%)a,b	
Motor impairment [β]				
Paresis grade 0	11 (33.3%)a	8 (26.7%)a	12 (42.9%)a	0.012*
Paresis grade 1	11 (33.3%)a	21 (70.0%)b	13 (46.4%)a,b	
Paresis grade 2	10 (30.3%)a	1 (3.3%)b	3 (10.7%)a,b	
Paresis grade 3	1 (3.0%)a	0 (0.0%)a	0 (0.0%)a	
Active myofascial trigger points	3 (9.1%)a	22 (73.3%)b	9 (32.1%)a	<0.001*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction [β] Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). *p<0.05

Table 33 C - Functional and musculoskeletal assessment–Barthel index, Ashworth Spasticity grade, Medical Council Research, and myofascial trigger points groups according to their pain syndrome in spinal cord injury

Functional and Musculoskeletal assessment				
	Neuropathic pain n= 39	Non-neuropathic pain n =13	No-Pain n =18	p effects between groups
Barthel index	73.5 (26.0)	82.3 (24.3)	74.7 (26.0)	0.259
Ashworth Spasticity grade				
Absence	5 (12.8%)	2 (15.4%)	6 (33.3%)	0.353
Low to moderate (1-2)	22 (56.4%)	9 (69.2%)	9 (50.0%)	
Moderate to severe (3-5)	12 (30.8%)	2 (15.4%)	3 (16.7%)	
Motor impairment [β]				
Paresis grade 0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.567
Paresis grade 1	19 (48.7%)	9 (69.2%)	10 (55.6%)	
Paresis grade 2	14 (35.9%)	4 (30.8%)	5 (27.8%)	
Paresis grade 3	6 (15.4%)	0 (0.0%)	3 (16.7%)	
Active myofascial trigger points	9 (25.0%)a,b	7 (53.8%)a	0 (0.0%)b	0.003*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction [β] Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). *p<0.05

Pain areas and sensory assessment were described in Tables 34 and 35. Patients with neuropathic pain had more anxiety and depression symptoms and higher pain scores. Catastrophization was similar between groups. According to the NPSI, the pain descriptors were significantly different between groups; the majority of non-neuropathic pain was classified as deep pain (80%, n=32), whereas neuropathic pain was distributed into three clusters: deep pain (55.4%, n=41), provoked pain (25.7%, n=19), and pinpointed pain (18.9%, n=14) – Table 36.

Table 34-Somatosensory assessment and comparative analysis groups according to their pain syndrome in stroke and spinal cord injury patients

	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p between groups
Somatosensory assessment (physical examination)				
Tactile hypoesthesia	65 (87.8%)a	29 (67.4%)b	30 (65.2%)b	0.003*
Cold hypoesthesia	62 (83.7%)a	29 (67.4%)b	29 (63.0%)b	0.015*
Mechanical hypoalgesia	28 (37.8%)	20 (46.5%)	13 (28.3%)	0.216
Mechanical hyperalgesia	45 (60.8%)a	15 (34.9%)b	18 (39.1%)b	0.010*
Dynamic mechanical allodynia	34 (45.9%)a	2 (4.7%)b	0 (0.0%)b	<0.001*
Cold allodynia	27 (36.5%)a	1 (2.3%)a	2 (4.3%)b	<0.001*
Hyperpathia	62 (83.8%)a	21 (48.8%)a	22 (47.8%)a	<0.001*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction *p < 0.05

Table 35 - Pain location in stroke and spinal cord injury patients according to their pain syndrome

	Neuropathic pain n= 74	Non-neuropathic pain n =43	p between groups
Face	5 (6.8%)	5 (11.6%)	<0.001*
Upper limb	11 (14.9%)	9 (20.9%)	
Lower limb	18 (24.3%)	15 (34.9%)	
Hemibody	18 (24.3%)	0 (0.0%0	
Cervical level and bellow	7 (9.5%)	1 (2.3%)	
Thoracic level and bellow	11 (14.9%)	3 (7.0%)	
Cervical	3 (4.1%)	4 (9.3%)	
Thoracic	1 (1.4%)	1 (2.3%)	
Lumbar	0 (0%)	5 (11.6%)	

Categorical variables are expressed in absolute numbers and percentages. *p < 0.05

Table 36 - Mood, pain catastrophization, and pain descriptors comparisons between groups according to their pain group in stroke and spinal cord injury patients

	Neuropathic pain n= 74	Non-neuropathic pain n =43	No-Pain n =46	p effects between groups
HAD_A	37 (50.7%)a	19 (44.2 %)a	8 (17.4%)b	0.001*
HAD_D	29 (39.7%)a	16 (38.1%)a,b	7 (15.6%)b	0.017*
Pain Catastrophizing Scale (0-52)	21.2 (14.3)	21.2 (11.4)		0.875
NPSI				
Pressing pain (0-10)	3.9 (3.3)	2.7 (3.1)		0.036*
Paroxysmal pain (0-10)	2.3 (2.9)	1.0 (1.8)		0.019*
Evoked pain (0-10)	3.5 (2.8)	2.0 (1.8)		0.009*
Paresthesia (0-10)	3.8 (2.9)	0.9 (1.7)		<0.001*
Total score (0-50)	19.5(10.0)	8.9 (8.8)		<0.001*
NPSI three clusters				
Pinpointed pain	14 (18.9%)	1 (2.5%)		0.013*
Provoked pain	19 (25.7%)	7 (17.5%)		
Deep pain	41 (55.4%)	32 (80.0%)		
McGill total score (0-45)	10.1 (2.8)	8.1 (3.1)		0.002*
BPI worse pain (0-10)	7.5 (1.7)	6.6 (2.8)		0.161
BPI least pain (0-10)	4.3(2.9)	3.1 (1.7)		0.005*
BPI mean pain (0-10)	6.5 (1.6)	5.3 (2.2)		0.003*

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction HAD _A Hospital Anxiety and Depression Scale- Anxiety, HAD_D Hospital Anxiety and Depression Scale- Anxiety, NPSI: Neuropathic Pain Symptoms Inventory, BPI: Brief Pain Inventory. *p<0.05

4.3.3 Cortical excitability

Classifying patients' cortical excitability values according to healthy individuals' parameters(106) evidenced that most patients in all groups had abnormal measurements. Patients were heterogeneous; less than a quarter had normal parameters for RMT and MEP in all groups, and less than one-third had normal parameters for SICI and ICF in CNP and non-neuropathic pain groups (Table 37). Notwithstanding, group comparisons evidenced that neuropathic pain patients had a

significantly higher proportion of participants with low MEPs (75%, n= 56 vs. 46.%, n=20 in non-neuropathic pain vs.37%, n=17 in no-pain, p<0.001) (Table 37).

Table 37 - Cortical excitability classification according to healthy individuals

Cortical excitability parameters	Neuropathic pain n= 74	Non-neuropathic pain n =42	No pain n =46	p effects between groups
RMT				
Low	26 (35.1%)	16 (37.2%)	20 (43.5%)	0.772
Normal	10 (13.5%)	7 (16.3%)	8 (17.4%)	
High	38 (51.4%)	20 (46.5%)	18 (39.1%)	
MEP 120				
Low	51 (68.9%)	24 (57.1%)	21 (45.7%)	0.107
Normal	8 (10.8%)	4 (9.5%)	6 (13.0%)	
High	15 (20.3%)	14 (33.3%)	19 (41.3%)	
MEP 140				
Low	56 (75.7%)a	20 (46.5%)b	17 (37.0%)b	<0.001*
Normal	4 (5.4%)a	10 (23.3%)b	9 (19.6%)b	
High	14 (18.9%)a	13 (30.2%)a,b	20 (43.5%)b	
MEP 140/120				
Low	44 (59.5%)	25 (59.5%)	23 (50.0%)	0.258
Normal	12 (16.2%)	7 (16.7%)	15 (32.6%)	
High	18 (24.3%)	10 (23.8%)	8 (17.4%)	
SICI				
Low (defective)	40 (54.8%)	14 (35.9%)	18 (40.9%)	0.184
Normal	20 (27.4%)	13 (33.3%)	11 (25.0%)	
High	13 (17.8%)	12 (30.8%)	15 (34.1%)	
ICF				
Low (defective)	29 (39.2%)	23 (57.5%)	14 (31.1%)	0.127
Normal	24 (32.4%)	11 (27.5%)	19 (42.2%)	
High	21 (28.4%)	6 (15.0%)	12 (26.7%)	

Categorical variables are expressed in absolute numbers and percentages. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction. RMT: rest moto threshold MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF intracortical facilitation * p<0.05

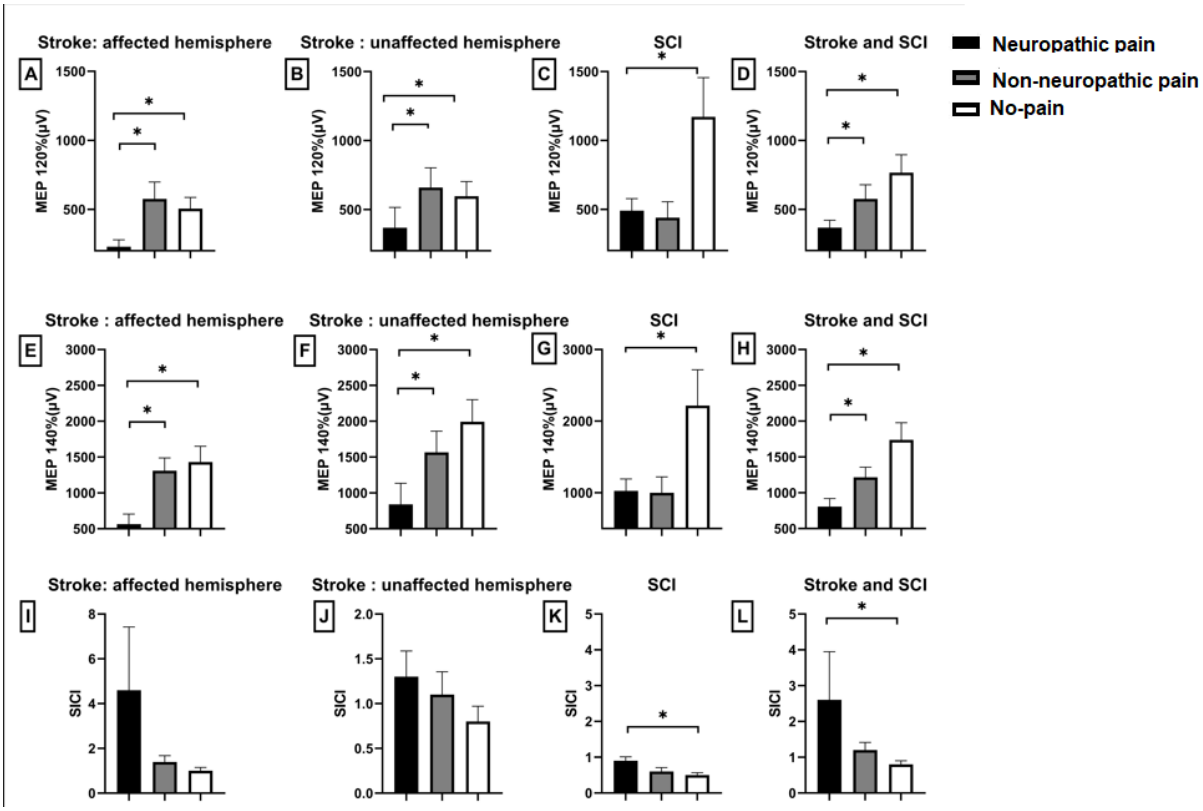
4.3.4 Stroke patients

Comparisons according to the pain syndrome: The neuropathic pain group had lower MEP amplitude than the non-neuropathic pain and the no-pain group. Interestingly, MEPs measured at both intensities (120% and 140%) were lower in central neuropathic pain compared to controls in both the affected and unaffected

hemispheres (Figure 10). Other CE measures were not significantly different between groups (Table 38).

Side-to-side comparisons: When comparing cortical excitability parameters found in the hemisphere affected by stroke to the unaffected hemisphere, through the Wilcoxon signed rank test, most measures were not statistically different, except for RMT in the No-Pain group, where p was 0.047 (Table 38).

Figure 10 - Comparison of cortical excitability measurements according to pain group



Data are expressed as the mean and the standard error of the mean. A and B: Motor evoked potential at 120% of the RMT in stroke patients' affected and unaffected hemispheres. C: MEP 120% in spinal cord injury patients. D: MEP 120% in pooled analysis (stroke and spinal cord injury patients). E and F: Motor evoked potential at 140% of the RMT in stroke patients' affected and unaffected hemispheres. G: MEP 140% in spinal cord injury patients. H: MEP 140% in a pooled analysis. I and J: Short interval intracortical inhibition (SICI) in stroke patients' affected and unaffected hemispheres. K: SICI in spinal cord injury patients. L: SICI in a pooled analysis.

RMT: rest motor threshold, represented as a percentage of the maximal stimulator output. Stimulus-response curve, assessed by the MEP 140 and 120 ratio. SCI: spinal cord injury. RMT: rest motor threshold, represented as a percentage of the maximal stimulator B MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT SICI: short-interval intracortical inhibition ICF Intracortical facilitation.

Table 38 - Cortical excitability evaluation in patients with stroke according to pain syndrome

Cortical excitability parameters	Neuropathic pain (stroke) n= 35	Non-neuropathic pain (stroke) n = 30	No pain (stroke) n = 28	p effects between groups
RMT (%) affected hemisphere	48.3 (10.1)	47.5 (8.9)	48.3 (10.2)β	0.938
RMT (%) unaffected hemisphere	47.8 (7.8)	46.3 (9.0)	44.4 (8.2) β	0.247
MEP 120 (μV) affected hemisphere	229.7 (296.7)a	575.6 (673.0)b	505.6 (431.0)b	<0.001*
MEP 120 (μV) unaffected hemisphere	367.8 (870.3)a	658.8 (780.5)b	595.9 (560.7)b	0.001*
MEP 140 (μV) affected hemisphere	563.6 (843.8)a	1310.3 (977.8)b	1429.7 (1170.0)b	<0.001*
MEP 140 (μV) unaffected hemisphere	841.2 (1732.9)a	1564.6 (1626.1)b	1992.1 (1637.3)b	<0.001*
MEP 140/120 affected hemisphere	16.7 (49.1)	3.6 (2.7)	3.4 (2.0)	0.269
MEP 140/120 unaffected hemisphere	4.0 (6.2)	3.3 (2.7)	4.6 (3.7)	0.209
SICI affected hemisphere	4.6 (16.7)	1.4 (1.5)	1.0 (0.8)	0.145
SICI unaffected hemisphere	1.3 (1.7)	1.1 (1.4)	0.8 (0.9)	0.644
ICF affected hemisphere	8.6 (38.5)	2.1 (2.4)	2.2 (1.5)	0.463
ICF unaffected hemisphere	3.0 (5.4)	2.6 (2.6)	2.1 (2.0)	0.368

Variables are expressed in mean and standard deviation Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167). Wilcoxon signed-rank test was performed to compare affected and unaffected hemispheres parameters, β: p was <0.005 only in RMT in the no-pain group.RMT: rest motor threshold, represented as a percentage of the maximal stimulator output) MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF Intracortical facilitation. *p<0.05

4.3.5 SCI patients

SICI was more impaired in the neuropathic pain compared to the no-pain group. Although analysis between groups evidenced statistically significant lower MEP at 120% and 140% intensities in the neuropathic pain group compared to the no-pain group, no statistical differences were found in comparisons between neuropathic pain

vs. non-neuropathic pain and non-neuropathic pain vs. no-pain. RMT and ICF were similar (Table 39 and Figure 10).

Table 39 - Cortical excitability evaluation in patients with spinal cord injury according to pain syndrome

Cortical excitability parameters	Neuropathic pain (SCI) n= 39	Non-neuropathic pain (SCI) n = 13	No pain (SCI) n = 18	p effects between groups
RMT (%)	52.9 (10.6)	56.9 (10.7)	50.9 (6.4)	0.303
MEP 120 (μV)	490.0 (549.6)a	438.7 (418.5)a,b	1170.7 (1212.4)b	0.009*
MEP 140 (μV)	1026.0 (1038.1)a	1000 (798.1)a,b	2217.8 (2120.9)b	0.008*
MEP 140/120	2.7 (1.6)	2.8 (1.4)	2.5 (1.5)	0.785
SICI	0.9 (0.7)a	0.6 (0.4)a,b	0.5 (0.3)b	0.018*
ICF	3.2 (3.1)	1.6 (0.9)	2.9 (3.5)	0.070

Variables are expressed in mean and standard deviation Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) RMT: rest motor threshold, represented as a percentage of the maximal stimulator output) MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF Intracortical facilitation. SCI: spinal cord injury *p<0.05

4.3.6 Group comparisons

When pooling results from both etiologies of CNS injuries (stroke and SCI), the CNP group had lower MEP values at both tested intensities compared to both control groups (patients with non-neuropathic pain and without chronic pain), p<0.001. Furthermore, SICI was defective (i.e., abnormally low) in the CNP group. Other CE measurements were not different between groups (Table 40 and Figure 10).

Table 40 - Cortical excitability evaluation according to pain syndrome

Cortical excitability parameters	Neuropathic pain n= 74	Non-neuropathic pain n =43	No pain n =46	p effects between groups
RMT (%)	50.7 (10.6)	50.3 (10.3)	49.3 (8.9)	0.742
MEP 120 (μV)	366.8 (464.1)a	575.6 (672.9)b	765.8 (880.0)b	<0.001*
MEP 140 (μV)	807.3 (972.9)a	1216.5 (929.0)b	1738.1 (1634.5)b	<0.001*
MEP 140/120	9.3 (34.3)	3.4 (2.4)	3.0 (1.8)	0.206
SICI	2.6 (11.6)a	1.2 (1.4)a,b	0.8 (0.7)b	0.021*
ICF	5.8 (26.5)	2.0 (2.1)	2.4 (2.5)	0.099

Variables are expressed in mean and standard deviation. Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) RMT: rest motor threshold, represented as a percentage of the maximal stimulator output. MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF Intracortical facilitation.*p<0.05

4.3.7 Effects of motor weakness and spasticity on MEP amplitudes

The neuropathic pain group had some clinical differences compared to the control groups, such as heart disease, hypertension, disability, motor weakness, spasticity, and medication use, the last three are known to influence CE. Therefore, we performed secondary analyzes to determine if these three factors could influence the results.

Compared to patients with non-neuropathic pain and without chronic pain, CNP patients had more motor impairment and spasticity, and a substantial number of patients were taking centrally acting drugs, potentially influencing the amplitude of MEPs. We thus conducted a supplementary analysis excluding patients using medications known to alter cortical excitability: lamotrigine, carbamazepine, phenytoin, baclofen, gabapentin, and benzodiazepines(117) (Table 41). After excluding these patients, results were not changed, and medication-free CNP patients had a significant

reduction in MEP 120 and 140 compared to the control groups. In addition, supplementary analyses excluding patients with major motor weakness (MRC lower than four) and excluding those with any spasticity level further confirmed our findings as MEPs remained lower in CNP patients compared to controls (Tables 42 and 43). A general linear model was run to assess if spasticity, motor impairment, or medication use could significantly contribute to lowering MEP 120% and 140%. The model was run with MEP 120 and 140% as the dependent variable, pain groups as fixed factor and medication, and spasticity and motor impairment as covariates. It was observed that motor impairment affected the MEP 120% but not the MEP 140%. Medication and spasticity did not influence the MEP 120% and 140% (Tables 44 and 45).

Table 41 - Cortical excitability evaluation according to pain syndrome excluding patients using carbamazepine, lamotrigine, baclofen, gabapentin, and benzodiazepines

Cortical excitability parameters	Neuropathic pain n= 18	Non-neuropathic pain n =36	No pain n =38	p effects between groups
RMT (%)	51 (12.2)	49.2 (10.1)	48.8 (9.3)	0.750
MEP 120 (μV)	252 (267.3)a	475.1 (496.1)a,b	751.2 (910.8)b	0.007*
MEP 140 (μV)	677.1 (775.8)a	1217.5 (932.3)b	1730.1 (1719.1)b	0.003*
MEP 140/120	8.0 (19.7)	3.5 (2.6)	3.1 (1.9)	0.788
SICI	1.4 (1.5)	1.3 (1.5)	0.8 (0.7)	0.330
ICF	3.1 (3.0)	2.1 (2.3)	2.1 (1.3)	0.770

Variables are expressed in mean and standard deviation Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) RMT: rest motor threshold, represented as a percentage of the maximal stimulator output) MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF Intracortical facilitation. SCI: spinal cord injury.*p<0.05

Table 42 - Cortical excitability evaluation according to pain syndrome excluding patients with spasticity

Cortical excitability parameters	Neuropathic pain n= 23	Non-neuropathic pain n =26	No pain n =31	p effects between groups
RMT (%)	47.1 (11.8)	48.8 (9.8)	49.3 (10.0)	0.648
MEP 120 (μV)	313.7 (473.1)a	552.3 (552.7)b	649.5 (846.8)b	0.003*
MEP 140 (μV)	853.2 (1057.8)a	1368.1 (1040.2)b	1481.9 (1171.8)b	0.014*
MEP 140/120	15.7 (47.5)	3.1 (1.9)	3.3 (2.0)	0.732
SICI	1.6 (1.5)	1.5 (1.6)	0.9 (0.8)	0.307
ICF	2.4 (1.8)	2.3 (2.6)	2.5 (2.8)	0.560

Variables are expressed in mean and standard deviation Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) RMT: rest motor threshold, represented as a percentage of the maximal stimulator output) MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short interval intracortical inhibition ICF Intracortical facilitation. SCI: spinal cord injury. *p<0.05

Table 43 - Cortical excitability evaluation according to pain syndrome excluding patients with paresis moderate to severe (MRC <4)

Cortical excitability parameters	Neuropathic pain n= 41	Non-neuropathic pain n =38	No pain n =35	p effects between groups
RMT (%)	50.2 (12.1)	49.3 (9.8)	49.3 (9.0)	0.829
MEP 120 (μV)	275.7 (333.5)a	486.0 (491.3)b	624.9 (525.1)b	<0.001*
MEP 140 (μV)	804.7 (996.6)a	1203.6 (926.0)b	1801.4 (1715.2)b	<0.001*
MEP 140/120	13.1 (44.1)	3.2 (2.1)	3.3 (1.8)	0.822
SICI	3.8 (15.5)	1.3 (1.5)	0.8 (0.7)	0.122
ICF	8.1 (35.6)	2.1 (2.2)	2.5 (2.6)	0.234

Variables are expressed in mean and standard deviation Numbers followed by different letters are statistically different in subgroup analysis with Bonferroni correction (p<0.0167) RMT: rest motor threshold, represented as a percentage of the maximal stimulator output) MEP 120: motor evoked potential for stimulus intensity at 120% of the RMT. MEP 140 motor evoked potential for stimulus intensity at 140% of the RMT. SICI: short intracortical inhibition ICF Intracortical facilitation. SCI: spinal cord injury. *p<0.05

Table 44 - General linear model with MEP 120% as the dependent variable, pain groups as fixed factor and medication, spasticity, and motor impairment as covariates

	Beta coefficient	Significance	Confidence interval
Neuropathic vs. non-neuropathic pain	243.1	0.093	-41.2 –527.4
Neuropathic pain vs. no-pain	438.7	0.002	157.8 –719.6
Non- neuropathic pain vs. no pain	-195.6	0.154	-465.5–74.2
Motor impairment	276.5	0.0326	23.0 –529.9
Spasticity	-30.9	0.786	-255.6–193.8
Medication	-10.7	0.936	-277.0–255.5

MEP: Motor evoked potential

Table 45 - General linear model with MEP 140% as the dependent variable, pain groups as fixed factor and medication, spasticity, and motor impairment as covariates

	Beta coefficient	Significance	Confidence interval
Neuropathic vs. non-neuropathic pain	469.5	0.084	-63.9 –1003.0
Neuropathic pain vs. no-pain	1012.7	0.001	485.6 –1539.8
Non- neuropathic pain vs. no pain	-543.2	0.036	-1049.6 – -36.8
Motor impairment	-131.0	0.587	-603.6 – 344.6
Spasticity	99.2	0.643	-322.5 –521.0
Medication	125.2	0.621	-374.5 –624.9

MEP: Motor evoked potential

Considering MEP can be influenced by lesion location, groups were paired according to this variable. We also performed a two-way ANOVA to compare the main effects of type of pain (neuropathic, non-neuropathic, and no-pain) and lesion location (cortical, subcortical, brainstem and cerebellum, cervical and thoracic) as well as their interaction effects on the MEP 120 and 140. For the MEP 120, the type of pain was statistically significant (p=0.001), while lesion location was not (p=0.085). The main effect of pain type yielded an effect size of 0.089, indicating that 8.9% of the variance in MEP 120 was explained by pain type (F(2,148)=7.25, p=0.001). Levene's test showed that the variances of the groups were not equal ((14,148)=4.553, p<0.001. For the MEP 140, the type of pain was statistically significant (p<0.001), while lesion location was not (p=0.299). The main effect of pain type yielded an effect size of 0.11, indicating that 11%

of the variance in MEP 140 was explained by pain type ($F(2,148)=9.46$, $p<0.001$). Levene's test showed that the variances of the groups were not equal ($(14,148)=2.069$, $p=0.017$.

4.3.8 Correlation analyses

There was a moderate negative correlation between MEP and dynamic mechanical allodynia ($\rho =-0.36$, $p<0.001$) and a negative correlation between MEP and cold allodynia ($\rho =-0.30$, $p<0.001$). There was no significant correlation between pain intensity, motor impairment, Barthel index, and spasticity with MEP changes.

Discussion

5. Discussion

In CPSP patients' characterization, we compared the study group to stroke patients with non-neuropathic post-stroke pain and pain-free, matched by sex, age, and stroke region (cortical, subcortical, and cerebellum). CPSP patients reported higher sensory and affective pain sub-scores, as well as a trend toward more functional impairment compared to non-neuropathic PSP patients. Using standardized manikin-based assessment, we found that CPSP was distributed over more extensive and also spatially diverse body areas, such as the face, arms, legs, or hemi-body, which contrasted with PSP-Non where the pain was present more frequently axially: in the neck, shoulders, and knees. The quality of pain was also different between groups, with CPSP being more frequently continuous, burning, tingling, and evoked by cold stimuli, compared to non-neuropathic PSP, which was, in turn, more commonly located, intermittent, as pressure and deeply never reported as tingling or as electric shocks. Four of the five original neuropathic pain symptom clusters were more common in CPSP, except for deep spontaneous pain. In CPSP, burning (superficial) spontaneous pain was the symptom cluster with the highest scores, followed by paresthesia/dysesthesia.

At bedside examination, cold/mechanical dynamic allodynia occurred mainly in CPSP and was present in the majority of these patients. Also, hyperpathia was one of the most frequent signs found in the CPSP group, present in more than 70% of patients. Under QST, CPSP had more thermal detection deficits in the painful area compared to the two control groups. These differences were present not only in side-to-side comparison within each patient but also in comparison with both control groups.

In addition, there was a positive correlation between abnormal thermal pain thresholds and paroxysmal pain, while altered mechanical pain thresholds correlated with burning pain/evoked pain scores. From the logistic regression, the association of pain NPSI score, presence of allodynia on bedside examination, and cold threshold detection abnormalities on QST [CDT from painful side/mirror side < 41% (30)] explained 77% of the occurrence of neuropathic pain.

In the investigation between lesion location, pain symptoms, and sensory profile in central neuropathic, we have observed that the two groups (CPSP and CPSCI), despite presenting similar pain intensity, have significant differences in pain descriptors, standardized bedside examination, and QST findings. CPSP patients had more evoked and paroxysmal pain, while CPSCI patients had more paresthesia, squeezing, and deep pain symptoms. In addition, CPSP patients had more pinprick hypoalgesia and allodynia to thermal and mechanical stimuli, while CPSCI patients had more sensory hypoesthesia (to touch and to cold), more pinprick hyperalgesia, and hyperpathia. On QST, CPSP had lower cold limen, mechanical and cold pain thresholds. In summary, CPSP presented more evoked and paroxysmal pain and lower cold detection thresholds and cold limen difference, while CPSCI showed more deep pain with more signs of impairment of spinothalamic (mechanical pain thresholds) and lemniscal pathways (higher mechanical detection thresholds). There was a negative correlation between evoked pain and MPT (-0.38, $p<0.001$) and wind-up ratio (-0.38, $p<0.001$).

Cortical excitability assessment evidenced significant changes in CNP compared to normative data from healthy people(106), including changes in parameters related to GABA and glutamate activity and neuronal membrane excitability. In particular, about three-fourths of CNP patients had abnormally reduced MEPs. When comparing

CNP patients with control individuals presenting no pain after lesion or chronic pain of non-neuropathic origin, some CE changes remained significant. Notably, in patients with CNP due to stroke, there were marked reduced MEP values compared to the other control groups. These changes were found even in the brain hemisphere not affected by the lesion. In CPSCI, we observed a more defective SICI compared to control groups, while in stroke, SICI seems to be defective in the CPSP and PSP-Non groups, with mean values greater than one; however, the differences were not statistically different. MEP changes correlated with two of the most common abnormalities in the physical examination in central pain patients: mechanical and thermal allodynia, and exclusion of patients with motor weakness, spasticity, or taking psychoactive drugs known to affect MEP had no significant changes in these findings.

5.1 Central post-stroke pain: a controlled symptom-psychophysical characterization

We have reported symptom profile correlations with sensory characteristics of CPSP patients compared to matched pain-free and post-stroke pain without neuropathic pain groups. This was an original approach to dissect what in CPSP is specific to this condition relative to other post-stroke chronic pain syndromes or stroke in general.

The differences between CPSP and PSP-Non distribution were in line with previous reports (20,39,50,97,149,163–166). CPSP patients referred intense pain, higher sensory and affective pain sub-scores, as well as a trend toward more functional impairment and more severe motor impairment in the upper limbs. The quality of pain was also different between groups, with CPSP being more frequently continuous, burning, tingling, and evoked by cold stimuli, compared to non-neuropathic PSP, which

was more commonly deeply located, intermittent, in pressure, and never reported as tingling or as electric shock.

Regarding non-neuropathic post-stroke pain, the most prevalent pain areas corroborate the importance of the mechanical component in its development. Nociceptive pain (musculoskeletal) and headaches were the most common non-neuropathic pain reported here (163). Persistent post-stroke headache affects up to 23% of stroke patients and has a tension-type phenotype (167,168), as we found in most patients with new-onset headaches. Additionally, most cases of headache were associated with musculoskeletal pain and myofascial trigger points. Musculoskeletal pain is one of the most common post-stroke complications and can significantly impact physical independence (164,165,169). Also, myofascial pain syndrome was frequent in PSP-Non, affecting 75% of the sample. This component was rarely investigated in post-stroke pain syndromes (39,170).

Notwithstanding, these issues are underreported and underdiagnosed. Patients with non-neuropathic pain were under regular medical follow-up. However, almost half of them had no diagnosis regarding their painful condition and were not under treatment, despite the negative impact non-neuropathic pain had on daily activities.

Burning (superficial) spontaneous pain was the NPSI phenotype with the highest scores among CPSP patients, followed by paresthesia/dysesthesia and evoked pain. Burning was also the most freely reported descriptor in other CPSP studies, mentioned by more than half of the patients. (20,21,39,50,71,97,160,171) When NPSI was applied to assess central and peripheral neuropathic pain, burning pain remained among the most common pain descriptors. However, pain evoked by cold was among the least frequently reported, especially in peripheral neuropathies (30,45,115,172,173). Although neuropathic pain descriptors seem to vary little despite

the etiology and are considered trans-etiological, central post-stroke pain had more cold-pain-related descriptors as described here (28,30).

One previously postulated explanation for the high prevalence of burning and evoked by cold pain descriptors associated with a high prevalence of spinothalamic tract impairment would be that the disinhibition resulting from this pathway's impairment could trigger these sensations. Blocking cold-specific afferent input can release cold-induced burning pain. (174) Through neurophysiological recordings, it has been put forth that the burning pain sensation elicited by touching warm and cold bars was due to central disinhibition. (175) Although burning pain and CDT changes were the most frequent symptoms and signs in our study, they were not correlated, suggesting different primary driving mechanisms. Burning pain score was rather correlated with altered mechanical detection and pain abnormalities (i.e., hypersensibility), while evoked pain was correlated with higher mechanical evoked pain scores and lower mechanical pain thresholds (mechanical hyperalgesia and allodynia). It was paroxysmal pain that was rather correlated with thermal pain denervation. Previous studies reported that patients with burning pain had more remarkable changes in thermal thresholds(175)(51). On the other hand, few studies have explored the relationship between neuropathic pain descriptors and sensory changes, and studies with large sampling have found no correlations between pain symptoms and somatosensory abnormalities in mainly peripheral neuropathic pain. (28,176)

At bedside examination, negative signs such as cold and tactile hypoesthesia and hypoalgesia were present in the three groups and, unlike the positive signs [i.e., thermal hyperesthesia(47), hyperalgesia(11) and allodynia(11,48)], that were more frequent in CPSP. 37.5% of PSP-Non had pain in negative signs regions, pointing out

that pain in regions with sensory abnormalities is not necessarily neuropathic. Although hypoesthesia presence or absence did not differ between groups, when assessing its spatial distribution, patients with CPSP present more areas of impairment compared to the No-Pain group. Cold and mechanical dynamic allodynia occurred almost exclusively in CPSP patients. It was present in 61.5% of the sample. However, allodynia is not pathognomonic of neuropathic pain and was reported in a small percentage of sensory stroke patients without pain. (11,47) Hyperpathia was one of the most frequent signs found in the CPSP group, making up 71,8%, with significantly higher proportions than controls. This sign was also previously reported and prevalent in CPSP (39,51,171), although it was not compared to control groups. While dysesthesia, allodynia, or hyperalgesia have been reported to predict CPSP(75), hyperpathia remains a relatively underexplored sign that may also be a useful predictor of CPSP and was previously reported to be prevalent in this condition (39,51,171)

Our static and dynamic QST battery included detection determination, experimental pain stimuli, and conditioned pain modulation determination. When considering all QST results and classifying sensory inputs into spinothalamic tract (STT) or dorsal column-medial lemniscal related, CPSP patients had significantly more STT and lemniscal dependent deficits and gains of function compared to the control groups (Figure 7).

We also have reported that CPSP had more thermal detection deficits in the affected area compared to the two control groups. This is one of the main findings of this study since these differences were present not only in side-to-side asymmetry within each patient but also in comparison with both control groups. This motivated us to examine whether cold and warm detection thresholds were affected to the same extent by using the CDT/WDT ratio calculation. In fact, we found that CPSP patients

have a disproportionately higher asymmetry in WDT and CDT compared to controls, and these differences, explored by the sensory limen, correlated with the presence of neuropathic pain. This finding is original and is in line with several studies on experimental thermal allodynia triggered by the thermal grill illusion of pain, showing that higher differences between non-painful cold and warm are responsible for more intense and more robust thermal heat allodynia as triggered by the technique(177).

Similarly, thermal deficit asymmetry was the only discriminative variable between pain and pain-free syringomyelia patients(22). These findings are also in accordance with the report that central pain in patients with Wallenberg's syndrome was less frequent when thermal abnormalities tended towards symmetry(97). Indeed, it has been proposed that more rostral sites of CNS lesions would affect sensory modalities more disproportionately than spinal lesions so that more cranial lesions would dissociate warm/cold and mechanical thresholds more markedly compared to spinal lesions(81).

This data suggest that CPSP patients have altered cold and warm detection thresholds, and that both sensory channels are disproportionally affected, with warm sensation showing greater side-to-side asymmetry compared to cold. The correlation analysis revealed an interesting trend, with a positive correlation between altered thermal pain thresholds and paroxysmal pain, while mechanical pain thresholds correlated with burning pain/evoked pain scores. Similar correlations between paroxysmal pain intensity and thermal sensitivity were reported in peripheral neuropathic pain studies (178–180). It has also been reported that patients with syringomyelia having exclusively spontaneous pain (which included paroxysmal pain) had more asymmetrical and more severe thermal deficits, while patients with allodynia had less affected thermal deficits(41). Furthermore, a large body of evidence from

human neurophysiology studies assessing thinly-myelinated (e.g., laser-evoked potentials) and large-myelinated (e.g., somatosensory evoked potentials-SEPs) has suggested that continuous ongoing pain would be related to injuries affecting small fibers. In contrast, paroxysmal pain would be related to lesions to large myelinated fibers(27). However, even in these reports, these distinctions are not unequivocal: in patients with multiple sclerosis, about a third of those with pain due to Lhermitte's sign (shock-like triggered though the neck-dorsum by neck flexion) had normal SEPs, while SEPs were abnormal in about a third of those presenting with ongoing extremity pain(42). Importantly, most hypothesis linking myelinated fiber lesions leading to abnormal discharges and paroxysmal pain relies on an otherwise normal second/third order wide-dynamic range neurons (WDR) that would receive high-frequency discharges conveyed by injured myelinated fibers (from peripheral nerves(181) or from the dorsal column lemniscal pathways(42,182) and would then divert them into nociceptive pathways, where discharges would eventually be perceived as painful. In central neuropathic pain, second or third-order sensory neurons are frequently included within the lesion area, thus potentially altering the central processing of thermo-nociceptive inputs. It must also be kept in mind that correlations found here and elsewhere do not imply causality and may be due to an undetermined mediating cofactor between paroxysms and thermal thresholds abnormalities, such as the severity of the lesion.

CPSP had higher disproportions of CDT and WDT impairment than control groups and a moderate correlation with neuropathic pain. In paradoxical painful sensation induced by a thermal grill investigation, the frequency and intensity of painful sensations were directly related to the magnitude of the difference in the temperature between the warm and cold bars of the grill, suggesting that pain can be the result of

an addition of non-noxious warm and cold signals(154). This painful sensation seems to be inhibited by the CPM in healthy individuals(183). In our study, stroke patients generally have low conditioned pain modulation (CPM), although those without chronic pain tended to present CPM closer to normal values than those with neuropathic and non-neuropathic pain. This may be related to lesions in the pathways involved in the descending inhibitory control of pain or to the individual's own characteristics before the stroke. We cannot rule out that these low CPM values, in general, could be related to lesions of the descending CPM system by the stroke itself, as has been proposed for spinal cord lesions, irrespective of the presence of chronic pain (13,144). The number of CPSP patients included in the CPM assessment was restricted, and we could not differentiate whether the reduction in CPM would be related to neuropathic pain or chronic pain in general.

Previous studies on central neuropathic pain have reported that patients had altered spinothalamic-dependent abnormalities, while lemniscal pathways could be either intact or affected (19,20,50,51,149,184). This has led to the imbalance theory(185), postulating that CPSP would occur due to residual lemniscal inputs arriving in the absence of STT information in higher-order neurons. Our results are in line with this view, since QST-based thermal cold hypoesthesia carried the highest odds ratio for CPSP (=12.0), and CPSP patients had more widespread sensory abnormalities. However, classic QST batteries offer a relatively limited assessment of lemniscal function, and one cannot refute that concomitant lemniscal abnormalities were not present in our samples.

Most clinically relevant results came from the logistic regression. The association of pain NPSI score, presence of allodynia on bedside examination, and cold detection threshold abnormalities on QST [CDT from painful side/mirror side < 41% (40)]

explained 77% of the occurrence of neuropathic pain. Interestingly, this model comprises the basic steps in the clinical diagnosis of neuropathic pain: use of pain descriptors, presence of abnormal sensory gain on bedside examination, and the determination of STT-related deficits (CDT). This may be potentially useful information in the distinction between neuropathic from non-neuropathic PSP and may help better design interventional trials in the future.

One important finding, with a potential impact on CPSP definitions and how to differentiate it from its mimics, was that a third of non-neuropathic PSP patients had their pain located within the sensory deficit area. These patients did not fulfill the criteria for neuropathic pain and had other clear causes of non-neuropathic pain, such as headaches and musculoskeletal pain. This finding has been previously reported for spinal cord pain(14) but not yet in CPSP. This information has clinical relevance and calls attention to the necessity to have pain descriptors included in neuropathic pain definitions, as well as to the requirement to proactively search for sources of nociceptive pain within the deafferented area in a patient with clear neuropathy(12).

Interestingly, up to 10% of CPSP had neither STT nor lemniscal deficits on QST (Figure 8 and Table 15). This suggests that QST, a test restricted to a body segment of a few square centimeters, may fail to detect sensory abnormalities such as cold hypoesthesia and other bedside sensory changes used here as an inclusion criterion. Similar to others(21,47,48,50,51,73,97,149–151,171) (Table 46), we performed QST in the area with more intense pain, which may not necessarily be the body area with more prominent sensory abnormalities. In fact, we have shown that the sensory deficit area is not only wider but qualitatively different between groups, and sensory assessments based on the area of maximal pain may miss areas with maximal sensory denervation or non-painful sensory gain of function. This also highlights the challenge

related to the choice of the control area in central pain studies. In these instances, since the painful area may vary significantly in body location across individuals from the same experimental group, control areas cannot be compared to healthy volunteers-based normative data and are, instead, based on the same rationale used during the neurological examination, comparing dermatomes above and below the sensory level in spinal cord injury(14) or syringomyelia(22,41), or the mirror area in cases of stroke (21,47,48,50,51,73,97,149–151).

It has been proposed that, compared to healthy volunteers-based normative data,(47) stroke patients may present subtle sensory abnormalities even on the normal body side. However, it remains unknown whether the origin of these ipsilateral changes is related to concomitant diseases associated with stroke (e.g., diabetic polyneuropathy), bias related to slower reaction time in stroke patients, or maladaptive plasticity after stroke. The fact is that these reports highlight the need to have control groups with pain and stroke in order to account for these abnormalities ipsilateral to the stroke side.

Another challenge is related to the inclusion and assessment of patients with stroke-related acquired language dysfunction. Here, patients with cognitive impairment were excluded in order to perform a detailed assessment of pain descriptors and sensory profiles. However, this is a limitation of our results' external validity since only language-spared patients were assessed, and our findings may not apply to those with different degrees of aphasia.

Table 46 - Quantitative sensory test studies for central post-stroke pain investigation

Study	Patient sample	Control group	Methods	Findings
Boivie J, *et al.* 1989 [35]	27 CPSP (Eight brainstem lesions, nine thalamic, six suprathalamic, and four undetermined)		Area: feet, hand, and face vs. contralateral side Abnormal: thresholds at least twice as high as the control side.	All had abnormal temperature and pain sensibility: Hypoalgesia: 37% Mechanical hypoesthesia: 52% Abnormal vibration sensibility: 41% Hyperpathia: 88% Hyperalgesia: 60% Dysesthesia: 85% Allodynia: 23%
Leijon G and Bowsher D, 1990 [40]	36 CPSP	13 Stroke with a sensory deficit and without CPSP	Area: Side with symptoms and mirror Method of limits Descriptive analysis	Cold, warm, and cold pain thresholds abnormalities: 89% vs. 50% Heat pain thresholds – normal in all subjects. Abnormal tactile sensation: 86% vs. 38%, Abnormal pinprick sensation: 86% vs. 54% Allodynia: 57% (28% to touch, 42% to cold) vs. 0%. All CPSP had cold, warm, or pinprick abnormalities.
Vestergaard K. *et al.* 1994 [86]	11 CPSP All had a supratentorial lesion (five thalamic, six solely extrathalamic, seven also brainstem		Area: worst pain area (all in the thenar eminence) and mirror area Methods of limits Statistical comparison between pain area and mirror	Increased threshold of thermal (cold 91%, warm 100%) Abnormal sensibility to pain 36% Abnormal sensibility to touch 27% Allodynia: 72.7% (cold 56%, touch 54%)
Bowsher D, 1996 [32]	74 Central 61 CPSP		Measures at four sites: The greatest pain area and its mirror, and the least pain area and its mirror Methods of limits Statistical analysis between greatest pain vs. mirror and least pain vs. mirror, Greatest pain vs. least pain ($p<0.05$)	Greatest vs. least pain: Significant for pinprick, warm and cold. All modalities were significant for greatest vs. mirror and least vs. mirror. 72% allodynia (52% tactile, 19.5% thermal, 22% movement)

CPSP: Central post-stroke pain. VPL = ventroposterior thalamic nucleus.

Table 47 - Quantitative sensory test studies for central post-stroke pain investigation–continuation

Study	Patient sample	Control group	Methods	Findings
MacGowan DJL et al., 1997 [39]	9 CPSP with Wallenberg syndrome	10 Wallenberg syndrome without CPSP	Standard areas tested bilaterally Method of limits/forced-choice Comparison to healthy controls (classified as elevated or not)	CPSP thresholds from the cheek contralateral to the lesion were normal in eight of nine cases with CPSP and abnormal in all 10 cases without CPSP. CPSP allodynia – mechanical (50%) cold (75%)
Bowsher D *et al.*, 1998 [19]	32 CPSP VPL 21 Brainstem 11	20 Stroke patients with a sensory deficit and without CPSP	Side with symptoms and mirror Methods of limits The difference between the affected side and mirror compared between CPSP and control	CPSP and control had differences comparing maximally affected and mirror areas for warm, cold, pinprick, and heat pain) VPL vs. control: differences for pinprick and cold detection Brainstem vs. control: differences for pinprick, cold and warm, and hot pain. VPL vs. brainstem: differences only for warm detection.
Fitzek S. *et al* 2001 [87]	8 patients with Wallenberg syndrome and CPSP	Four patients with Wallenberg syndrome without CPSP	Both sides of the face (upper cheek). Method of limits Statistical comparison between affected and mirror area	Cold and warm detection, cold and heat pain, and touch thresholds in the ipsilateral face vs. mirror were significantly different in all patients with facial pain but not in patients without pain.
Greenspan JD *et al* 2004 [38]	13 CPSP		Affected and mirror area Method of limits Abnormal threshold: the value of the mean ± 2SD outside the normative range Included absolute values and differences between the affected and unaffected side	Cold hypoesthesia: 84.6% Warm hypoesthesia:92.3% Cold hypoalgesia: 46.1% Warm hypoalgesia: 7.6% Tactile hypoesthesia: 38.5% Cold allodynia: 23% Brushing allodynia: 53.8% More tactile allodynia in individuals with normal tactile detection.

CPSP: Central post-stroke pain. VPL = ventroposterior thalamic nucleus.

Table 47 - Quantitative sensory test studies for central post-stroke pain investigation–continuation

Study	Patient sample	Control group	Methods	Findings
Bowsher D 2005 [88]	64 CPSP		Means of somatosensory perception threshold differences (affected-mirror)	About half of patients with CPSP had allodynia Pure cold allodynia vs. cold plus mechanical allodynia: affected- unaffected cold threshold difference greater in the latter, but not significant (p=0.06)
Kalita J *et al.* 2011 [102]	23 CPSP		QST, SPECT, and MRI	Reduced pain threshold: 43.5% Increased pain threshold: 56.5% About half of CPSP had allodynia, temporal summation, or punctate hyperalgesia: Findings were similar in patients with thalami and extra thalamic lesions. SPECT and MRI findings were not different in CPSP patients with and without allodynia.
Krause T. *et al.* 2016 [37]	25 CPSP	25 sensory stroke without pain	Area of painful sensation and mirror confined to either the face, hand, or foot. Z score	CPSP: alterations of thermal and mechanical thresholds on the affected side. Higher values for paradoxical heat sensation and dynamic mechanical allodynia, and elevated cold detection threshold. Sensory stroke: similar albeit less pronounced changes in thermal and mechanical thresholds. Both groups: considerable QST changes on the unaffected side.

CPSP: Central post-stroke pain. VPL = ventroposterior thalamic nucleus.

5.2 Lesion location, pain symptoms, and sensory profile in central neuropathic pain

We evaluated a large sample of patients with CNP with lesion sites located in either the brain or the spinal cord. 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 (1,23,25,28–31,36,47,66). 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(186)(20) and extent of spinothalamic tract (STT) injury(41) within the same disease. Leijon G *et al*. were among the first to evaluate pain descriptors and somatosensory alterations according to lesion location in a standardized methodology. Patients were subdivided into three main groups (brainstem, thalamic and extrathalamic). It was 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, while burning was the main descriptor in the other two groups. There were no major differences regarding abnormalities in temperature and pinprick (20).

Additionally, sensory differences in CPSP were observed regarding supratentorial and infratentorial lesions. The former had sharpness and cold deficits, whereas the latter additionally had warm and heat pain deficits, suggesting that unmyelinated fiber-dependent inputs would be more affected in strokes located

infratentorially (50). 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(81). A small percentage of fibers ascending from the anterolateral funiculus reach the diencephalon directly, and the majority terminates in the infratentorial brainstem(81). This would explain some sensory differences found between 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 (32–35,37). In our study, we observed CPSCI had higher mechanical pain thresholds with similar cold detection and pain thresholds and warm detection and heat pain thresholds, suggesting dissociation of these spinothalamic pathways, as demonstrated in the study above

We found that patients with CPSP had more evoked pain, cold and mechanical allodynia, and lower cold limen. It was previously suggested that patients with allodynia had reduced thermal deficits(41), and patients with evoked pain had less structural damage and more preserved spinothalamic and lemniscal tracts on QST(22). Also, 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. (73) We also observed a moderate negative correlation

between MPT and evoked pain, cold allodynia, and wind-up, suggesting that less impairment of the spinothalamic tract could be associated with evoked pain.

On physical examination, CPSCI patients presented with more spontaneous deep pain and more signs of deafferentation of the lemniscal, spinothalamic, and corticospinal tract (more cold and tactile hypoesthesia, motor impairment, and spasticity) compared to CPSP. It was also previously described that neuropathic pain dimensions, deep pain, and paresthesia/dysesthesia correlated with indices of spinal cord structural damage(22). 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 SCI (NMOSD). 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 level in SCI, similar to what is performed in clinical practice. CNP sensory evaluation by QST can be challenging in such instances because pain areas may be located in diverse body segments (18,39), not necessarily those previously mapped by initiatives to create normative data for QST(40). Furthermore, inherent innervation density, innervation quality, and skin thickness differences across body regions may affect the interpretation of QST results(40). Still, in relation to the comparison with the control areas, it is not possible to affirm that the differences between the pain area and the control are similar when comparing sides or somatosensory levels. On the other hand, most thresholds were similar between groups except for MPT, STCP, cold limen, MDT ratio, and CPT difference, which were congruent with the different clinical manifestations of neuropathic pain between the two groups, as discussed above.

Here we have also compared standardized bedside clinical examination with results from a comprehensive battery of QST. We found several differences 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 biophysical of the stimulus delivered in each of the scenarios, the body area assessed, and the directions given to patients in order 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 that 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 critical point is that in the present study CPSP group were older (59.2 ± 11.2 vs. 48.2 ±11.1, $p<0.001$) and had a higher proportion of male (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 (20,21,187), while NMO is in middle-aged women (188). Even though stimulus-specific changes in pain perception according to sex and age were previously reported(40,189,190), most differences found here 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 present findings to other patients with central pain of distinct etiology remains unclear.

5.3 Corticomotor excitability in central neuropathic pain

We have shown that individuals with CNP have changes in corticomotor excitability compared to normative data from healthy people, including changes in parameters related to GABA and glutamate activity, as well as to neuronal membrane excitability. In particular, about three-fourths of CNP patients had abnormally reduced MEPs. When comparing CNP patients with control individuals presenting no pain after lesion or chronic pain of non-neuropathic origin, some CE changes remained significant. Notably, in patients with CNP due to stroke, there were marked reduced MEP values compared to the other control groups. These changes were so stark that they could be found even in the brain hemisphere not affected by the lesion in the case of stroke patients.

Interestingly, MEP changes correlated with two of the most common abnormalities in the physical examination of central pain patients: mechanical and thermal allodynia(65). Exclusion of patients with motor weakness, spasticity, or taking psychoactive drugs known to affect MEPs had no significant changes in these findings. However, the general linear model did not rule out the influence of motor impairment in MEP 120%, even though motor impairment, spasticity, and medication did not influence MEP 140%.

Among the CE measures, MEP is one of the most studied parameters in clinical neurophysiology(46). Stimuli over the motor cortex (M1) excite intracortical neurons and corticospinal cells, followed by spinal motoneurons, producing a motor evoked response. MEP evaluates the synaptic excitability of cortico-cortical, cortico-motoneuronal, and spinal motoneurons(107). However, MEP changes are not only present in diseases involving the motor pathways. Different neurological conditions have been associated with MEP reduction, such as stroke, multiple sclerosis, cervical

myelopathy, cerebellar ataxia, and epilepsies(107,109). MEP reduction has also been reported in healthy individuals undergoing acute experimental pain(191–193). A meta-analysis revealed moderate to strong evidence of reduced S1 and corticomotor excitability during acute pain and up to 30 minutes following its resolution(191). In a study with rTMS and anodal stimulation of the motor cortex, the selective activation of nociceptive fibers (Aδ and C) resulted in MEP reduction in both hemispheres. Conversely, non-nociceptive stimuli failed to elicit the same effect, suggesting the reduction of the M1 excitability was specifically due to the activation of nociceptive pathways(109).

It has long been demonstrated in cats that thalamic hyperactivity after spinothalamic transection could be inhibited by stimulation of the motor cortex(194). In addition, motor cortex electrical stimulation can provide pain relief in CPSP, while thalamic relay nucleus deep stimulation did not have the same results(194). Therefore, these authors postulated that motor cortex afferents and efferents could inhibit abnormal hyperactivity within the CNS underlying deafferentation pain. (194,195).

In addition, repetitive high-frequency TMS delivered to M1, which has an excitatory effect, can reduce neuropathic pain and restore cortex excitability abnormalities such as defective intracortical inhibition (86,90) and also alter functional connectivity between the mediodorsal nucleus of the thalamus and the amygdala(92). Organized reciprocal connections between the motor cortex and the sensory system, including the amygdala, medial thalamus, anterior cingulate, and sensory cortex, were described (92,196), and brain network reorganization and maladaptive neural plasticity in different brain circuits, including the motor pathway, considered to contribute to neuropathic pain development(102).

This is the first study to include a large sample of CNP patients for CE assessment. Only two previous studies have assessed CE parameters (RMT and MEP) in CPSP, with conflicting results (90,99). Moreover, since the control group was composed of healthy individuals, it was not possible to ascertain which changes were due to stroke per se, which were related to chronic pain in general, and which were specifically associated with CNP. In one study, RMT was higher in the stroke group(90). However, CE was assessed only in the affected hemisphere, and high RMTs were interpreted as related to motor impairment since 68% of CPSP had mild to moderate weakness(90).

We also found significantly defective SICI in patients with neuropathic pain compared to those without chronic pain, as previously reported in samples of neuropathic pain of central and peripheral etiologies(86,88). Studies assessing samples composed of patients with peripheral and central neuropathic pain have shown a reduction of intracortical inhibition, suggesting motor cortex disinhibition with impaired GABAergic neurotransmission (86,113,197). Defective intracortical inhibition was also reported in other chronic pain syndromes (52) and acute pain (112). Reduction of intracortical inhibition was described in the affected and unaffected hemispheres during the acute phase of stroke and tended to be normalized during the chronic phase(103,104). Loss of inhibition and reduction of GABA activity have been hypothesized to allow for cortical plasticity to occur as a way to allow for motor function recovery(103,104) after CNS injury.

Additionally, compared to normative data based on healthy individuals matched for age and sex, more than half of the CNP and a third of the non-neuropathic pain patients had defective SICI. One important point is that if on a group level, changes in cortical excitability were present in a reasonably homogenous pattern in CNP, with a

clear MEP reduction, the individual classification of patients based on normative data disclosed a rather non-monotonic pattern: When looking at CE changes in each patient and classifying them as normal, high, or low according to healthy volunteer data, we not only confirmed that a significantly higher proportion of CNP patients had low MEPs but additionally found considerable inter-individual variability in CE results. In fact, a paradoxical augmented MEP amplitude was observed in 20.3%, for MEP 120%, and 19.9% for MEP 140% in CNP patients, which could not be detected on a group level assessment. This argues for the concept that there is more heterogeneity between individuals than differences between different etiologies of CNP. In part, it should explain why non-individualized pain treatments, based on a single mechanism of action, usually provide pain relief to only a limited proportion of patients.

Previous studies on non-neuropathic or mixed neuropathic pain patients reported correlations between CE and clinical manifestation of neuropathic pain, including pain intensity(86,113), thermal paresthesia(113), and allodynia(88,108). Additionally, repetitive TMS was associated with thermal sensory perception improvement(99,198). We reported that CNP is associated with the two most common evoked pain findings in CNP patients: mechanical and thermal allodynia. These findings are interesting since both types of allodynia are more common in CNP due to stroke compared to stroke patients with non-neuropathic pain and those without pain, and may suggest that loss of inhibition and sensory discrimination due to top-down modulatory centers such as M1 could lead to pain hypersensitivity. Indeed, M1 noninvasive stimulation has been shown to relieve pain in patients with peripheral neuropathic pain while improving cold thermal discrimination in patients with neuropathic pain of peripheral and central etiologies(198)

Due to the cross-sectional design of the present study, one cannot determine causality, and it remains unknown whether CE changes found here are driving the occurrence of CNP or are just epiphenomena. Even though subgroup analyses excluding patients with significant motor impairment did not affect the results and the correlation analysis, it is not possible to rule out that spinothalamic tract impairment would contribute to lower MEP. Moreover, the comparisons with previous studies are limited due to parameter heterogeneity and lack of control groups. Our study groups were matched for sex and lesion location but were not according to incapacity, motor impairment, spasticity, or spinothalamic tract lesion. Such pairing or matching is not only challenging in practical terms but is, instead, methodologically undesired. Previous studies evidenced that CNP patients were more functionally impaired than those without CNP(72), so functional loss may be considered part of the CNP syndrome, and by selecting only CNP with mild functional impairment, one would lose the external validity of the findings.

The study has some limitations. Data on non-pharmacological treatments of our samples were not systematically collected and could not be used as a covariate in our analyses. Another limitation is that the CE protocol used had a reduced number of pulses to measure MEPs compared to those used in other neurophysiology studies. This was an active choice aimed at decreasing the length of the experimental study session and maintaining patient collaboration and was based on several previous studies in chronic pain patients(63,199–201) and one of the largest normative data studies to date(106). Additionally, the natural variability of MEPs should add bias and noise to our assessments, hiding MEP changes in our patients. However, in reality, MEPs changes were the most consistent changes found here, being persistent despite all our efforts to prove it being influenced by lesion location, etiology, medication use,

loss of motor strength, and spasticity. Despite these facts, it remains to be determined if our results would be changed by employing more pulses to measure MEPs. One interpretation is that MEP changes in central neuropathic pain are robust enough to be detected despite the presence of other variables influencing these variables. It may also be that in patients with central neuropathic pain, MEP variability is not as marked as in healthy volunteers, allowing us to measure them with a lower number of pulses due to lower variability. These hypotheses remain to be tested(88).

CE corresponding to the area of the hand seems to reflect global changes in the motor cortex, as we observed in this study and previously demonstrated(199–202). However, studies assessing CE corresponding to the specific area of pain, other than hand, could clarify whether evaluating specific regions would provide additional information.

Conclusions

6. Conclusions

Central neuropathic pain substantially impacts patients' future quality of life, performance, and gains during rehabilitation. Management of CNP is often challenging. Many patients will need drugs combination, which increases the risk of adverse effects and drug interactions. One of the major barriers to optimizing the response to CNP treatment is the lack of knowledge about the multiple mechanisms involved in this painful syndrome, lack of diagnostic accuracy, and relatively ineffective drugs. The wide variety of neuropathic symptoms and signs could underlie different pain mechanisms, and profiling patients according to specific clinical manifestation (pain descriptor and somatosensory abnormalities), but not according to the disease related to neuropathic pain, would allow for the design of individualized treatment strategies.

Central post-stroke pain is among the most frequent causes of CNP and its mechanisms, as in CNP in general, remain poorly understood. Insights have been gained from neuroimaging, neurophysiology, basic research, and psychophysics evaluation. However, the integration of a comprehensive clinical characterization of these patients with the concomitant abnormalities of the somatosensory system in a controlled fashion that includes PSP of non-neuropathic origin, by far the most common PSP subtype, could contribute to determining clinical features typical of CPSP or related to other post-stroke pain syndromes or the stroke.

We compared a sample of CPSP patients with non-neuropathic PSP patients and stroke patients without chronic pain matched by age and stroke location in order to

dissect pain descriptors and somatosensory abnormalities from CPSP to PSP and stroke in general. We also correlated potential symptom-QST specific to CPSP. We observed that CPSP was associated with thermal detection deficits, allodynia, and hyperpathia, on bedside assessment, and several of the symptom clusters of CPSP were correlated to discrete QST parameters, which may provide pathophysiology insights into a mechanism-based approach to CPSP. Also, a combination of neuropathic pain symptoms, the presence of cold detection deficits, and allodynia explained a significant proportion (77%) of the occurrence of CPSP in our model. However, patients may present CPSP even in the absence of detectable abnormalities of the STT pathway by QST. These findings might have diagnostic utility and help better design personalized treatments based on clinical and QST findings for CPSP in the near future.

CNP can result from somatosensory system lesions anywhere or at any level along the neuroaxis. Additionally, the affected region seems to influence neuropathic pain characteristics e somatosensory abnormalities and indirectly courses with distinct pain mechanisms. We described and compared the sensory profile of CNP through pain descriptors, standardized bedside examination, and a comprehensive QST battery in two different etiologies of CNS lesions related to distant and nosologically different: stroke and spinal cord injury due to NMOSD. We observed that patients with CPSCI had more deep pain and signs of deafferentation of lemniscal and spinothalamic pathways, while CPSP had more paroxysmal and evoked pain and less somatosensory impairment, especially in mechanical pain and detection 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. Those with brain injury

had more paroxysmal and evoked pain and allodynia, while those with spinal cord injury had deep pain and higher mechanical pain thresholds. 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. This information may help better design phenotype-mechanism correlations for CPN and impact treatment choice.

Several hypotheses have been put forward to explain CNP, including both bottom-up and top-down processes such as thalamic deafferentation, spinothalamic dysfunction, central sensitization, and disinhibition of nociceptive networks. A brain network disorganization disorder has also been proposed as a mechanism of CNP. Maladaptive neuroplasticity is thought to occur insidiously after injury and to be responsible for the gradual installation of symptoms and signs that are not present right after the injury but, instead, develop insidiously, such as neuropathic and non-neuropathic chronic pain. Cortical excitability can be an additional tool to access plastic changes in the CNS through the evaluation of motor evoked potential, intracortical facilitation (glutamatergic interneurons), and short interval inhibition (GABAergic interneurons).

To describe CE changes attributable to CNP after CNS injury, we compared CNP related to brain injury after stroke or spinal cord injury (SCI) due to NMOSD to patients presenting similar CNS injury with non-neuropathic pain and those without chronic pain, matched by sex and lesion location (for stroke: cortical, subcortical and brainstem, and cerebellum; and SCI: cervical and thoracic), through a battery of CE measurements and a comprehensive pain, neurological, functional, and quality of life assessments. We found that CNP was associated with CE changes, mainly in MEP

reduction for CPSP and SICI for CPSCI. These changes correlated with clinical findings seen in CNP. They may provide neurophysiological markers of pain development and persistence after CNS injury as a keyhole view into global cortical excitability plastic changes occurring in people with CNS lesions leading to CNP. New studies will help determine whether these plastic changes can be detected and monitored since pain development after CNS injury and whether systematic monitoring of patients since stroke or SCI onset could provide a neurophysiological marker of CNP development and potentially guide the development of preventive interventions aiming at CNP control and influence treatment choice efficacy.

Annexes

7. Annexes

Annexe A - Research ethics committee evaluation of the research project

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA USP - HCFMUSP

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Estimulação Magnética Transcraniana para Dor Central
Pesquisador: Daniel Ciampia Araujo de Andrade
Área Temática:
Versão: 8
CAAE: 05832812.6.0000.0068
Instituição Proponente: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.634.258

Apresentação do Projeto:
Nova documentação foi enviada.

Objetivo da Pesquisa:
Trata-se de relatório parcial, e pedido de inclusão de subtítulo (subprojeto).

Avaliação dos Riscos e Benefícios:
Sem alterações.

Comentários e Considerações sobre a Pesquisa:
No relatório, informa-se que 102 pacientes já foram avaliados, e o estudo prossegue. O subprojeto solicitado destina-se ao doutorado de uma participante, com o título "Dor central decorrente de acidente vascular encefálico: estudo controlado", de Luciana M. Barbosa.

Considerações sobre os Termos de apresentação obrigatória:
Não se aplica.

Recomendações:
Não há.

Conclusões ou Pendências e Lista de Inadequações:
Não há pendências.

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA USP - HCFMUSP

Plataforma Brasil

Continuação do Parecer: 1.634.258

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_750021_E5.pdf	29/06/2016 17:58:57		Aceito
Outros	Adendo_segundoLuciana_Barbosa.pdf	29/06/2016 17:57:38	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Adendo_Luciana_Barbosa.pdf	04/02/2016 11:13:14	Daniel Ciampia Araujo de Andrade	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	04/01/2016 22:08:35	Daniel Ciampia Araujo de Andrade	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	WORDTCLE_FVS.docx	18/12/2015 10:11:22	Daniel Ciampia Araujo de Andrade	Aceito
Outros	AdendoFelongitudinal.pdf	11/11/2015 09:48:25	Daniel Ciampia Araujo de Andrade	Aceito
Outros	digitalizar1230001 (1).pdf	29/06/2015 15:01:34		Aceito
Outros	CartaAdendo_Priscila_RG.04.05.15.v2.pdf	04/05/2015 14:29:02		Aceito
Projeto Detalhado / Brochura Investigador	PROJETO Insula Longterm DCA_RG_30.12.12.doc	25/11/2014 12:43:51		Aceito
Outros	cópia de Imagem (96).jpg	25/11/2014 12:41:18		Aceito
Outros	Carta Resposta Pendências_RG_DCA_30.12.12.doc	30/12/2012 13:48:35		Aceito
Outros	PROJETO Insula Longterm DCA_RG_30.12.12.doc	30/12/2012 13:48:03		Aceito
Outros	Carta Resposta Pendências_RG_DCA_22.10.12.doc	22/10/2012 16:14:13		Aceito
Outros	PROJETO Insula Longterm DCA_RG_22.10.10.doc	22/10/2012 16:13:53		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Anexo I - V4_RG.doc	22/10/2012 16:13:20		Aceito
Outros	ANUENCIA IPQ.pdf	07/08/2012 11:33:04		Aceito

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

TCLE / Termos de Assentimento / Justificativa de Ausência	Anexo I - V3_RG.doc	07/08/2012 10:52:43		Aceito
Outros	Anexo II- EMTDC.pdf	07/08/2012 07:49:16		Aceito
Folha de Rosto	EMTDC.pdf	24/07/2012 15:52:11		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 13 de Julho de 2016

Assinado por:
Joel Faintuch
(Coordenador)

Annexe B - Free, prior, and informed consent

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .:..... .....

DOCUMENTO DE IDENTIDADE Nº : ..... SEXO : .M ☐ F ☐

DATA NASCIMENTO: ...../...../.....

ENDEREÇO ..... Nº ..... APTO: .....

BAIRRO: ..... CIDADE .....

CEP:..... TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....

NATUREZA (grau de parentesco, tutor, curador etc.) .....

DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐

DATA NASCIMENTO.: ...../...../.....

ENDEREÇO: ..... Nº ..... APTO: .....

BAIRRO: ..... CIDADE: .....

CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA **"Estimulação Magnética Transcraniana para dor Central"**

PESQUISADOR : **Dr. Daniel Ciampi de Andrade**

CARGO/FUNÇÃO: **Coordenador do Centro de Dor do Departamento de Neurologia** INSCRIÇÃO CONSELHO RE GIONAL Nº **108.232**

UNIDADE DO HCFMUSP: **Divisão de Clínica Neurológica**

3. AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MÍNIMO ☐ RISCO MÉDIO ☐

RISCO BAIXO X RISCO MAIOR ☐

4.DURAÇÃO DA PESQUISA : **vinte e quatro meses**

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

1 – Apresentação do estudo e objetivo(s):

O (a) senhor (a) está sendo convidado a participar da pesquisa "Estimulação Magnética Transcraniana Profunda para Dor Central".

Estão sendo estudados pacientes que começaram a ter dor após um derrame cerebral (AVC) ou uma lesão medular. Este tipo de dor é conhecido como dor neuropática do tipo central.

A dor neuropática do tipo central tem um tratamento difícil e muitas vezes não pode ser controlada com as medicações e medidas habituais. Daí nasce a necessidade do desenvolvimento de novas armas para o controle desta dor.

Nesta fase do estudo, temos o objetivo de comparar pacientes que tiveram AVC e possuem dor com os pacientes que tiveram AVC e não tem dor, essas informações podem ajudar a esclarecer as diferenças entre essas pessoas e talvez ajudar em prevenções e tratamentos futuros.

2 **– Descrição dos procedimentos que serão realizados, com seus propósitos.**

Para esta pesquisa o (a) senhor (a) terá que realizar inicialmente uma ressonância magnética do crânio, caso ainda não tenha feito esse exame após o AVC, para que possamos documentar e localizar a região do cérebro que foi comprometida.

Em seguida, o (a) senhor (a) passará por uma avaliação com duração de aproximadamente 1h30, na qual será examinado e em seguida irá realizar o teste de excitabilidade cortical e teste quantitativo de sensibilidade, além questionários sobre, entre outras coisas, a sua dor, seu humor e sua qualidade de vida.

Estes testes ocorrerão de forma controlada, em laboratório especializado, não causando qualquer tipo de lesão temporária ou definitiva.

Teste de excitabilidade cortical

O teste de excitabilidade cortical é feito através de um aparelho de estimulação magnética. A estimulação magnética transcraniana, EMT, foi desenvolvido há mais de 25 anos e estimula o cérebro através de ondas magnéticas. O teste de excitabilidade cortical é feito através da estimulação do cérebro por ondas magnéticas e mede a velocidade com que o cérebro faz a mão mexer. A medidas são feitas no músculo da mão, em uma única sessão de 30 minutos. O aparelho ficará encostado na sua cabeça para produzir um estímulo não doloroso que fará a musculatura da sua mão contrair. Enquanto é feita a medida, podem aparecer sensações fracas, não dolorosas no braço. O (a) senhor (a) poderá apresentar uma dor fraca ou sensação de cansaço nos músculos do braço ou pescoço após a medida.

A estimulação não causa dor, choques ou qualquer tipo de lesão, porém podem surgir contrações fracas com discreto desconforto.

Algumas pessoas podem apresentar dor de cabeça leve e passageira após a EMT. Esta pode ser facilmente controlada com o uso de paracetamol. Caso a apresente, comunique ao médico, que este lhe ofertará o medicamento.

Outro efeito que a EMT pode causar é a crise convulsiva, a estimulação pode ser realizada em diferentes intensidades. Dentre mais de 25 estudos realizados em todo o mundo, incluindo mais de 500 doentes, até hoje só houve relato de uma crise convulsiva. Neste caso em especial, o paciente era tratado com uma estimulação em alta intensidade, o que não é mais usado nos estudos clínicos. Até hoje, nunca se relatou crise convulsiva em um estudo em doentes com dor utilizando-se a intensidade de tratamento que foram determinadas para este estudo.

Em relação a mulheres grávidas em geral não podem participar de estudos clínicos para tratamentos novos pelo risco de existir reações indesejadas ao feto. Não há relatos de malformações fetais após o uso de estimulação magnética transcraniana em doentes com dor. Mas para termos um grau de segurança maior, todas as mulheres em idade fértil incluídas no estudo realizarão teste de gravidez antes do início do tratamento e ao seu término, e terão que utilizar obrigatoriamente métodos anticoncepcionais como pílula anticoncepcional e DIU (dispositivo intra-uterino).

Para a sua segurança realizaremos, por protocolo, uma observação por pelo menos 3 horas a fim de observar eventuais problemas decorrentes da estimulação. Durante esta observação solicitaremos para que você preencha um questionário relatando suas impressões e sensações.

Desta forma, o (a) senhor (a) que não apresenta dor mas teve AVC está sendo convidado a participar do estudo e realizar uma sessão única de cerca de 12 minutos para medidas de potenciais evocados motores. São medidas indolores não invasivas que medem a condução dos estímulos motores pelo trato cortico-espinal. Há fortes evidências de que pacientes com dor apresentam alterações destes parâmetros, e desejamos avaliar se estas alterações descritas são relacionadas ao AVE propriamente dito ou, segundo nossa hipótese científica, à presença de dor. Marcadores biológicos da ocorrência de dor são raros e diversos esforços tem sido empregados para detectá-los.

Todos os cuidados serão tomados para evitar estas complicações.

O médico estará ao seu lado durante toda a sessão que poderá ser interrompidas por qualquer motivo e a qualquer momento.

O (a) senhor (a) não deixará de realizar o tratamento farmacológico ao qual já está realizando em nenhum momento deste estudo.

Ressonância Magnética:

A Ressonância Magnética é um exame amplamente usado na prática clínica sendo considerado um método não invasivo e inócuo ao paciente.

A principal contra indicação ao procedimento é a presença de metais implantados no crânio (como clips de cirurgia de aneurisma) ou em outras partes do corpo (como marca passo cardíaco).

A Estimulação Magnética Transcraniana também possui estas contra indicação, por este motivo, pessoas com estas características não participarão do estudo.

Pessoas que tem medo de locais apertados (claustrofóbicas) podem sentir desconforto no aparelho de ressonância. Avise o médico se este for o seu caso.

Teste Quantitativo de Sensibilidade:

O Teste Quantitativo da Sensibilidade (QST) avalia a sua percepção a diversos estímulos táteis, térmicos, vibratórios e dolorosos.

O QST, embora mais utilizado no ambiente de pesquisa do que na prática clínica, não é um procedimento experimental. Ele será realizado de forma controlada, em laboratório especializado, não causando qualquer tipo de lesão temporária ou definitiva.

Os testes poderão ser interrompidos a qualquer momento, caso você deseje.

5 – Benefícios:

O principal objetivo desta fase do estudo será procurar se existem diferenças nas avaliações descritas acima entre os pacientes que tem dor e os que não tem. Pacientes com dor após AVC frequentemente apresentam dor intensa e de difícil controle. Há poucos medicamentos e procedimentos que trazem benefício e boa parte dos pacientes permanecem com dor apesar de tudo o que se faça. Até hoje, não se sabe porque alguns paciente tem dor após AVC e outros não. Conhecer essas diferenças poderá ajudar a compreender melhor os mecanismos que causam a dor e na prevenção e tratamento desse quadro.

6 – Relação de procedimentos alternativos que possam ser vantajosos, pelos quais o paciente pode optar:

A dor neuropática pós-AVC em geral é de difícil controle. Há poucas medicações que têm efeito comprovado e a maior parte dos pacientes com esta condição utilizarão várias drogas e ainda assim permanecerão com dor.

Você pode optar por não participar deste estudo e continuar com seu tratamento habitual no Hospital das Clínicas da Universidade de São Paulo.

7 – Garantia de acesso:

Em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas.

O principal investigador é o Dr. Daniel Ciampi de Andrade e o pesquisador executante é o Ricardo Galhardoni que poderão ser encontrados no endereço Av. Dr. Enéas de Carvalho Aguiar, 255, São Paulo – SP e Telefones (11) 2661-7152.

Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5º andar – tel: 2661-6442 ramais 16, 17, 18 – E-mail: cappesq.adm@hc.fm.usp.br

8 – É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

09 – Você tem direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgada a identificação de nenhum paciente;

10 – É seu direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

11 – Despesas e compensações:

Não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas.

Também não há compensação financeira relacionada à sua participação.

12 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo "**Estimulação Magnética Transcraniana da Ínsula: Um Projeto Piloto".**

Eu discuti com o Dr. Daniel Ciampi de Andrade/ Ricardo Galhardoni/ Dra Luciana Barbosa sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante legal Data ___/___/___

Assinatura da testemunha Data ___/___/___

para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo Data ___/___/___

Annexe C - Clinical evaluation form

Protocolo: Dor central, avaliação de pacientes com acidente vascular cerebral .

Nome:_____ N ° no Estudo_____

RGHC: _____ Telefones ( )_____

I.DADOS SÓCIODEMOGRAFICOS		
SEXO	**IDADE**	**DATA DE NASCIMENTO**
1.Fem ( ) 2.Masc ( )	_____ anos	/ /
NÍVEL EDUCACIONAL:		
1.Analfabeto ( ) 2. Ensino fundamental ( ) 3. Ensino médio ( ) 4.Superior ( ) 5. Pós-graduação ( )		
ESTADO CIVIL:		
1.Solteiro ( ) 2.Casado ( ) 3.União consensual ( ) 4.Separado( ) 5.Divorciado ( ) 6.Viúvo ( )		
SITUAÇÃO CONJUGAL: 1.Com companheiro ( ) 2.Sem companheiro ( )		
RELIGIÃO:		**PRATICANTE:**
1.Ateu( ) 2.Católico( ) 3. Espírita ( ) 4.Evangélico( ) 5. Judeu ( ) 6.Outro_____		0. Não ( ) 1. Sim ( )
HÁBITOS E VÍCIOS		
TABACO ( ) SIM ( ) NÃO Carga:_____m/a ( ) Prévio ( ) Atual ÁLCOOL ( ) SIM ( ) NÃO ( ) Prévio ( ) Atual OUTROS: ( ) Crack ( ) Cocaína ( ) Outros		
SITUAÇÃO DE TRABALHO:		
Você está trabalhando atualmente? 0.Não ( ) 1.Sim ( )		
1.Empregado ( ) 2.Desempregado ( ) 3.Aposentado ( ) 4.Dona de casa ( ) 5.Autônomo ( ) 6.Estudante ( ) 7.Licença saúde ( ) 8.Informal ( )		
Ocupação: _____		

Iniciais:_____ Data :__/__/____

RENDA:	
I. Individual (mensal): R$	
II.Suficiente para suprir necessidades? 0.Não ( ) 1.Sim ( )	
III. Familiar (mensal): R$	IV. Nº de pessoas que vivem com esta renda:
VI.Você é o principal responsável pelo sustento de sua família? 0.Não ( ) 1.Sim ( )	
CASO VOCÊ NÃO TENHA RENDA PRÓPRIA	
I. Como você se mantém?	
1. Ajuda da família ( ) 2. Ajuda de instituição ( ) qual?_____ 3. Ajuda de vizinhos ou amigos ( ) 4. Ajuda de pessoas estranhas ( )	
II. DADOS CLÍNICOS	
Data do Acidente Vascular Cerebral:_____ Isquemico ( ) Hemorrágico ( ) Qual foi o lado afetado? ( ) direito ( ) esquerdo ( ) direito e esquerdo Sintomas:_____ Sequelas:_____ Episódios prévios ? ( ) Sim ( )Não Realizou reabilitação ? ( ) Sim ( )Não Se, sim, por quanto tempo? _____ Dor antes do acidente vascular cerebral? ( ) Sim ( ) Não Há quanto tempo? _____ Local:_____ Dor após o acidente vascular cerebral? ( )Sim ( ) Não Quanto tempo após o acidente vascular cerebral a dor iniciou? _____meses Local:_____ Medicamentos em uso (Dor):	

Iniciais:_____ Data :__/__/____

Medicamentos em uso (Gerais):

III DADOS CLÍNICOS- DOR

1.Diagnóstico (da Dor):_____

2.Tempo de diagnóstico:_____meses

3.Tempo de tratamento da dor: _____ meses 4.Tempo de tratamento farmacológico:_____meses

5. Tratamentos realizados: 1.Acupultura ( )___m 2.TENS ( )____m 3. Hipnose( ) ___m 4.Massagem ( )___m 5. Distração ( )___m 6. Chá ( )___m 7.Música ( )___m 8.Calor ( ) ___m 9. Frio ( ) ___m 10.Exercício ( )___m 10. Relaxamento ( )___m 11.Fisioterapia ( ) ___m.

6. Tratamentos Concomitantes:

_____

7. Etiologia da dor:

_____

8. Duração da dor:

_____

9. Fatores de início da dor:

_____

10. Fatores de piora da dor:_____

11. Fatores de melhora da dor:

_____

12. A Dor é contínua ou intermitente?

_____

DADOS CLÍNICOS GERAIS

1. Cirurgias Anteriores:

_____

Iniciais:_____ Data :__/__/____

2.Você tem alguma das seguintes doenças:

	Não [0]	Sim[1]
1. Diabetes Mellitus		
2. Cerebrovascular		
3. Hipertensão arterial		
4. Doenças vascular periférica		
5. Doença renal crônica		
6. Neoplasia maligna		
7. Doença cardiocirculatória		
8. Doença hepática		
9.Depressão		
10. Doença do trato gastrointestinal		
11. Doença autoimune		
12.Outras:_____		

IV. EXAME FISÍCO

Alterações nos sistemas:

	Não [0]	Sim[1]	Quais alterações
Neurológico			
Circulatório			
Respiratório			
Gastrointestinal superior			
Gastrointestinal inferior			
Geniturinário			
Esquelético			
Dermatológico			

Peso: Altura:

Iniciais:_____ Data :__/__/____

EXAME NEUROLÓGICO:

Força:

Coordenação:

ROT:

Marcha:

Funções corticais:

Quadro 1 - Escala de Ashworth modificada

Grau	Observação clínica
0	Tônus normal.
1	Aumento do tônus no início ou no final do arco de movimento.
1+	Aumento do tônus em menos da metade do arco de movimento, manifestado por tensão abrupta e seguido por resistência mínima.
2	Aumento do tônus em mais da metade do arco de movimento.
3	Partes em flexão ou extensão e movidos com dificuldade.
4	Partes rígidas em flexão ou extensão.

Fonte: Dados da pesquisa.

FONTE: MODIFIED Ashworth scale (Katz et al. 1992)

MSD:_____ MSE:_____ MID:_____ MIE:_____

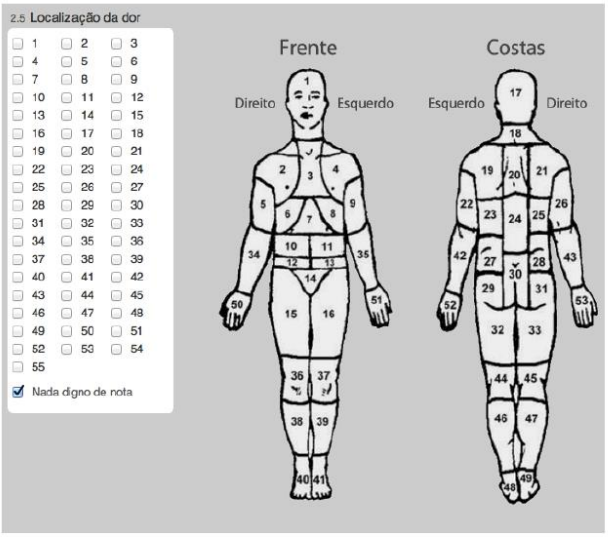
Iniciais:_____ Data :__/__/____

Assinale o achado relativo a área de dor neuropática.

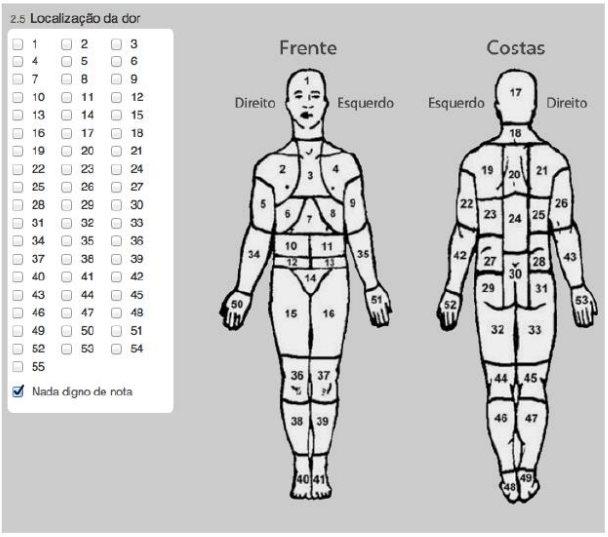
Qual área foi examinada?

Prencher com a área e hipoestesia térmica , com a área de dor neuropática e a área de dor Geral.

Área de Dor Geral:

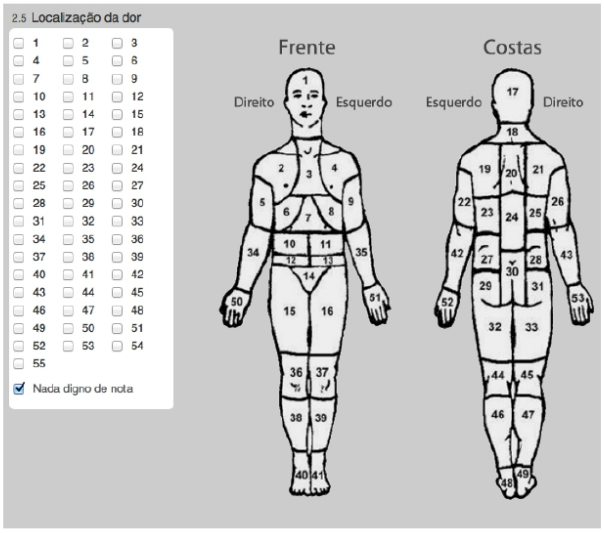


Área de dor neuropática



Iniciais:_____ Data :__/__/____

Área de Hipoestesia térmica



Exame Físico de Sensibilidade

	SIM	NÃO
Hipoestesia tátil (algodão)		
Hipoestesia térmica		

VAS com alfinete na área normal _____

Hipoalgesia mecânica (alfinete) (VAS_____)

Hiperalgesia mecânica (alfinete) (VAS_____)

Alodínea tátil dinâmica (Algodão) (VAS_____)

Alodínea térmica ao frio (VAS_____)

Iniciais:_____ Data :__/__/____

Somação temporal (alfinete): Estímulo 1: VAS = /10 ; 10 Estímulos : VAS= /10

Sensibilidade Profunda: normal 0, alterado 1
a) posição dedo média de 10x D: mão ( ) pé ( )
E: mão ( ) pé ( )

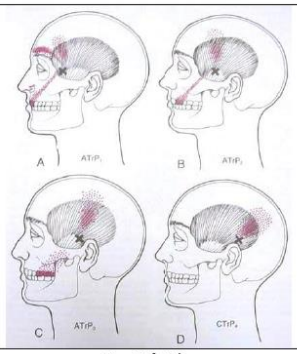
b) vibração 128Hz diapasão:

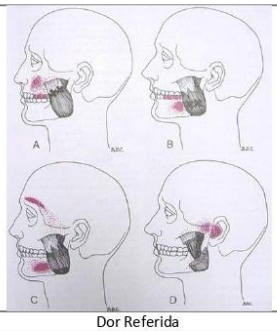
Espasmos? ( )Sim ( )Não

Quantas vezes ao dia?_____

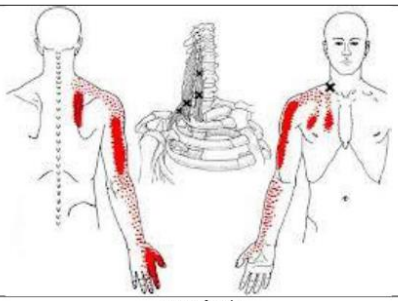
Avaliação de Pontos Gatilhos

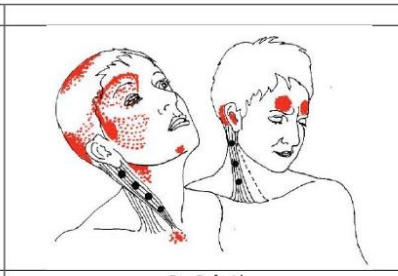
Ponto Zero: medir dolorimetria na glabela _____

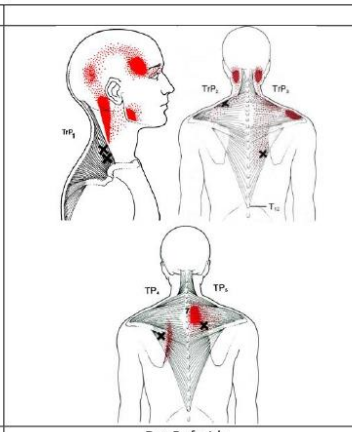
Músculo	Dolorimetria		
Temporal	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida

Músculo	Dolorimetria		
Masseter	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida

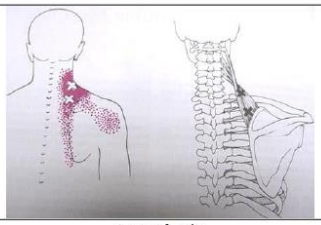
Iniciais:_____ Data :__/__/____

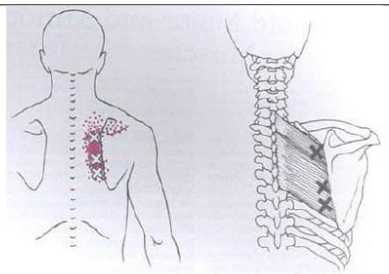
Músculo	Dolorimetria		
Escalenos (nervos espinhais – C2 a C7)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Palpação do músculo em direção aos processos transversos subjacentes das vértebras C2 a C7			Região peitoral, torácica superior, faces anterior e posterior do braço e antebraço, polegar e indicador

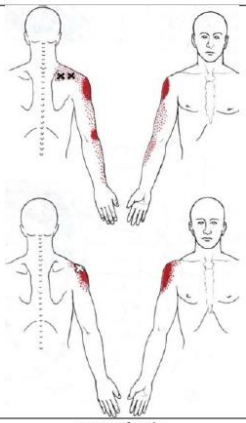
Músculo	Dolorimetria		
Esterno cleido mastoideo (n. acessorio – XI par)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo do ventre do músculo (do processo mastóide até esterno e clavícula)			Dor frontal, mastóidea (divisão clavicular) e Dor em forma de arco na bochecha, maxilar, crista supra- orbital , e pode descer até porção superior do esterno (divisão esternal)

Músculo	Dolorimetria		
Trapézio (n. acessorio – XI par	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
PG1:Porção média da borda anterior do trapézio superior PG2: caudal e levemente lateral ao PG1			PG1: Dor região postero-lateral do pescoço associado à dor em Hemi-crânio temporal ipsilateral até órbita ipsilateral PG2: occiptal e cervical posterior ipsilateral

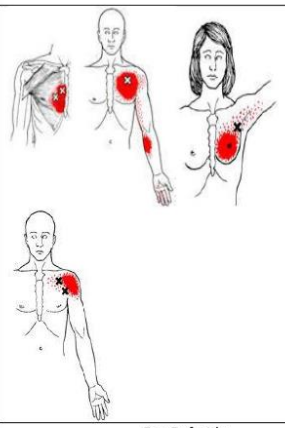
Iniciais:_____ Data :__/__/____

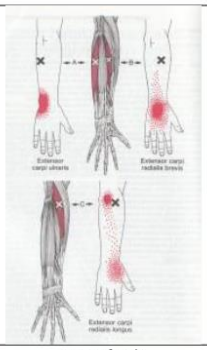
Músculo	Dolorimetria		
Elevador da escápula (C3-C4)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ponto médio entre processos transversos de C4 a C5 e ângulo superior da escápula e junto à inserção no ângulo superior da escápula			Base do pescoço, margem medial da escápula e face posterior do ombro

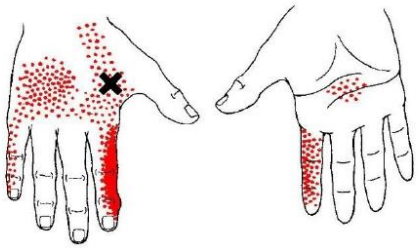
Músculo	Dolorimetria		
Romboide (escapular dorsal – C5)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo da borda vertebral da escápula			Ao longo da borda vertebral da escápula, entre a escápula e a musculatura paravertebral, região supraespinhal.

Músculo	Dolorimetria		
Supra-espinhal (supra-escapular – C5-C6)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo da borda superior da espinha da escápula, principalmente ângulo da espinha			Dor profunda em aspecto posterior e profundo do deltóide, face radial do braço, epicôndilo lateral, antebraço e punho

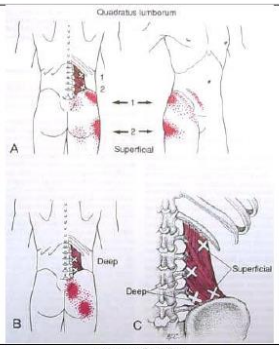
Iniciais:_____ Data :__/__/____

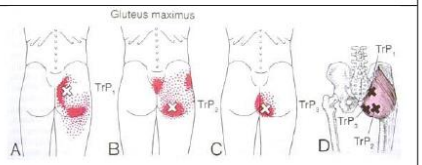
Músculo	Dolorimetria		
Peitoral maior (peitoral – C5 a C7)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Palpação em pinça na região axilar. Palpação plana na região esternal e clavicular com o braço em abdução.			PG1 clavicular: dor sobre o músculo deltóide anterior e localmente para a seção clavicular do proprio peitoral maior. PG2 esternal: dor no torax e face interna do braço, antebraço e porção ulnar da mão.

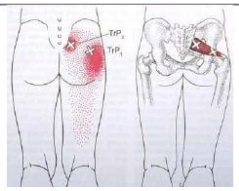
Músculo	Dolorimetria		
Extensor de Punho e Dedos	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida

Músculo	Dolorimetria		
Interosseo do 1° compartimento	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida

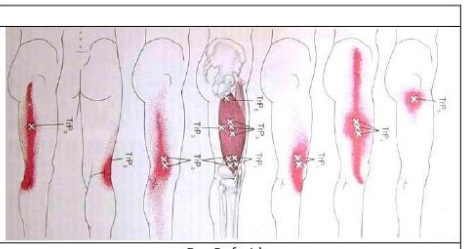
Iniciais:_____ Data :__/__/____

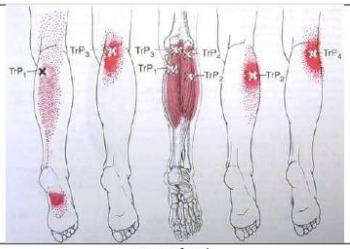
Músculo	Dolorimetria		
Quadrado Lombar	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ponto médio da borda superior da porção posterior do ilíaco, paravertebral profundo de L3 a L5, borda inferior da 12° arco costal			Região sacro ilíaca, glútea inferior, ao longo da crista ilíaca posterior

Músculo	Dolorimetria		
Glúteo Máximo	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo de sua inserção nas vértebras sacrais			Região glútea

Músculo	Dolorimetria		
Piriforme	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Entre porção média e lateral, quando dividimos o músculo em três partes do trocanter maior do fêmur até superfície interna do sacro.			Dor ciática, sacroiliaca, região glútea lateral, face posterior do quadril e 2/3 proximais da coxa

Iniciais:_____ Data :__/__/____

Músculo	Dolorimetria		
Vasto lateral	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
			Face lateral da coxa e joelho

Músculo	Dolorimetria		
Gastroc-nêmios (medial)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ponto médio do ventre muscular da cabeça medial e da cabeça lateral, e porção inferior da fossa poplítea medial e lateral			Região sural, fossa poplítea, porção inferior da coxa e superfície plantar do pé, ao longo do tendão calcâneo

Iniciais:_____ Data :__/__/____

Annexe D - Scales and questionnaires

ESCALA DE BARTHEL

ATIVIDADE	PONTUAÇÃO
ALIMENTAÇÃO 0 = incapacitado 5 = precisa de ajuda para cortar, passar manteiga, etc, ou dieta modificada 10 = independente	
BANHO 0 = dependente 5 = independente (ou no chuveiro)	
ATIVIDADES ROTINEIRAS 0 = precisa de ajuda com a higiene pessoal 5 = independente rosto/cabelo/dentes/barbear	
VESTIR-SE 0 = dependente 5 = precisa de ajuda, mas consegue fazer uma parte sozinho 10 = independente (incluindo botões, zipers, laços, etc	
INTESTINO 0 = incontinente (necessidade de enemas) 5 = acidente ocasional 10 = continente	
SISTEMA URINÁRIO 0 = incontinente, ou caracterizado e incapaz de manejo 5 = acidente ocasional 10 = continente	
USO DO TOILET 0 = dependente 5 = precisa de alguma ajuda parcial 10 = independente (pentear-se, limpar se)	
TRANSFERÊNCIA (DA CAMA P/ CADEIRA E VICE VERSA) 0 = incapacitado, sem equilíbrio para ficar sentado 5 = muita ajuda (uma ou duas pessoas, física), pode sentar 10 = pouca ajuda (verbal ou física) 15 = independente	
MOBILIDADE (EM SUPERFÍCIES PLANAS) 0 = imóvel ou < 50 metros 5 = cadeira de rodas independente, incluindo esquinas, > 50 metros 10 = caminha com ajuda de uma pessoa (verbal ou física) > 50 metros 15 = independente (mas pode precisar de alguma ajuda; ex.: bengala) > 50 metros	
ESCADAS 0 = incapacitado 5 = precisa de ajuda (verbal, física ou ser carregado) 10 = independente	
TOTAL:	

Orientações:

1. A pontuação na Escala de Barthel refere se ao que os sujeitos fazem e não ao que eles recordam ter feito um dia.
2. Seu principal objetivo é saber sobre o grau de independência em relação a qualquer tipo de ajuda (física ou verbal).
3. Se o sujeito não consegue ler o questionário, alguém pode ler o mesmo para ele. É permitido que algum amigo ou parente responda pelo sujeito (caso este esteja impossibilitado de responder).
4. Preferencialmente procure obter respostas relativas às últimas 48 horas, dependendo do caso, pode ser por períodos maiores.

14

Iniciais:_____ Data :__/__/____

Rankin – Escala Modificada:

Score	Classificação	Descrição
0	*Assintomático .*	Regressão dos sintomas.
1	*Sintomas sem incapacidade.*	Capaz de realizar suas tarefas e atividades habituais prévias.
2	*Incapacidade leve.*	Incapaz de realizar todas suas atividades habituais prévias, mas capaz de realizar suas necessidades pessoais sem ajuda.
3	*Incapacidade moderada.*	Requer alguma ajuda para as suas atividades, mas é capaz de andar sem ajuda de outra pessoa.
4	*Incapacidade moderada a grave.*	Incapacidade de andar sem ajuda, incapacidade de realizar suas atividades sem ajuda.
5	*Incapacidade grave .*	Limitado a cama, incontinência, requer cuidados de enfermeiros e atenção constante.
6	*Óbito .*	

SF 12 QUESTIONÁRIO SOBRE QUALIDADE DE VIDA

1. **Em geral, o (a) Sr (a) diria que sua saúde é:**

☐ Excelente ☐ Muito Boa ☐ Boa ☐Regular ☐Ruim

2. **O Sr acha que sua saúde, agora, o dificulta de fazer algumas coisas do dia a dia, como por exemplo: atividades médias (como mover uma cadeira, fazer compras, limpar a casa, trocar de roupa)?**

☐Sim, dificulta muito ☐ Sim, dificulta um pouco ☐Não, não dificulta de modo algum

3. **O Sr acha que sua saúde, agora, o dificulta de fazer algumas coisas do dia a dia, como por exemplo: subir três ou mais degraus de escada?**

☐Sim, dificulta muito ☐ Sim, dificulta um pouco ☐ Não, não dificulta de modo algum

4. **Durante as últimas 4 semanas, o(a) Sr(a) teve algum dos seguintes problemas com seu trabalho ou em suas atividades do dia a dia,: fez menos do que gostaria, por causa de sua saúde física ?**

☐Sim ☐Não

5. **Durante as últimas 4 semanas, o(a) Sr(a) teve algum dos seguintes problemas com seu trabalho ou em suas atividades do dia a dia,: sentiu-se com dificuldade no trabalho ou em outras atividades, por causa de sua saúde física?**

☐Sim ☐Não

6. **Durante as últimas 4 semanas, o(a) Sr(a) teve algum dos seguintes problemas: fez menos do que gostaria, por causa de problemas emocionais?**

Iniciais:_____ Data :__/__/____

☐Sim ☐Não

7. **Durante as últimas 4 semanas, o(a) Sr(a) teve algum dos seguintes problemas: deixou de fazer seu trabalho ou outras atividades cuidadosamente, como de costume, por causa de problemas emocionais?**

☐Sim ☐Não

8. **Durante as últimas 4 semanas, alguma dor atrapalhou seu trabalho normal (tanto o trabalho de casa como o de fora de casa)?**

☐Não, nem um pouco ☐Um pouco ☐Moderadamente ☐ Bastante ☐Extremamente

9. **Quanto tempo durante as últimas 4 semanas: o(a) Sr(a) tem se sentido calmo e tranqüilo?**

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐ Nunca

10. Quanto tempo durante as últimas 4 semanas: o(a) Sr(a) teve bastante energia?

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐ Nunca

11. Quanto tempo durante as últimas 4 semanas: o(a) sr(a) sentiu-se desanimado e deprimido ?

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐Nunca

12. Durante as últimas 4 semanas, em quanto do seu tempo a sua saúde ou problemas emocionais atrapalharam suas atividades sociais, tais como:visitar amigos, parentes, sair, etc. ?

☐ Todo o tempo ☐A maior parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐Nunca

Ware JE, Sherbourne DC. The MOS 35 item short form survey (SF-36) Conceptual Framework and item selection. Med Care 1992;30:473-83

Iniciais:_____ Data :__/__/____

Questionário para Diagnóstico de Dor Neuropática 4 – DN4

Versão Brasileira 1.0

Por favor, nas quatro perguntas abaixo, complete o questionário marcando uma resposta para cada número:

ENTREVISTA DO PACIENTE

Questão 1: A sua dor tem uma ou mais das seguintes características?

	Sim	Não
1 – Queimação		
2 - Sensação de frio dolorosa		
3 - Choque elétrico		

Questão 2: Há presença de um ou mais dos seguintes sintomas na mesma área da sua dor?

	Sim	Não
4 – Formigamento		
5 - Alfinetada e Agulhada		
6 – Adormecimento		
7 – Coceira		

EXAME DO PACIENTE

Questão 3. A dor está localizada numa área onde o exame físico pode revelar uma ou mais das seguintes caraterísticas?

	Sim	Não
8- Hipoestesia ao toque		
9- Hipoestesia a picada de agulha		

Questão 4. Na área dolorosa, a dor pode ser causada ou aumentada por:

	Sim	Não
10 – Escovação		

Bouhassira D et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005 Mar;114(1-2):29-36.
Santos JG, Brito JO, de Andrade DC, Kaziyama VM, Ferreira KA, Souza I, Teixeira MJ, Bouhassira D, Baptista AF. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain. 2010 May;11(5):484-90. Epub 2009 Dec 16.
Ferreira KASL, Teixeira MJ. Tradução e validação da versão brasileira do Questionário DN4 para identificação de dor neuropática. Revista Dor é Coisa Séria. 2008;26 – 29

17

Iniciais:_____ Data :__/__/____

McGILL breve		
Dimensão	**Presente**	**Ausente**
Sensorial 1.Latejante		
2.Pontada		
3.Choque		
4.Fina-Agulhada		
5.Fisgada		
6.Queimação		
7.Espalha		
8.Dolorida		
Afetivo 9.Cansativa-exaustiva		
10.Enjoada		
11.Sufocante		
12.Apavorante-Enlouquecedora		
13.Aborrecida		
Avaliativo 14.que incomoda		
15.Insuportável		

Intensidade Da Dor

Presente

0 1 2 3 4 5 6 7 8 9 10

Sem Dor Pior Dor Possível

Iniciais:_____ Data :__/__/____

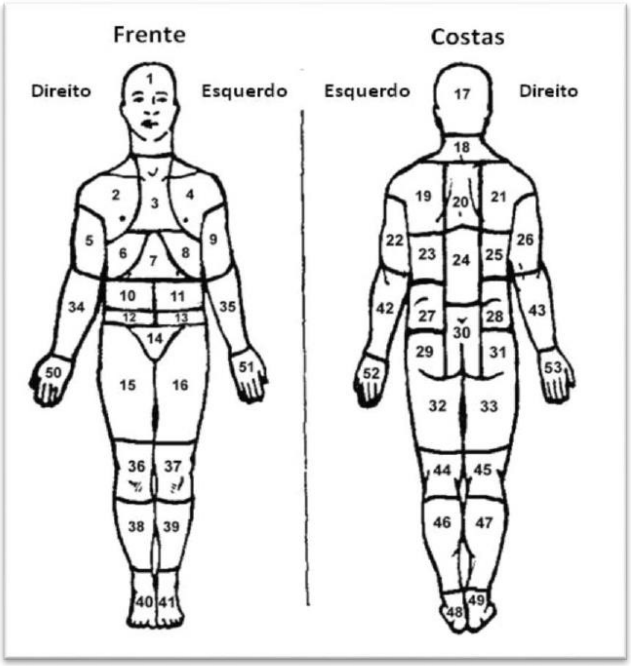
Inventário Breve de Dor

123

1. Durante a vida, a maioria das pessoas apresenta dor de vez em quando (dor de cabeça, dor de dente, etc.). Você teve hoje, dor diferente dessas?

1.Sim ☐ 2.Não ☐

2. Marque sobre o diagrama, com um X, as áreas onde você sente dor, e onde a dor é mais intensa.



3. Circule o número que melhor descreve a pior dor que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

4. Circule o número que melhor descreve a dor mais fraca que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

5. Circule o número que melhor descreve a média da sua dor.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

6. Circule o número que mostra quanta dor você está sentindo agora (neste momento).

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

19

Iniciais:_____ Data :__/__/____

7. Quais tratamentos ou medicamentos você está recebendo para dor

Nome	**Dose/ Freqüência**	**Data de Início**

8. Nas últimas 24 horas, qual a intensidade da melhora proporcionada pelos tratamentos ou medicações que você está usando?

Circule o percentual que melhor representa o alívio que você obteve.

Sem alívio 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Alívio completo

9. Circule o número que melhor descreve como, nas últimas 24 horas, a dor interferiu na sua

Atividade geral

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Humor

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Habilidade de caminhar

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Trabalho

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Relacionamento com outras pessoas

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Sono

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Habilidade para apreciar a vida

Não interferiu O 1 2 3 4 5 6 7 8 9 10 Interferiu completamente

Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of Brief Pain Inventory to Brazilian patients with pain. Support Care Cancer. 2010 Mar 10. [Epud ahead of print].

Iniciais:_____ Data :__/__/____

Inventário de Sintomas de Dor Neuropática (NPSI)

Você tem sofrido de dor devido a lesão ou doença do sistema nervoso. Esta dor pode ser de diversos tipos. Você pode ter dor espontânea, ex: dor na ausência de qualquer estímulo, que pode ser duradoura ou ocorrer em ataques breves. Você pode também ter dor provocada ou aumentada por leve toque, pressão ou contato com o frio na área dolorosa. Você pode sentir um ou mais tipos de dor. Este questionário foi desenvolvido para ajudar o seu médico a melhor avaliar e tratar diferentes tipos de dor que possa sentir.
Nós queremos saber se você sente dor espontânea, isto é dor sem qualquer estímulo. Para cada uma das seguintes questões, por favor selecione o número que melhor descreve a sua gravidade média da dor espontânea durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule o número apenas).

Q1. A sua dor dá a sensação de queimação?

Não queima 0 1 2 3 4 5 6 7 8 9 10 A pior Queimadura Imaginável

Q2. A sua dor dá a sensação de apertar?

Não aperta 0 1 2 3 4 5 6 7 8 9 10 Aperta o pior imaginável

Q3. A sua dor dá a sensação de pressão?

Sem pressão 0 1 2 3 4 5 6 7 8 9 10 A pior pressão imaginável

Q4. Durante as últimas 24 horas, a sua dor espontânea tem estado presente:
Selecione a resposta que melhor descreve o seu caso
Permanentemente ( )
Entre 8 e 12 h ( )
Entre 4 e 7 h ( )
Entre 1 e 3 h ( )
menos que 1 h ( )

Nós queremos saber se você teve ataques breves de dor. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a gravidade média dos seus ataques de dor durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).
Q5 A sua dor dá a sensação de choque elétrico?

Sem choque elétrico 0 1 2 3 4 5 6 7 8 9 10 O pior choque elétrico imaginável

Q6 A sua dor dá a sensação de apunhalar?

Sem apunhalar 0 1 2 3 4 5 6 7 8 9 10 A Pior punhalada imaginável

Q7. Durante as últimas 24 horas, quanto destes ataques de dor teve? Selecione a resposta que melhor descreve o seu caso.

Mais de 20 ( )

21

Iniciais:_____ Data :__/__/____

Entre 11 e 20 ( )
Entre 6 e10 ( )
Entre 1 e 5 ( )
Sem ataque de dor ( )

Nós queremos saber se você sente dor provocada ou aumentada por leve toque, pressão, contacto com frio na área onde dói. Para cada das seguintes questões, por favor selecione o número que melhor descreve a gravidade media da dor provocada durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q8. A sua dor é provocada ou aumentada por um leve toque na área dolorosa?

Sem dor 0 1 2 3 4 5 6 7 8 9 10 A pior dor imaginável

Q9. A sua dor é provocada ou aumentada por pressão na área dolorosa?

Sem dor 0 1 2 3 4 5 6 7 8 9 10 A pior dor Imaginável

Q10. A sua dor é provocada ou aumentada por contacto com algo frio na área dolorosa?

Sem dor 0 1 2 3 4 5 6 7 8 9 10 Pior dor Imaginável

Nós queremos saber se você sente sensações anormais na zona onde dói. Para cada uma das seguintes questões, por favor selecione o número que melhor descreve a gravidade média das sensações anormais durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q11. Sente alfinetadas e agulhadas?

Sem alfinetes nem agulhas 0 1 2 3 4 5 6 7 8 9 10 Os piores alfinetadas e agulhadas Imaginável

Q12. Sente Dormente?

Sem Dormência 0 1 2 3 4 5 6 7 8 9 10 O mais dormente Imaginável

Iniciais:_____ Data :__/__/____

Escala de Catastrofismo Associado à Dor (PCS)

Toda a pessoa passa por situações de dor em certos momentos da vida. Estas experiências podem incluir dores de cabeça, dores de dentes, dores articulares ou dores musculares. As pessoas estão 1de dentistas ou cirurgias.

Queremos conhecer os pensamentos e sentimentos que você tem quando está sentindo dores. Abaixo encontra-se uma lista com treze afirmações que descrevem diferentes pensamentos e sentimentos que podem estar associados à dor. **Por favor, leia atentamente cada uma das afirmações e assinale, com um X, nas colunas o quanto você tem estes pensamentos e sentimentos quando está com dores. As suas respostas podem variar de nunca (0) a sempre (4).**

Quando estou com dores...	**Nunca**	**Ligeiramente**	**Moderadamente**	**Bastante**	**Sempre**
1.Estou constantemente preocupado (a) em saber se a dor terá fim.	0	1	2	3	4
2.Sinto que não consigo continuar.	0	1	2	3	4
3.É terrível e penso que nunca mais vai melhorar.	0	1	2	3	4
4.É horrível e sinto que me ultrapassa completamente.	0	1	2	3	4
5.Sinto que já não agüento mais.	0	1	2	3	4
6.Fico com medo que a dor piore.	0	1	12	3	4
7.Estou sempre a pensar noutras situações dolorosas.	0	1	2	3	4
8.Quero ansiosamente que a dor desapareça.	0	1	2	3	4
9.Não consigo deixar de pensar nisso.	0	1	2	3	4
10.Estou sempre a pensar no quanto dói.	0	1	2	3	4
11.Estou sempre a pensar que quero muito que a dor passe.	0	1	2	3	4
12.Não há nada que eu possa fazer para reduzir a intensidade da dor.	0	1	2	3	4
13Pergunto-me se poderá acontecer algo grave.	0	1	2	3	4

Pontuação total:_____

Escala Hospitalar de Ansiedade e Depressão (HADS)

Este questionário ajudará o seu médico, a saber, como você está se sentindo. Leia todas as frases. Marque com um "X" a resposta que melhor corresponder a como você tem se sentido

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Iniciais:_____ Data :__/__/____

na ÚLTIMA SEMANA. Não é preciso ficar pensando muito em cada questão. Neste questionário as respostas espontâneas têm mais valor do que aquelas em que se pensa muito. Marque apenas uma resposta para cada pergunta.

A 1) Eu me sinto tenso ou contraído:

3 ( ) A maior parte do tempo

2 ( ) Boa parte do tempo

1 ( ) De vez em quando

0 ( ) Nunca

D 2) Eu ainda sinto gosto pelas mesmas coisas de antes:

0 ( ) Sim, do mesmo jeito que antes

1 ( ) Não tanto quanto antes

2 ( ) Só um pouco

3 ( ) Já não sinto mais prazer em nada

A 3) Eu sinto uma espécie de medo, como se alguma coisa ruim fosse acontecer:

3 ( ) Sim, e de um jeito muito forte

2 ( ) Sim, mas não tão forte

1 ( ) Um pouco, mas isso não me preocupa

0 ( ) Não sinto nada disso

D 4) Dou risada e me divirto quando vejo coisas engraçadas:

0 ( ) Do mesmo jeito que antes

1 ( ) Atualmente um pouco menos

2 ( ) Atualmente bem menos

3 ( ) Não consigo mais

A 5) Estou com a cabeça cheia de preocupações:

3 ( ) A maior parte do tempo

2 ( ) Boa parte do tempo

1 ( ) De vez em quando

0 ( ) Raramente

D 6) Eu me sinto alegre:

3 ( ) Nunca

2 ( ) Poucas vezes

1 ( ) Muitas vezes

Iniciais:_____ Data :__/__/____

0 ( ) A maior parte do tempo

A 7) Consigo ficar sentado à vontade e me sentir relaxado:

0 ( ) Sim, quase sempre

1 ( ) Muitas vezes

2 ( ) Poucas vezes

3 ( ) Nunca

D 8) Eu estou lento para pensar e fazer as coisas:

3 ( ) Quase sempre

2 ( ) Muitas vezes

1 ( ) De vez em quando

0 ( ) Nunca

A 9) Eu tenho uma sensação ruim de medo, como um frio na barriga ou um aperto no estômago:

0 ( ) Nunca

1 ( ) De vez em quando

2 ( ) Muitas vezes

3 ( ) Quase sempre

D 10) Eu perdi o interesse em cuidar da minha aparência:

3 ( ) Completamente

2 ( ) Não estou mais me cuidando como deveria

1 ( ) Talvez não tanto quanto antes

0 ( ) Me cuido do mesmo jeito que antes

A 11) Eu me sinto inquieto, como se eu não pudesse ficar parado em lugar nenhum:

3 ( ) Sim, demais

2 ( ) Bastante

1 ( ) Um pouco

0 ( ) Não me sinto assim

D 12) Fico esperando animado as coisas boas que estão por vir:

0 ( ) Do mesmo jeito que antes

1 ( ) Um pouco menos do que antes

2 ( ) Bem menos do que antes

Iniciais:_____ Data :__/__/____

3 ( ) Quase nunca

A 13) De repente, tenho a sensação de entrar em pânico:

3 ( ) A quase todo momento

2 ( ) Várias vezes

1 ( ) De vez em quando

0 ( ) Não sinto isso

D 14) Consigo sentir prazer quando assisto a um bom programa

de televisão, de rádio ou quando leio alguma coisa:

0 ( ) Quase sempre

1 ( ) Várias vezes

2 ( ) Poucas vezes

3 ( ) Quase nunca

MARCOLINO, MATHIAS, PICCININI FILHO E COL. Revista Brasileira de Anestesiologia 53 Vol. 57, No 1, Janeiro-Fevereiro, 2007

QUESTIONÁRIO DE INCAPACIDADE PELA DOR

1	2	3	4	5
Nenhuma dificuldade	Um pouco difícil	Moderada-Mente difícil	Extremamente difícil	Não consegue

1) A sua dor interfere no seu trabalho dentro e fora de casa?

|_____1____|_____2_____|_____3_____|_____4_____|_____5____|

Trabalho normalmente Não consigo fazer nenhum trabalho

2) A sua dor interfere com seus cuidados pessoais (como tomar banho, vestir-se, etc)?

|_____1____|_____2_____|_____3_____|_____4_____|_____5____|

Iniciais:_____ Data :__/__/____

Cuido de mim completamente — Preciso de ajuda em todos os cuidados pessoais

3) A sua dor interfere na sua locomoção?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Vou para onde quiser — Apenas viajo para as consultas médicas

4) A sua dor afeta a sua capacidade de se sentar ou ficar em pé?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Não tenho problemas — Não consigo sentar/ficar em pé

5) A sua dor afeta a sua capacidade de levantar, agarrar objetos, ou tentar alcançar coisas?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nenhum problema — Não posso realizá-los

6) A sua dor afeta a sua capacidade de levantar objetos do chão, enclinar-se, ou agachar-se?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nenhum problema — Não posso realizá-los

7) A sua dor afeta a sua capacidade de caminhar ou correr?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nenhum problema — Não consigo caminhar/correr

Iniciais:_____ Data :__/__/____

8) A sua renda diminuiu desde que a sua dor começou?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Não diminuiu Perdi toda a renda

9) Você tem que tomar medicamentos todos os dias para controlar a sua dor?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Não preciso de medicação Utilizo medicação durante todo o dia

10) A sua dor obriga você a procurar médicos com muito mais frequência do que antes da sua dor começar?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nunca vou ao médico Consulta médicos semanalmente

11) A sua dor interfere na sua capacidade de ver as pessoas que são importantes para você tanto quanto você gostaria?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nenhum problema Eu nunca os vejo

12) A sua dor interfere nas atividades recreativas e passatempos que são importantes para você?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Não interfere Interfere totalmente

Iniciais:_____ Data :__/__/____

13) Você precisa de ajuda dos seus familiares e amigos para completar suas tarefas diárias (incluindo tanto trabalho fora de casa quanto doméstico) por causa de sua dor?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nunca preciso de ajuda Preciso de ajuda o tempo todo

14) Você se sente agora mais deprimido, tenso ou ansioso do que antes da sua dor começar?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Sem depressão/Tensão Depressão/tensão grave

15) Há problemas emocionais causados por sua dor que interferem na sua família, na vida social ou nas atividades do trabalho?

|_____1____|_____2____|____3_____|_____4_____|_____5___|

Nenhum problema Problemas graves

Giordano, Patrícia Cantu Moreira Adaptação cultural e validação do instrumento: "The pain disability questionnaire" / Patrícia Cantu Moreira Giordano. Campinas, SP : [s.n.], 2009.

QUICK DASH

Instruções

Esse questionário pergunta sobre seus sintomas, assim como suas habilidades para fazer certas atividades.

29

Iniciais:_____ Data :__/__/____

Por favor responda cada questão, baseando se em sua condição na semana passada, circulando o número apropriado.

Se você não teve a oportunidade de fazer uma das atividades na semana passada, por favor, tente estimar qual resposta seria a mais correta.

Não importa qual mão ou braço você usa para fazer a atividade; Por favor, responda baseando-se na sua habilidade independentemente da forma como você faz a tarefa.

Nome:_____

Data: ___/ ___/ ____

Por favor, meça sua habilidade para realizar as seguintes atividades ma semana passada, circulando o número apropriado da resposta.

ATIVIDADES	Não houve dificuldade	Houve pouca dificuldade	Houve dificuldade moderada	Dificuldade severa	Não Conseguiu fazer
1. Abrir vidro novo ou com a tampa muito apertada	1	2	3	4	5
2. Fazer tarefas domésticas pesadas. (ex.: lavar paredes ou lavar o chão)	1	2	3	4	5
3. Carregar uma sacola ou uma maleta.	1	2	3	4	5
4. Lavar suas costas.	1	2	3	4	5
5. Usar uma faca para cortar alimentos.	1	2	3	4	5

Iniciais:_____ Data :__/__/____

6. Atividades recreativas que exigem alguma força ou impacto nos braços, ombros ou mãos (ex.: jogar vôlei, martelar	1	2	3	4	5

ATIVIDADES	Não afetou	Afetou pouco	Afetou Moderadamente	Afetou muito	Afetou extremamente
7. Durante a semana passada, em que ponto o seu problema com o braço, ombro ou mão afetaram suas atividades normais com família, amigos, vizinhos ou colegas?	1	2	3	4	5
	Não limitou	Limitou pouco	Limitou moderadamente	Limitou muito	Não conseguiu fazer
8. Durante a semana passada, o seu trabalho ou outras atividades diárias regulares foram limitadas devido ao seu problema com braço, ombro ou mão?	1	2	3	4	5

Por favor, meça a gravidade dos seguintes sintomas na semana passada.	Nenhuma	Pouca	Moderada	Severa	Extrema

Iniciais:_____ Data :__/__/____

(circule o número)					
9. Dor no braço, ombro ou mão.	1	2	3	4	5
10. Desconforto na pele (alfinetadas) no braço, ombro ou mão.	1	2	3	4	5
	Não houve dificuldade	Pouca Dificuldade	Dificuldade moderada	Dificuldade severa	Tão difícil que eu não pude dormir
11. Durante a semana passada, quanto de dificuldade você teve para dormir por causa da dor no seu braço, ombro ou mão? (circule o número)	1	2	3	4	5

ESCORES DOS SINTOMAS E DISFUNÇÃO DO QuickDASH = [(soma das respostas/n)-1] x 25, quando o n é o número completo de respostas.

O escore do QuickDASH não pode ser calculado se houver mais de um item não válido.

Iniciais:_____ Data :__/__/____

Annexe E - Complementary exams

Exames complementares:

RM de crânio:

AngioRM:

Angio TC:

USG de vasos cervicais:

Ecocardiograma:

Exames laboratoriais:

Iniciais:_____ Data :__/__/____

Annexe F - Stroke region classification

Áreas comprometidas pelo AVC- avaliação da neurorradiologia

Data dos exames

	D (número)	E (número)
Lado		
Cortical (F/T/P/O/ Insular)		
Subcortical (F/T/P/O)		
Talamo-capsular		
Tronco		
Cerebelo		
Ausente		

34

Iniciais:_____ Data :__/__/____

Annexe G - Cortical excitability assessment

Data:_____

Medida de excitabilidade cortical

Visita: ( ) 1/ ( ) S2/ ( ) M1 D ( )/ M1 E ( )

Medidas	Valores	Comentários
Limiar motor de repouso	__ % da estimulação máxima da maquina	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Média da Amplitude _____µV		
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Média da Amplitude _____µV		

35

Iniciais:_____ Data :__/__/____

Pulso Pareado	Condicionamento à 80%_____ Teste à 120%_____	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Média Amplitude____ µV		

Iniciais:_____ Data :__/__/____

Medida de excitabilidade cortical

Nome:_____

Data:_____

Visita: ( ) 1/ ( ) S2/ ( ) **M1 D ( )/ M1 E ( )**

Medidas	Valores	Comentários
Limiar motor de repouso	__ % da estimulação máxima da maquina	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Amplitude da PEM à 120%	120%_____ Amplitude_____µV	
Média da Amplitude _____µV		
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Amplitude da PEM à 140%	140%_____ Amplitude_____µV	
Média da Amplitude _____µV		

37

Iniciais:_____ **Data :**__/__/____

Pulso Pareado	Condicionamento à 80%_____ Teste à 120%_____	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Intervalo 2 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Intervalo 15 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Intervalo 10 mseg	Amplitude_____µV	
Média Amplitude____ µV		
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Intervalo 4 mseg	Amplitude_____µV	
Média Amplitude____ µV		

Iniciais:_____ Data :__/__/____

Annexe H - Quantitative sensory testing assessment

QST

GRUPO ( )COM DOR ( )SEM DOR PAREAMENTO: _____

Local afetado: _____ Área controle : _____LADO_____

Area afetada		Media	Area Controle		Media
Limiar detecção ao frio (Média)	ºC		Limiar detecção ao frio (Média)	ºC	
Limiar detecção ao quente (Média)	ºC		Limiar detecção ao quente (Média)	ºC	
Limiar de dor ao quente (Média)	ºC		Limiar de dor ao quente (Média)	ºC	
Limiar de dor ao frio (Média)	ºC		Limiar de dor ao frio (Média)	ºC	
SUPRA limiar de dor ao quente (2x)			SUPRA limiar de dor ao quente (2x)		
SUPRA limiar de dor ao frio (2x)			SUPRA limiar de dor ao frio (2x)		
Limiar detecção mecânico (Média)	mN		Limiar detecção mecânico (Média)	mN	
Limiar doloroso mecânico (Média)	mN		Limiar doloroso mecânico (Média)	mN	
SUPRA limiar de dor mecânica(+ 4 filamentos) (1x)	(VAS)		SUPRA limiar de dor mecânica(+ 4 filamentos)(1x)	(VAS)	
Alodínea mecânica dinâmica (Média)	(VAS)		Alodínea mecânica dinâmica (Média)	(VAS)	
Estimulação dolorosa 156mN 1x (VAS)	(VAS)		Estimulação dolorosa 156mN 1x (VAS)	(VAS)	
Estimulação dolorosa 156mN 10x (VAS)	(VAS)		Estimulação dolorosa 156mN 10x (VAS)	(VAS)	
Relação "Wind up"			Relação "Wind up"		

39

Iniciais:_____ Data :__/__/____

Annexe I - Conditioned pain modulation

Realizar o estímulo térmico no membro que apresentar menor comprometimento da sensibilidade térmica.

	MID (coxa)	MIE (coxa)
Limiar dor quente oC		
Supra limiar Dor Quente + 4° C VAS mm		

Estímulo não condicionado

Quente

- dor pior dor +

Estímulo Condicionante

Quente

- dor pior dor +

T1:

T2:

Grau de desconforto

- Menor desc. Pior desc. +

40

Iniciais:_____ Data :__/__/____

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