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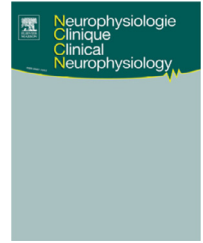
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ORIGINAL ARTICLE

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

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 Transcranial magnetic
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Abstract

Objectives: Central neuropathic pain (CNP) is associated with altered corticomotor excitability (CE), which can potentially provide insights into its mechanisms. The objective of this study is to describe the CE changes that are specifically related to CNP.

Methods: We evaluated CNP associated with brain injury after stroke or spinal cord injury (SCI) due to neuromyelitis optica through a battery of CE measurements and comprehensive pain, neurological, functional, and quality of life assessments. CNP was compared to two groups of patients with the same disease: i. with non-neuropathic pain and ii. without chronic pain, matched by sex and lesion location.

Results: We included 163 patients (stroke=93; SCI=70: 74 had CNP, 43 had non-neuropathic pain, and 46 were pain-free). Stroke patients with CNP had lower motor evoked potential (MEP) in both affected and unaffected hemispheres compared to non-neuropathic pain and no-pain patients. Patients with CNP had lower amplitudes of MEPs ($366 \mu V \pm 464 \mu V$) than non-neuropathic (478 ± 489) and no-pain ($765 \mu V \pm 880 \mu V$) patients, $p < 0.001$. Short-interval intracortical inhibition (SICI) was defective (less inhibited) in patients with CNP (2.6 ± 11.6) compared to

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no-pain (0.8 ± 0.7), $p = 0.021$. MEPs negatively correlated with mechanical and cold-induced allodynia. Furthermore, classifying patients' results according to normative data revealed that at least 75% of patients had abnormalities in some CE parameters and confirmed MEP findings based on group analyses.

Discussion: CNP is associated with decreased MEPs and SIC1 compared to non-neuropathic pain and no-pain patients. Corticomotor excitability changes may be helpful as neurophysiological markers of the development and persistence of pain after CNS injury, as they are likely to provide insights into global CE plasticity changes occurring after CNS lesions associated with CNP.

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Introduction

Central neuropathic pain (CNP) occurs following a lesion or disease of the central somatosensory system [45]. CNP is common after stroke, affecting up to 12% of survivors [25], and after spinal cord injury (SCI), where CNP is present in up to 53% [8]. The management of CNP is challenging, with up to 50% of individuals resistant to available treatment [14,34]. This is partly due to limited knowledge of the mechanisms of pain initiation and maintenance after CNS lesions [14].

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 [14,25,30]. Recently, CNP has also been proposed as a disorder of brain network reorganization [21]. Maladaptive neural plasticity in different brain circuits, including the motor system, may play a role in the development of CNP [21]. After stroke and SCI, circuit reorganization with changes in cortical excitability (CE) have been described [30,39,41]. Maladaptive neuroplasticity is thought to occur perniciously after injury and to be responsible for the gradual development of symptoms and signs that are not present immediately after the injury but, instead, develop insidiously, such as spasticity, mood disorders, chronic pain, and fatigue. However, it remains unclear why patients with similar CNS lesions develop such symptoms to different extents. One way to assess changes in plasticity in the CNS is through CE measurements. CE based on motor evoked potentials (MEP) can provide insights into GABAergic, glutamatergic and general neuronal membrane excitability of motor networks.

Interestingly, corticomotor-based CE is sensitive to excitability changes in neuronal networks beyond motor networks [13,28,35,37,50] and cortical and subcortical motor circuits can be modulated through excitatory and inhibitory exchanges with the somatosensory system¹⁹. This influence has been studied for the last two decades [43,50,53] and is supported by experimental [40,43,50,53] and clinical studies [35]. Indeed, altered motor CE has been observed in different pain syndromes, such as neuropathic pain of peripheral origin, fibromyalgia, and primary headaches [35]. The most commonly described findings in patients with chronic pain suggest motor cortex disinhibition with impaired GABAergic neurotransmission, which has been reported in both hemispheres [10,26,35]. The motor cortex is also the main target for invasive and non-invasive neuromodulation strategies for pain treatment. These data suggest that the 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. 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 [5].

To describe CE changes attributable to CNP after CNS injury, we compared CNP associated with brain injury after stroke or SCI due to neuromyelitis optica (NMO) to patients with similar CNS lesions who developed non-neuropathic pain after injury and to a group without chronic pain, matched by sex and lesion location. Participants underwent a battery of CE measurements and 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 [13] based on the exact same techniques used here.

Methods

This controlled cross-sectional study, part of the Central Pain Initiative Project, focused on assessing and treating CNP [3,15,51]. The present study aimed to compare the CE profile of CNP secondary to stroke or spinal cord lesion in NMO with two control groups: i. patients with non-neuropathic pain after stroke or spinal cord lesion due to NMO and ii. Patients without chronic pain (no-pain) after stroke or spinal cord lesion due to NMO.

Standard protocol approvals and patient consent

Data collection took place at the Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HCFMUSP). The study was approved by the Institution's Ethics Review Board (No. 690.455). All patients were volunteers, informed about the procedures, and provided written informed consent before inclusion. Some clinical data from participants from SCI [51] and stroke [3] groups has been previously reported.

Patients

According to clinical evaluation and imaging information, three neurologists trained in pain management and one neuroradiologist (LMB, FVS, 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 [25,45]. All participants had suffered an ischemic or hemorrhagic stroke at least three months before the evaluation confirmed by imaging (CT or MRI) or had previous myelitis secondary to NMO diagnosed by a neuroinflammatory diseases specialist using the revised diagnostic criteria [52]. Patients with inflammatory SCI needed to be in remission of their inflammatory disease to avoid patient evaluation during its acute, inflammatory phase, which could be a confounding factor, 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 would jeopardize the proper answering of 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 MEP due to an extensive CNS lesion even at stimulation intensities at 100% of maximal stimulator output (Fig. 1). 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 [45]; b. occurrence of de novo pain attributed to a central lesion due to stroke or SCI; c. pain characteristics not compatible with other etiologies of pain (previous fibromyalgia, migraine, nociceptive pain) [25].

Control groups

Controls were recruited from the cerebrovascular diseases and neuroimmunology outpatient clinics from the Department of Neurology, University of São Paulo. i. Non-Neuropathic pain group: post-stroke and post-spinal cord injury pain symptoms present on the majority of 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 [25]. 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.

Assessments

Participants were assessed in a single visit, including evaluation of current symptoms and limitations and standardized physical examination focused on sensory and musculoskeletal systems. Sociodemographic information, medical comorbidity status, and medication use were registered. Concomitantly, functional scores questionnaires to evaluate pain, incapacity, mood, and catastrophization, were also filled out, as detailed below:

- Functional status: Barthel index [29]
- Pain scales and questionnaires: Short-form McGill Pain Questionnaire (SF-MPQ) [31], Brief Pain Inventory (BPI)

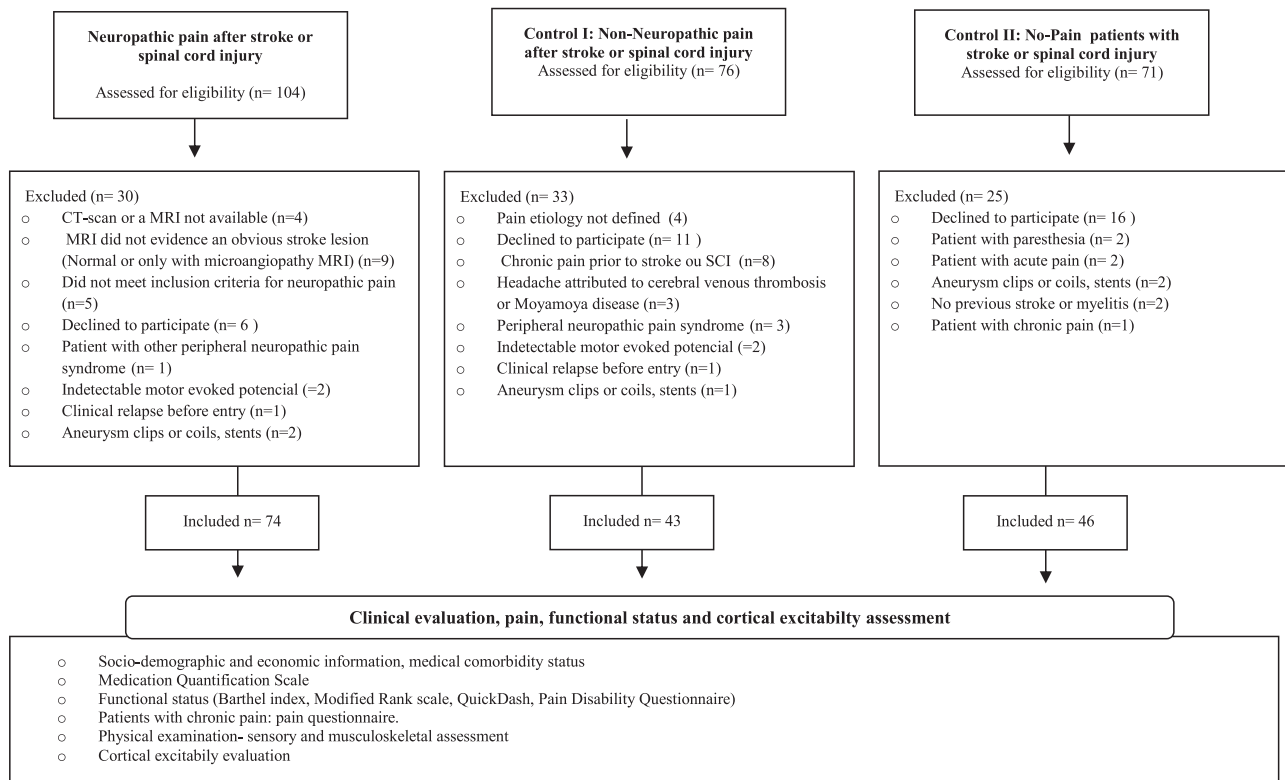


Fig. 1 Stroke flow diagram.

- [12], Douleur Neuropathique Questionnaire-4 (DN-4) [6] and Neuropathic Pain Symptoms Inventory (NPSI) [7].
- c) Mood and catastrophization assessment: Hospital Anxiety and Depression Scale (HADS) [55] and The Pain Catastrophizing Scale: [42].

Musculoskeletal assessment

Spasticity in the upper and lower limbs was quantified according to the modified (m-) Ashworth spasticity scale (AS) [23]. 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). Muscle strength was measured according to the Medical Research Council Scale for Muscle Strength (MRC) scoring system. Motor impairment 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) [49].

Sensory examination

The sensory assessment employed standardized bedside examination, including touch with graded monofilaments and allodynia with a piece of cotton wool, cold sensitivity and cold allodynia with a metal rod at room temperature, and mechanical pain sensitivity by light prick with a pin. Regions of the face, trunk, arms, and legs were compared with the contralateral side and proximal and distal body regions, and classified by the patient as normal, reduced, or increased [3,51].

Cortical excitability

CE 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 Elektronik, Denmark) and surface electrodes (Alpine Biom, Skovlunde, Denmark) were used to record MEP 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. RMT was considered the lowest output intensity capable of eliciting a 50 μ V MEP in five out of ten trials and is represented as a percentage of maximal generator output [13,49].

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) [15,18]. We performed eight pulses for each MEP and

averaged responses. 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 SICI and 10 and 15 ms to investigate ICF [1,13,18,37,49]. The mean result of the eight trials was considered. SICI was calculated as a ratio of the conditioned and unconditioned MEPs delivered at an inter-stimulus interval (ISI) of 2ms and 4ms. A similar ratio was calculated for ICF, but after measurements performed at 10ms and 15ms ISI [13,15,18,26,32,33,37].

We classified individual parameters of RMT, MEP 120, MEP 140, SICI, and ICF according to previous published normative data of CE from healthy subjects, adjusted according to age (above or below 50 years) in “low,” “normal,” or “high” for each parameter [13].

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 following comparisons. 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, CE 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. Adjusting for multiple testing was not mandatory in exploratory studies [2,4]. However, we opted to evaluate the subgroup analysis with a pairwise correction to identify the more robust findings.

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 for 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 [17].

Results

251 patients were screened for participation, and a total of 163 patients (50.3% female) were included (stroke $n = 93$, SCI $n = 70$): 74 had CNP, 43 had chronic pain of non-neuropathic

origin, and 46 were pain-free (Fig. 1). Demographic data are available in Supplementary Tables 2 (A-C); and 3 (A-C). For most variables, there were no significant differences (i.e., sex, educational level, and medical comorbidities), except for the mean age, working status, and some medical comorbidities (heart and chronic kidney disease). Age was slightly higher in non-neuropathic pain patients (53.0 ± 12.6 in the neuropathic pain group vs. 57.6 ± 12.3 in the non-neuropathic pain group and 47.2 ± 18.1 in the no-pain, $p = 0.021$) with pairwise comparison differences only between the control groups (non-neuropathic pain vs. no-pain). The prevalence of employed patients was lower in patients with central post-stroke pain (CPSP) than in stroke patients with non-neuropathic pain and without pain (5.7% vs. 20% vs. 32.1%, $p = 0.020$). Heart and chronic kidney disease had a lower prevalence in patients with neuropathic pain compared to patients with non-neuropathic pain (Supplementary Table 3C).

The time elapsed from the appearance of a 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 (Supplementary Table 4).

Physical examination, functional status, pain scales, and questionnaires

Patients with CNP were more functionally impaired (Barthel index = 81 ± 23.9 vs. 90.8 ± 15.7 in the non-neuropathic pain

group and 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 and 32.6% in the pain-free group $p < 0.001$) and had more severe motor impairment than both control groups (84.7% vs. 81.4% in the non-neuropathic pain group and 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 and 19.6% in the pain-free group, $p < 0.001$)–Table 1A. CPSP had more spasticity and motor impairment than control groups with stroke–Table 1B. While in patients with spinal cord lesions, spasticity and motor impairment were similar between the three groups (with neuropathic pain, non-neuropathic pain and pain-free)–Table 1C). The somatosensory assessment is summarised in Table 2 and show differences for all tested modalities except for mechanical hypoalgesia. Pain areas are detailed in Supplementary Table 5.

Patients with neuropathic pain had more symptoms of anxiety and depression and higher pain scores (McGill total score and pain intensity (BPI) scores) than patients with non-neuropathic pain or pain-free patients. However, pain catastrophizing scores with similar between the three groups. (Supplementary Table 6). According to 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%, $n = 14$)–Supplementary Table 7.

Table 1A 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	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
Barthel index	81.0 (23.9)	90.8 (15.7)	88.8 (20.0)	0.009*	0.008**	0.016**	0.866
Ashworth Spasticity grade							
Absence	23 (31.1%)	26 (60.5%)	31 (67.4%)	<0.001*	0.001**	<0.001**	0.419
Low to moderate (1-2)	31 (41.9%)	15 (34.9%)	11 (23.9%)				
Moderate to severe (3-5)	20 (27.0%)	2 (4.7%)	4 (8.7%)				
Motor impairment							
Paresis grade 0*	11 (15.3%)	8 (18.6%)	12 (26.1%)	0.010*	0.003**	0.165	0.162
Paresis grade 1*	30 (41.7%)	30 (69.8%)	23 (50.0%)				
Paresis grade 2*	24 (33.3%)	5 (11.6%)	8 (17.4%)				
Paresis grade 3*	7 (9.7%)	0 (0.0%)	3 (6.5%)				
Active myofascial trigger points	12 (17.4%)	29 (67.4%)	9 (19.6%)	<0.001*	<0.001**	0.769	<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 *Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

Table 1B 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 <i>n</i> = 35	Non-neuropathic pain <i>n</i> = 30	No-Pain <i>n</i> = 28	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
Barthel index	89.4 (18.3)	94.5 (9.2)	97.9 (4.6)	0.081			
Ashworth Spasticity grade							
Absence	18 (5.4%)	24 (80.0%)	25 (89.3%)	0.002*	0.007**	0.183	0.228
Low to moderate (1-2)	9 (25.7%)	6 (20.0%)	2 (7.1%)				
Moderate to severe (3-5)	8 (22.9%)	0 (0.0%)	1 (3.6%)				
Motor impairment							
Paresis grade 0*	11 (33.3%)	8 (26.7%)	12 (42.9%)	0.012*	0.004**	0.006**	0.256
Paresis grade 1*	11 (33.3%)	21 (70.0%)	13 (46.4%)				
Paresis grade 2*	10 (30.3%)	1 (3.3%)	3 (10.7%)				
Paresis grade 3*	1 (3.0%)	0 (0.0%)	0 (0.0%)				
Active myofascial trigger points	3 (9.1%)	22 (73.3%)	9 (32.1%)	<0.001*	<0.001**	0.025	0.002**

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 *Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

Table 1C 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 <i>n</i> = 39	Non-neuropathic pain <i>n</i> = 13	No-Pain <i>n</i> = 18	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
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*							
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%)	7 (53.8%)	0 (0.0%)	0.003*	0.06	0.021	0.011**

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 *Paresis grade 0 (MRC=5), grade 1 (MRC=4), grade 2: (MRC=2 or 3), grade 3 (MRC=1 or 0). * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

Table 2 Somatosensory assessment and comparative analysis groups according to their pain syndrome in stroke and spinal cord injury patients.

	Neuropathic pain <i>n</i> = 74	Non-neuropathic pain <i>n</i> = 43	No-Pain <i>n</i> = 46	<i>p</i> between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
Somatosensory assessment (physical examination)							
Tactile hypoesthesia	65 (87.8%)	29 (67.4%)	30 (65.2%)	0.003*	0.006**	0.002**	0.501
Cold hypoesthesia	62 (83.7%)	29 (67.4%)	29 (63.0%)	0.015*	0.036	0.006**	0.416
Mechanical hypoalgesia	28 (37.8%)	20 (46.5%)	13 (28.3%)	0.216	0.436	0.326	0.059
Mechanical hyperalgesia	45 (60.8%)	15 (34.9%)	18 (39.1%)	0.010*	0.006**	0.025	0.423
Dynamic mechanical allodynia	34 (45.9%)	2 (4.7%)	0 (0.0%)	<0.001*	<0.001**	<0.001**	0.231
Cold allodynia	27 (36.5%)	1 (2.3%)	2 (4.3%)	<0.001*	<0.001**	<0.001**	0.526
Hyperpathia	62 (83.8%)	21 (48.8%)	22 (47.8%)	<0.001*	<0.001**	<0.001**	0.546

Categorical variables are expressed in absolute numbers and percentages. Numerical variables are represented by mean and standard deviation. * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

Corticomotor excitability

Classifying patients' CE values according to the parameters of healthy individuals [13] showed that most patients in all groups had at least one abnormal measurement: less than a quarter had normal results 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 3.). Notwithstanding, group comparisons showed that patients with neuropathic pain had a significantly higher proportion of participants with low MEPs (75% vs. 46% in non-neuropathic pain vs. 37% in no-pain, $p < 0.001$) (Table 3).

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 CNP compared to controls in both the affected and unaffected hemispheres (Fig. 2). Other CE measures were not significantly different between groups (Table 4).

Side-to-side comparisons: when comparing CE 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 4).

SCI patients

SICI was more impaired in patients with neuropathic pain compared to the no-pain group. Although analysis between groups showed 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 between the three groups. (Table 5 and Fig. 2).

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 6 and Fig. 2).

No effects of motor weakness, lesion location, 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, of which the last three are known to influence CE. Therefore, we performed secondary analyses to determine if these three factors could influence the results.

Compared to patients with non-neuropathic pain and without chronic pain, patients with CNP 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 [54] (Supplementary Table 8). 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

Table 3 Cortical excitability classification according to normative data.

Cortical excitability parameters	Neuropathic pain <i>n</i> = 74	Non-neuropathic pain <i>n</i> = 42	No pain <i>n</i> = 46	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
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%)	20 (46.5%)	17 (37.0%)	<0.001*	0.002**	<0.001**	0.461
Normal	4 (5.4%)	10 (23.3%)	9 (19.6%)				
High	14 (18.9%)	13 (30.2%)	20 (43.5%)				
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 absolute numbers and percentage.. 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. * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

spasticity level further confirmed our findings as MEPs remained lower in CNP patients compared to controls (Supplementary Tables 9 and 10). Multiple linear regression was performed to assess if spasticity, motor impairment, or medication use could significantly contribute to lowering MEP 120% and 140%. The overall regression was not statistically significant for MEP 120% ($R^2=0.022$, $DF=3$, $F=2.02$ $p = 0.090$) and MEP 140% ($R^2=0.00$, $DF=3$, $F=1.01$ $p = 0.392$). Considering that 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 ($(14,148)=2.069$, $p = 0.017$).

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

We have shown that individuals with CNP have changes in corticomotor excitability compared to normative data from healthy individuals, including changes in parameters related to GABA and glutamate activity, as well as to neuronal membrane excitability. In particular, about three quarters of CNP patients had abnormally reduced MEPs. When comparing CNP patients with control patients who are no pain after

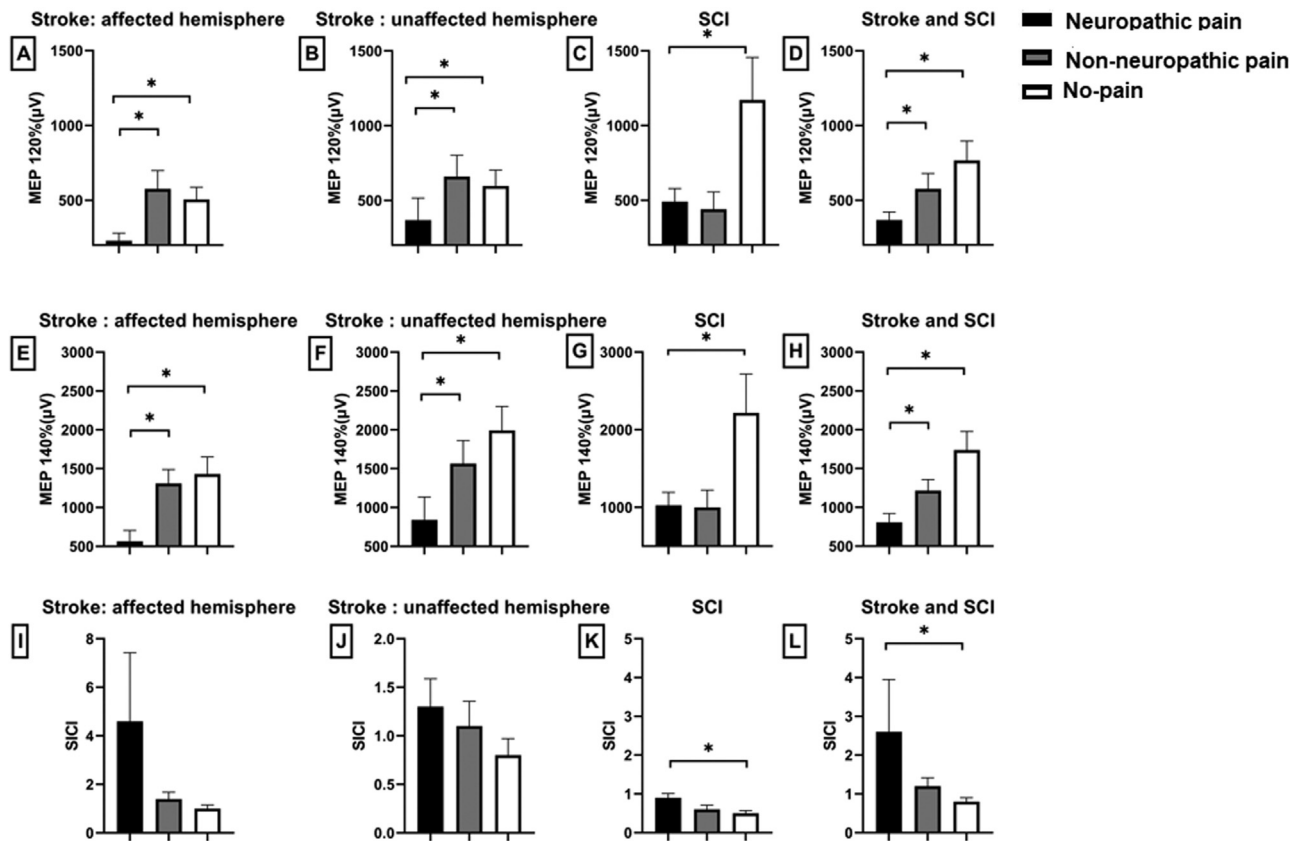


Fig. 2 Comparison of cortical excitability measurements according to pain group. Legend: Data are expressed as mean and standard error of the mean. A and B: Motor evoked potential at 120% of the RMT in stroke patients' affected and unaffected hemispheres. C: MEP 120% in spinal cord injury patients. D: 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. SCI: spinal cord injury. 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.

lesion or chronic pain of non-neuropathic origin, some specific CE changes remained significant. Notably, in patients with CNP due to stroke, there were markedly reduced MEP values compared to the two control groups. These changes were also found in the brain hemisphere not affected by the lesion in the case of stroke patients. The observed reduction in MEP 120 and 140 was apparently proportional and disappeared in the 120/140 ratio, which was not different between groups. Interestingly, MEP changes correlated with two of the most common abnormalities in physical examination in patients with central pain: mechanical and thermal allodynia [3]. Additionally, sensitivity analyses excluding patients with motor weakness, spasticity, or taking psychoactive drugs known to affect MEPs led to no significant changes in these findings, which remained significant. Our results support that these are genuine findings in CNP and suggest these are not uniquely related to corticospinal motor injury or non-specific effects of chronic pain in general (e.g., sleep abnormalities, mood, fatigue) or to psychotropic analgesic medication use.

Among the CE measures, MEP is one of the most studied parameters in cortical clinical neurophysiology [5].

Stimul 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 [37]. However, MEP changes are not only present in diseases exclusively affecting motor pathways. Different neurological conditions have been associated with MEP reduction, such as stroke, multiple sclerosis, cervical myelopathy, cerebellar ataxia, and epilepsy [37,50]. MEP reduction has also been reported in healthy individuals undergoing acute experimental pain [9,36,38]. A meta-analysis revealed moderate to strong evidence of reduced in the primary somatosensory cortex and corticomotor excitability during acute pain and up to 30 minutes following its resolution [9]. In a study with repetitive TMS 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 that the reduction of the M1 excitability was specifically related to the engagement of nociceptive systems [50].

Table 4 Cortical excitability evaluation in patients with stroke according to pain syndrome.

Cortical excitability parameters	Neuropathic pain (stroke) <i>n</i> = 35	Non-neuropathic pain (stroke) <i>n</i> = 30	No pain (stroke) <i>n</i> = 28	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No-pain	Non-neuropathic pain vs. No pain
RMT (%) affected hemisphere	48.3 (10.1)	47.5 (8.9)	48.3 (10.2) [†]	0.938			
RMT (%) unaffected hemisphere	47.8 (7.8)	46.3 (9.0)	44.4 (8.2) [†]	0.247			
MEP 120 (μ V) affected hemisphere	229 (296.)	575 (673)	505 (431)	<0.001*	<0.001**	<0.001**	0.907
MEP 120 (μ V) unaffected hemisphere	367 (870)	658 (780)	595 (560)	0.001*	0.002**	0.001**	0.876
MEP 140 (μ V) affected hemisphere	563 (843)	1310 (977)	1429 (1170)	<0.001*	<0.001**	<0.001**	0.864
MEP 140 (μ V) unaffected hemisphere	841 (1732)	1564 (1626)	1992 (1637)	<0.001*	0.001**	<0.001**	0.137
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, p was <0.05 only in RMT in 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. * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

It has long been demonstrated in cats that thalamic hyperactivity after spinothalamic transection could be inhibited by stimulation of the motor cortex [46]. Motor cortex electrical stimulation can provide pain relief in CPSP, while deep stimulation of thalamic relay nucleus did not have the same results [46]. These authors postulated that motor cortex afferents and efferents could inhibit abnormal hyperactivity within the CNS, underlying deafferentation pain. [46,47].

In addition, repetitive high-frequency TMS delivered to M1, which is considered to have an excitatory effect, can reduce neuropathic pain and restore cortex excitability abnormalities such as defective intracortical inhibition [20,26] and also alter functional connectivity between the

mediodorsal nucleus of the thalamus and the amygdala [22]. Organized reciprocal connections between the motor cortex and the sensory system, including the amygdala, medial thalamus, anterior cingulate, and sensory cortex, have been described [16,22], and brain network reorganization and maladaptive neural plasticity in different brain circuits, including the motor pathway, are considered to contribute to the development of neuropathic pain [21].

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 [19,20]. Moreover, since in these publications the control group was composed of healthy individuals, it was not possible to ascertain which changes were due to stroke

Table 5 Cortical excitability evaluation in patients with spinal cord injury according to pain syndrome.

Cortical excitability parameters	Neuropathic pain (SCI) <i>n</i> = 39	Non-neuropathic pain (SCI) <i>n</i> = 13	No pain (SCI) <i>n</i> = 18	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No pain	Non-neuropathic pain vs. No pain
RMT (%)	52.9 (10.6)	56.9 (10.7)	50.9 (6.4)	0.303			
MEP 120 (μ V)	490 (549)	438 (418)	1170 (1212)	0.009*	0.792	0.003**	0.020
MEP 140 (μ V)	1026 (1038)	1000 (798)	2217 (2120)	0.008*	0.642	0.003**	0.035
MEP 140/120	2.7 (1.6)	2.8 (1.4)	2.5 (1.5)	0.785			
SICI	0.9 (0.7)	0.6 (0.4)	0.5 (0.3)	0.018*	0.046	0.013**	0.622
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. * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

Table 6 Cortical excitability evaluation according to pain syndrome.

Cortical excitability parameters	Neuropathic pain <i>n</i> = 74	Non-neuropathic pain <i>n</i> = 43	No pain <i>n</i> = 46	p effects between groups	Neuropathic pain vs. Non-neuropathic pain	Neuropathic pain vs. No pain	Non-neuropathic pain vs. No pain
RMT (%)	50.7 (10.6)	50.3 (10.3)	49.3 (8.9)	0.742			
MEP 120 (μ V)	366 (464)	575 (672)	765 (880)	<0.001*	0.006**	<0.001**	0.132
MEP 140 (μ V)	807 (972)	1216 (929)	1738 (1634)	<0.001*	0.001**	<0.001**	0.131
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*	0.077	0.016**	0.634
ICF	5.8 (26.5)	2.0 (2.1)	2.4 (2.5)	0.099			

Variables are expressed in mean and standard deviation. 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 * $p < 0.05$ ** Statistically different in subgroup analysis with Bonferroni correction ($p < 0.0167$).

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 [20]. 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 [20].

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 mixed central and peripheral etiologies [26,44], suggesting motor cortex disinhibition with impaired GABAergic neurotransmission [10,26,48]. Defective intracortical inhibition was also reported in other chronic pain syndromes [35] and acute pain [40]. Reduction of intracortical inhibition has been described in the affected and unaffected hemispheres during the acute phase of stroke which tends to normalize during the chronic phase [30,41]. 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 [30,41] after CNS injury.

In the present study, more than half of the CNP and a third of the non-neuropathic pain patients had defective

SICI compared to normative data based on healthy individuals matched for age and sex. One important point is that if, on a group level, changes in CE 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 classifying CE results for each patient as normal, high, or low according to normative 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 in 19.9% (for MEP 140%) of CNP patients, which could not be detected on a group-level assessment. This argues for the notion that there is more heterogeneity between individuals than differences between different etiologies of CNP in terms of CE changes. In part, it could 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 manifestations of neuropathic pain, including

pain intensity [10,26], thermal paresthesia [10], and allodynia [28,44]. Additionally, repetitive TMS was associated with improvement in thermal sensory perception [19,27]. We reported that CNP is associated with the two most common evoked pain findings in CNP patients: mechanical and thermal allodynia [3]. 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 [27].

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 sensitivity 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 not according to incapacity, motor impairment, spasticity, or spinothalamic tract lesion. Such pairing or matching is not only challenging in practical terms but is also methodologically flawed. Previous studies have shown that CNP patients were more functionally impaired than those with non-neuropathic pain [11], 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 [1,15,32,33] and one of the largest normative data studies to date [13]. 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. This could be an argument suggesting that the MEP changes reported here for the CNP group were robust to the point of being significant despite all these aforementioned variability sources. It may also be the case that in CNP, MEP variability is not as marked as in healthy volunteers, thus allowing for its proper measurement by a lower number of pulses, while also allowing these changes to be detected both in group and in individual-patient basis comparisons. These hypotheses obviously remain to be tested [44].

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 [1,24,32,33]. However, studies assessing CE corresponding to the specific area of pain, other than hand, and examining MEP morphology in addition to its amplitude could provide additional information.

In conclusion, CNP is associated with consistent bilateral CE changes, mainly related to MEP reduction. These changes do not seem to be due to pyramidal tract lesions or dysfunction and correlate with clinical findings seen in CNP, such as allodynia. MEP reductions are present when comparing groups and are also present when patients are individually classified according to normative data, further supporting the group findings. Further studies may help determine whether the plasticity changes described here could be useful as predictors of CNP emergence after CNS injury and thus guide the development of early interventions aiming to prevent the development of chronic neuropathic pain.

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Declaration of Competing Interest

The authors report no conflict of interest or disclosures relevant to the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neucli.2023.102845](https://doi.org/10.1016/j.neucli.2023.102845).

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