

Corticospinal Excitability in Bilateral M1 Hand Areas: Association with Neuropathic Pain After Spinal Cord Injury

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Purpose: Neuropathic pain (NP) is a major and debilitating complication of spinal cord injury (SCI), frequently occurring bilaterally below the injury level. Repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex (M1) is suggested as a treatment for NP following SCI (SCI-NP). However, the specific changes in corticospinal excitability (CSE) within the bilateral M1 remain unclear, hindering the development of optimized rTMS parameters for SCI-NP.

Patients and Methods: This retrospective study analyzed data from 625 SCI patients and 131 healthy controls. Motor-evoked potential (MEP) was used to assess CSE in the bilateral M1 hand areas. The hemispheric asymmetry of bilateral M1 CSE was measured by calculating the natural logarithm of the MEP amplitude ratio between the dominant hemisphere (DH) and non-dominant hemisphere (NDH), expressed as $\ln(\text{DH}/\text{NDH}$ amplitude). The study utilized correlation analysis and multiple linear regression to examine the associations between hemispheric CSE asymmetry and the course, severity, and emotional disturbances of NP.

Results: SCI patients experiencing NP exhibited lower MEP amplitude than those without NP in bilateral M1 hand areas, with a more pronounced decrease in NDH. Hemispheric CSE asymmetry was found to be elevated and positively correlated with NP course ($r=0.213$, $P=0.034$), severity ($r=0.317$, $P=0.004$), and emotional disturbances ($r=0.294$, $P=0.009$). Notably, hemispheric CSE asymmetry was independently associated with NP severity and emotional disturbances, particularly in younger individuals (under 52 years), those with traumatic injuries, and those with non-cervical SCI.

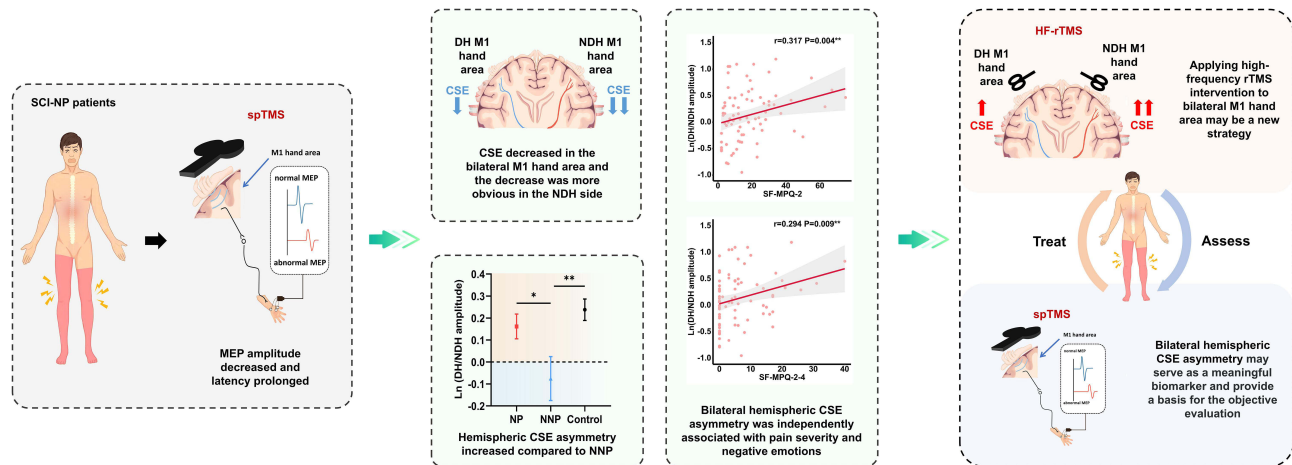
Conclusion: Hemispheric CSE asymmetry shows potential as a biomarker for assessing SCI-NP severity and emotional disturbances in SCI patients. High-frequency rTMS targeting bilateral M1 hand areas may provide improved analgesic effects. This finding could enhance neuropathic pain assessment and guide rTMS optimization, potentially improving the quality of life for individuals with SCI.

Keywords: spinal cord injury, neuropathic pain, corticospinal excitability, MEP, hemispheric CSE asymmetry, rTMS

Introduction

Spinal cord injury (SCI) predominantly affects individuals in their younger and middle adult years.¹ Neuropathic pain (NP), occurring in 84–92% of SCI patients, significantly impedes rehabilitation and exacerbates sleep disturbances, depression, and anxiety, creating a substantial economic burden on society.^{2,3} Although pharmacological interventions are the mainstay of NP management, their effectiveness is limited, and adverse effects, including increased overdose-related mortality, are concerning.^{4–6}

Graphical Abstract



Repetitive transcranial magnetic stimulation (rTMS) has shown promise as a non-pharmacological treatment for SCI-NP. The analgesic effects are linked to modulating the primary motor cortex (M1) excitability, affecting pain perception and emotional processing through cortico-limbic circuits.⁷ International guidelines suggest high-frequency rTMS on the contralateral M1 for unilateral NP.⁸ However, SCI often leads to bilateral NP in the trunk and lower limbs, creating uncertainty about the optimal side of M1 stimulation side.^{9,10} Furthermore, there is ongoing debate about whether the ideal stimulation site in M1 should be the somatotopic pain region or the more accessible hand area. For example, Jetté et al demonstrated effective SCI-NP relief with high-frequency rTMS targeting the M1 hand or leg area contralateral to the more affected or dominant hand side, while Defrin et al reported no significant difference between sham and active rTMS targeting the M1 lower limb region in SCI-NP patients.^{11,12} The deeper localization of the lower limb region complicates stimulation, favoring the hand area for its accessibility and clinical practicality.^{13,14} Our previous studies found that high-frequency rTMS of the left M1 hand area provided analgesic effects for SCI-NP. Nonetheless, these effects were restricted, necessitating a minimum of two weeks of treatment to achieve notable improvement over sham stimulation.^{15,16} The lack of clarity about excitability changes in the bilateral M1 hand areas adds to the ongoing discussion about rTMS parameters.

TMS-induced motor evoked potentials (MEPs) have been established as a reliable neurophysiological tool for assessing corticospinal excitability (CSE). This technique offers distinct advantages including excellent temporal resolution and non-invasive evaluation of corticospinal pathway integrity.¹⁷ As a stable and reproducible measure, MEPs provide valuable insights into the functional state of the corticospinal tract (CST), making them particularly useful for both research applications and clinical assessment. In complex regional pain syndrome (CRPS), Krause et al identified significant hemispheric asymmetry in motor cortical representation (size, MEP, and calculated volumes) in affected versus unaffected muscles.¹⁸ Similarly, Barbosa et al found that stroke patients with central neuropathic pain (CNP) exhibited significantly lower MEP amplitudes in both hemispheres compared to those with non-neuropathic pain or no pain.¹⁹ Thus, MEPs provide objective and quantifiable metrics for evaluating pain characteristics.

To comprehensively assess neuropathic pain characteristics, we employed the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2), a validated multidimensional pain assessment tool comprising 22 items across four subscales: continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors.^{20,21} While the full SF-MPQ-2 was used to evaluate overall neuropathic pain severity, we specifically utilized its fourth subscale (SF-MPQ-2-4) to quantify pain-related negative emotional states, as these affective components may independently influence corticospinal excitability in pain conditions.

This retrospective study examined alterations in CSE in the bilateral M1 hand areas of SCI-NP patients and analyzed its correlation with the NP course and severity, with the goal of offering objective evidence for NP assessment and the optimization of rTMS parameters.

Materials and Methods

Study Design

This retrospective cross-sectional study analyzed neurophysiological and pain-related data from patients with SCI who experienced NP or no neuropathic pain (NNP), as well as healthy controls. Data were gathered from January 2018 to April 2024 in the inpatient unit of the Department of Rehabilitation Medicine at the First Affiliated Hospital of Air Force Medical University of Chinese People's Liberation Army. The Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University of Chinese People's Liberation Army approved the study (No. KY20222096-C-1), and the study was registered in the Chinese Clinical Trial Registry (ChiCTR2300073824). Due to the retrospective nature of this study, informed consent was waived as it would not adversely affect the rights and welfare of the subjects, and it was objectively impossible to obtain informed consent from the subjects. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants

Inclusion criteria for SCI patients included: a. Age of 18–70 years, right hand dominance (as determined by the Edinburgh Handedness Inventory);²² b. Diagnosed with SCI;²³ c. Disease course ≤ 36 months (from SCI onset to clinical assessment and MEP measurement, with recovery from spinal shock); d. No rTMS therapy within the past 2 weeks; e. No cognitive impairment (Mini-Mental State Examination (MMSE) score ≥ 24);²⁴ f. For the NP group, diagnosis of NP following SCI.²⁵ Exclusion criteria included: a. Severe language impairment; b. Presence of conductive, ferromagnetic, or other magnetically sensitive metals in the head or neck, as well as a pacemaker; c. Seizures within the past six months; d. Severe local or systemic diseases that prevent tolerance of relevant tests; e. Other types of pain (eg, musculoskeletal pain, visceral pain, or non-neuropathic pain); f. Use of medications that may affect MEP recordings within the past week, such as baclofen, diazepam, or similar drugs;²⁶ g. MEP measurements of the M1 hand area were not conducted.

Healthy controls included individuals aged 18–70 years, matched with SCI patients, who were right-hand dominant (as determined by the Edinburgh Handedness Inventory) and had stable MEPs in bilateral M1 hand areas. Exclusion criteria encompassed conditions preventing TMS application and individuals with acute or chronic pain.

Motor Evoked Potentials

MEPs were captured using a TMS device (MEP-9404C, Japan) and 10 mm Ag-AgCl surface electrodes on the abductor pollicis brevis muscle, adhering to a standardized protocol.²⁷ The TMS coil was aligned with the M1 hand area's surface projection, precisely targeting the "hot spot" with single-pulse TMS at 80% of the stimulator's maximum output.²⁸ MEPs were recorded every 5 seconds. MEPs elicited from both bilateral M1 hand areas were classified as "Bilateral MEP Elicited" (B-MEP), while those elicited unilaterally or not at all were categorized as "Non-Bilateral MEP Elicited" (NB-MEP).

Evaluation of Hemispheric CSE in Bilateral M1 Hand Areas

A previously established method was used to assess hemispheric CSE symmetry in the bilateral M1 hand areas.²⁹ Hemispheric CSE asymmetry was quantified by calculating the natural logarithm of the MEP amplitude ratio between the dominant hemisphere (DH) and non-dominant hemisphere (NDH): $\ln(\text{DH}/\text{NDH} \text{ amplitude})$. An asymmetry value of 0 indicates equal excitability between the DH and NDH [$\ln(1) = 0$]; a value greater than 0 indicates greater excitability in the DH compared to the NDH [$\ln(>1) > 0$]; and a value less than 0 suggests lower excitability in the DH than in the NDH [$\ln(<1) < 0$].

NP Assessment

SF-MPQ-2, known for its clinical reliability and validity, was employed to assess the multidimensional aspects of NP.^{20,21} This tool comprises 22 items distributed across four subscales: continuous pain, intermittent pain, predominantly NP, and affective descriptors. Items are rated on a 0 to 10 scale, where higher scores denote more intense pain or negative emotional states.³⁰

Statistical Analysis

General Data Statistics

Continuous variables are expressed as mean \pm standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were represented as frequencies and percentages [N (%)]. Statistical analyses included the Kruskal–Wallis test for multiple group comparisons of continuous variables, Fisher’s exact test or the Chi-square test for categorical variables, and the Mann–Whitney U test for two independent groups of continuous or ordinal data. A *P*-value below 0.05 was deemed statistically significant.

MEPs and CSE Asymmetry

The Shapiro–Wilk test evaluated the normality of data for MEP amplitude, latency, and central motor conduction time (CMCT). The Kruskal–Wallis test was used to compare the variables among the NP, NNP, and control groups due to the non-normal distribution of the data. The Wilcoxon signed-rank test was used for post hoc comparisons. Additionally, a non-parametric paired test was utilized to compare the DH and NDH variables within each group. A one-way ANOVA was conducted on the natural logarithm of the dominant to non-dominant hand amplitude ratio to assess hemispheric CSE asymmetry, followed by post hoc comparisons using the least significant difference (LSD) test. The Kruskal–Wallis test was used to assess hemispheric symmetry of MEP latency and CMCT, followed by the Wilcoxon signed-rank test for post hoc analysis. Statistical significance was considered at a level of $P < 0.05$.

Analysis of Correlation and Regression

Following confirmation of non-normal distributions via Shapiro–Wilk testing, Spearman correlation analysis assessed the relationship between hemispheric CSE asymmetry and the course and intensity of NP. Subgroup analyses were performed to investigate the effects of age, etiology of SCI, and neurological level of injury (NLI). To assess the impact of age on MEP amplitude in bilateral M1 hand areas, patients were classified into two age groups: <52 years and ≥ 52 years, using receiver operating characteristic (ROC) curve analysis for optimal cut-off determination.^{31,32} Additionally, patients were categorized into traumatic (eg, compression by heavy objects, traffic accidents, falls) and non-traumatic (eg, congenital or disease-related factors) SCI groups. Patients were categorized into cervical and non-cervical (thoracic, lumbar, sacral) injury groups to assess the potential influence of cervical injuries on MEP amplitude stability.

Univariate and multivariate linear regression analyses were conducted to assess the effect of MEP hemispheric asymmetry in the M1 hand area on pain outcomes. The study examined MEP hemispheric asymmetry as the independent variable, while the SF-MPQ-2 total scores and its affective subscale (SF-MPQ-2-4) served as the dependent variables. Variables with *P*-values below 0.10 in the univariate analysis were incorporated into the multivariate model. Statistical significance was determined at a *P*-value threshold of 0.05.

All analyses were conducted using SPSS 27.0, and data visualizations were generated with GraphPad Prism 9.5 and R 4.4.1.

Results

Basic Characteristics of NP, NNP Patients, and Healthy Controls

Data were collected from 625 SCI patients admitted to the inpatient unit of the Department of Rehabilitation Medicine at the First Affiliated Hospital of Air Force Medical University of Chinese People’s Liberation Army between January 2018 and April 2024. A total of 78 patients were excluded for not meeting the inclusion criteria. A total of 325 patients were excluded due to exclusion criteria: 263 had other types of pain, and 62 lacked MEP measurements in the M1 hand area. The remaining 222 patients were categorized into B-MEP (N = 155) and NB-MEP (N = 67) groups based on whether MEPs were elicited from bilateral or unilateral M1 hand areas. The B-MEP group was further subdivided into the patients with NP (N = 114) and NNP (N = 41) (Figure 1). For comparison, 131 healthy controls matched by age and sex were analyzed alongside the NP and NNP groups.

Table 1 outlines the fundamental characteristics of the B-MEP and NB-MEP groups. While no significant disparities were observed in age or gender between the two groups, notable differences emerged in NLI, AIS grade, and the incidence of NP. Patients in the B-MEP group demonstrated a lower NLI, milder injury severity, and a higher incidence of NP. Table 2 presents the basic characteristics of NP, NNP patients, and healthy controls. Although no significant

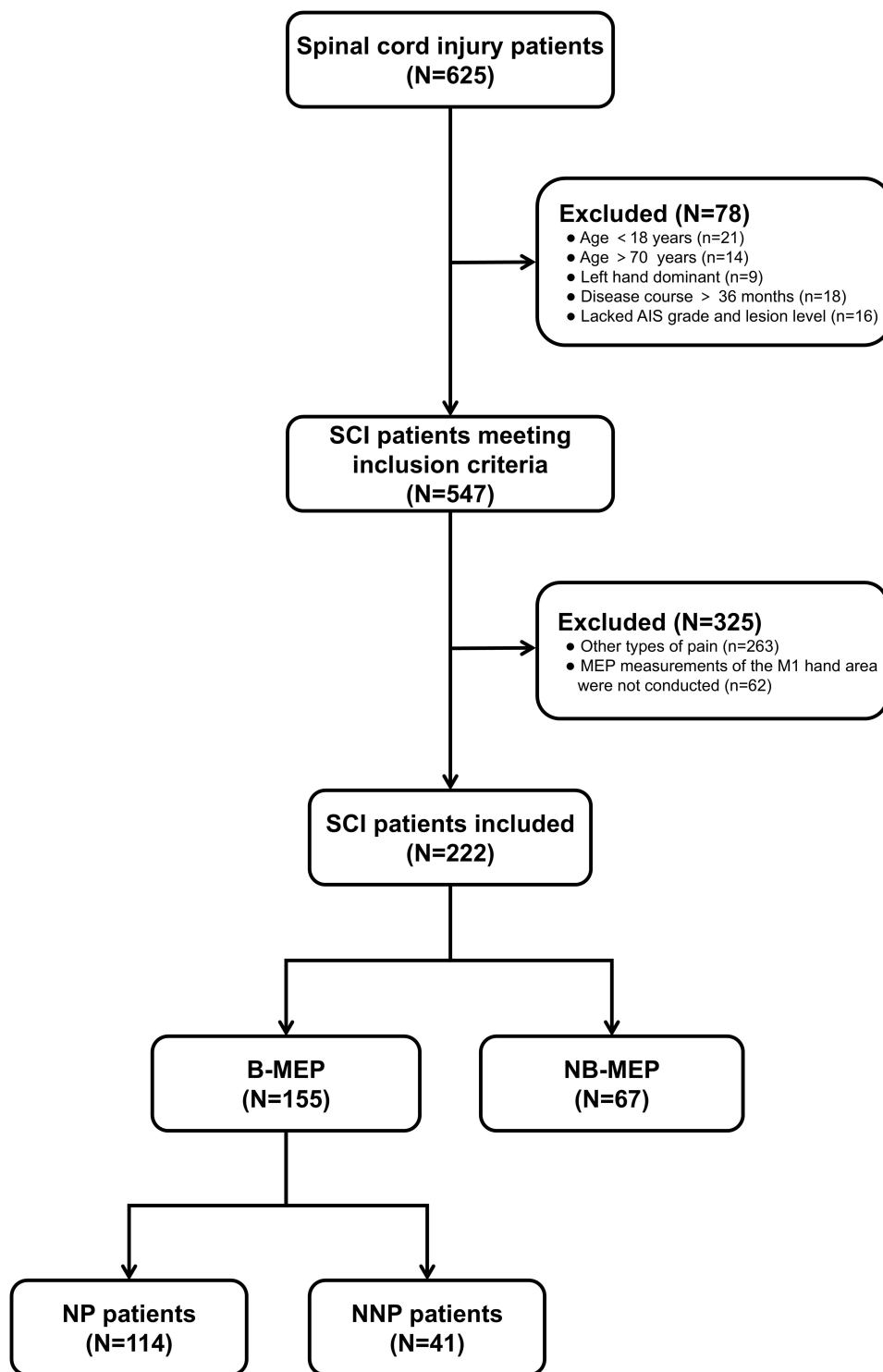


Figure 1 Study Flowchart. Data were collected from 625 SCI patients admitted to the inpatient unit of the Department of Rehabilitation Medicine at the First Affiliated Hospital of Air Force Medical University between January 2018 and April 2024. Of these, 78 patients were excluded for failing to meet the inclusion criteria, and 325 patients were excluded based on the exclusion criteria. The remained 222 patients were classified into B-MEP (N = 155) and NB-MEP (N = 67) groups based on MEPs elicited from bilateral or unilateral M1 hand areas. The B-MEP group was further subdivided into patients with NP (N = 114) or NNP (N = 41). For comparison, 131 healthy controls matched by age and sex were analyzed alongside the NP and NNP groups.

Table 1 Basic Characteristics of SCI Subgroup Patients with Tested MI Hand Area MEP

	B-MEP (155)	NB-MEP (67)	Z/χ^2/Fisher's	P
Age in Years, median (QR)	46.00 (34.50, 52.00)	44.00 (32.00, 50.00)	0.596	0.551 ^a
Gender [N (%)]				
Female	38 (24.52)	15 (22.39)	0.117	0.864 ^b
Male	117 (75.48)	52 (77.61)		
Disease Course [N (%)]				
0–6 m	123 (79.35)	52 (77.61)	0.085	0.858 ^b
6–36 m	32 (20.65)	15 (22.39)		
NLI [N (%)]				
C	31 (20.00)	67 (100)	139.247	<0.001^c
T	88 (56.77)	0		
L	31 (20.00)	0		
S	5 (3.23)	0		
AIS grade [N (%)]				
A	70 (45.16)	33 (49.25)	2.610	0.009^a
B	10 (6.45)	19 (28.36)		
C	25 (16.13)	11 (16.42)		
D	50 (32.26)	4 (5.97)		
Neuropathic pain [N (%)]				
With	114 (73.55)	33 (49.25)	12.342	<0.001^b
Without	41 (26.45)	34 (50.75)		

Notes: Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data or as median and interquartile range (IQR) for non-normally distributed data. Categorical variables are presented as counts and percentages. Bold text indicates statistical significance ($P < 0.05$). Statistical tests used include: ^amann–Whitney U -test; ^bChi square test; ^cFisher's exact test.

Abbreviations: SCI, spinal cord injury; MEP, motor evoked potential; NLI, neurological level of injury; AIS, American Spinal Injury Association (ASIA) impairment scale; B-MEP, bilateral MEP elicited; NB-MEP, non-bilateral MEP elicited.

Table 2 Basic Characteristics of B-MEP Patients and Healthy Controls

	B-MEP Patients		Control (131)	H/Z/χ^2/Fisher's	P
	NP (114)	NNP (41)			
Age in Years, median (QR)	46.50 (35.25, 52.75)	45.00 (29.00, 51.00)	44.00 (35.00, 54.00)	1.936	0.380 ^a
Gender [N (%)]					
Female	29 (25.44)	9 (21.95)	46 (35.11)	4.021	0.134 ^b
Male	85 (74.56)	32 (78.05)	85 (64.89)		
Disease Course in months, median (QR)	2.43 (1.13, 5.32)	2.33 (1.12, 6.95)	–	0.540	0.589 ^c
Etiology [N (%)]					
Non-Traumatic	32 (28.07)	12 (29.27)	–	0.021	0.884 ^b
Traumatic	82 (71.93)	29 (70.73)			
NLI [N (%)]					
C	21 (18.42)	10 (24.39)	–	3.030	0.374 ^d
T	69 (60.53)	19 (46.34)			
L	21 (18.42)	10 (24.39)			
S	3 (2.63)	2 (4.88)			
AIS grade [N (%)]					
A	52 (45.61)	18 (43.90)	–	–0.228	0.819 ^c
B	7 (6.14)	3 (7.32)			
C	19 (16.67)	6 (14.63)			
D	36 (31.58)	14 (34.15)			

(Continued)

Table 2 (Continued).

	B-MEP Patients		Control (131)	H/Z/ χ^2 /Fisher's	P
	NP (114)	NNP (41)			
Distribution of NP [N (%)]					
Upper limbs	18 (15.79)	–	–	–	–
Lower limbs	90 (78.95)				
Trunk	39 (34.21)				
Hip	22 (19.30)				
Laterality of NP [N (%)]					
Bilateral	100 (87.72)	–	–	–	–
Unilateral	14 (12.28)				

Notes: Continuous variables are presented as mean \pm standard deviation (SD) for normally distributed data or as median and quartile range (QR) for non-normally distributed data. Categorical variables are presented as counts and percentages. Bold text indicates statistical significance ($P < 0.05$). Statistical tests used include: ^aKruskal–Wallis test; ^bChi square test; ^cmann–Whitney *U*-test; ^dFisher's exact test.

Abbreviations: MEP, motor evoked potential; B-MEP, bilateral MEP elicited; NP, neuropathic pain; NNP, no neuropathic pain; NLI, neurological level of injury; AIS, American Spinal Injury Association (ASIA) impairment scale.

differences were found in age [44.00 (35.00, 54.00) years] or sex distribution [male N(%): 85 (64.89%)] among these groups, 78.95% of NP patients reported lower limb pain, and 87.72% experienced bilateral pain (Table 2). Additionally, NP and NNP patients showed no significant differences in disease course, etiology, NLI, AIS grade, or other baseline characteristics.

Comparison of M1 Hand Area MEPs Between Hemispheres in NP, NNP, and Healthy Control Groups

We analyzed MEP recordings to evaluate changes in CSE in the bilateral M1 hand areas of NP patients after SCI. Our study identified a reduction trend in MEP amplitudes from both hemispheres in NP patients relative to healthy controls. In the NP group, the MEP amplitude from the NDH M1 hand area was notably lower than that from the DH M1 hand area ($P < 0.05$). The NNP group showed no significant difference in MEP amplitude between the DH and NDH M1 hand areas (Figure 2A). Latency analysis revealed a notable delay in MEP onset from both hemispheres in NP patients relative to healthy controls ($P < 0.001$; Figure 2B). Figure 2C shows that CMCT did not significantly differ among the three groups.

In NP patients, MEP amplitudes in the M1 hand area were significantly lower on the NDH side compared to the DH side, a difference not observed in NNP patients. The asymmetry was corroborated by a notable rise in the $\ln(\text{DH}/\text{NDH}$ amplitude), increasing from -0.08 ± 0.62 in NNP patients to 0.16 ± 0.56 in NP patients (Figure 2D). No significant differences were found in hemispheric MEP latency or CMCT (Figure 2E and F).

Correlation Between Hemispheric CSE Asymmetry and NP Course and Severity

Spearman correlation analyses were carried out to examine the connection between hemispheric M1 hand area CSE asymmetry and the progression and intensity of NP. A significant positive correlation was observed between $\ln(\text{DH}/\text{NDH}$ amplitude) and the NP course in NP patients ($r = 0.213$, $P = 0.034$; Figure 3A). The $\ln(\text{DH}/\text{NDH}$ amplitude) showed significant positive correlations with both the total SF-MPQ-2 score (SF-MPQ-2, $r = 0.317$, $P = 0.004$; Figure 3B) and its affective subscale (SF-MPQ-2-4, $r = 0.294$, $P = 0.009$; Figure 3C).

Age Subgroup Analysis

In patients younger than 52, a positive correlation was found between the $\ln(\text{DH}/\text{NDH}$ amplitude) and NP course ($r = 0.306$, $P = 0.010$), SF-MPQ-2 ($r = 0.300$, $P = 0.022$), and SF-MPQ-2-4 ($r = 0.310$, $P = 0.019$). This trend was not significant in patients aged 52 or above (Figure 4A).

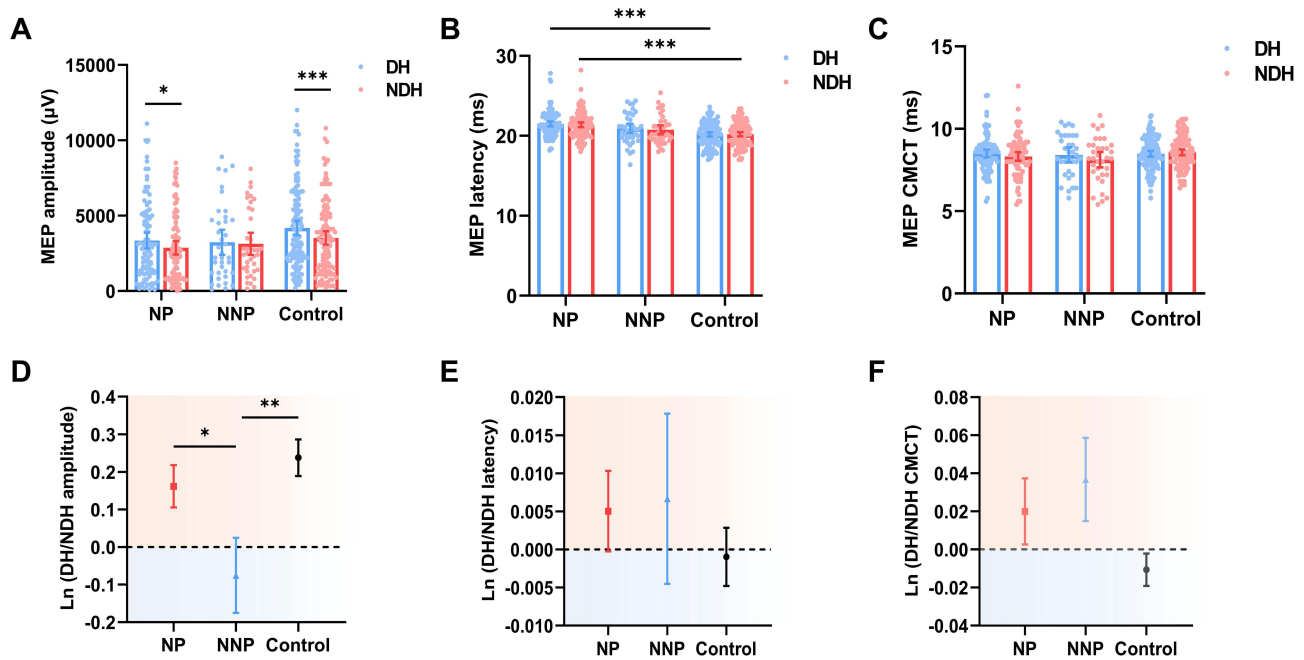


Figure 2 MEP Comparison of the M1 Hand Area Across Both Hemispheres in NP, NNP, and Healthy Control Groups. **(A)** Comparison of MEP amplitude between hemispheres in NP, NNP, and healthy control groups. In both healthy controls and the NP group, the MEP amplitude in the NDH M1 hand area was significantly smaller than in the DH M1 hand area. The NNP group showed no significant difference in MEP amplitude between the DH and NDH M1 hand areas. **(B)** Comparison of MEP latency between hemispheres in NP, NNP, and healthy control groups. The NP group exhibited a notable delay in bilateral M1 hand area MEP latency relative to healthy controls. **(C)** Comparison of MEP CMCT between hemispheres in NP, NNP, and healthy control groups. No significant differences were observed in M1 hand area MEP CMCT among the three groups. **(D)** Hemispheric CSE asymmetry was quantified by calculating the natural logarithm of the MEP amplitude ratio between the DH and NDH. The $\ln(\text{DH}/\text{NDH}$ amplitude) was 0.16 ± 0.56 in NP patients, 0.24 ± 0.55 in the control group, and -0.08 ± 0.62 in NNP patients. The degree of hemispheric asymmetry was greater in the NP group compared to the NNP group. **(E)** Bilateral hemispheric differences in MEP latency in the M1 hand area were quantified by calculating the natural logarithm of the MEP latency ratio between DH and NDH. No significant differences were found in $\ln(\text{DH}/\text{NDH}$ latency) among the three groups. **(F)** Bilateral hemispheric differences in MEP CMCT in the M1 hand area were quantified by calculating the natural logarithm of the MEP CMCT ratio between DH and NDH. No significant differences were found in $\ln(\text{DH}/\text{NDH}$ CMCT) among the three groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Abbreviations: NP, neuropathic pain; NNP, no neuropathic pain; M1, primary motor cortex; CSE, corticospinal excitability; MEP, motor evoked potential; DH, dominant hemisphere; NDH, non-dominant hemisphere; CMCT, central motor conduction time.

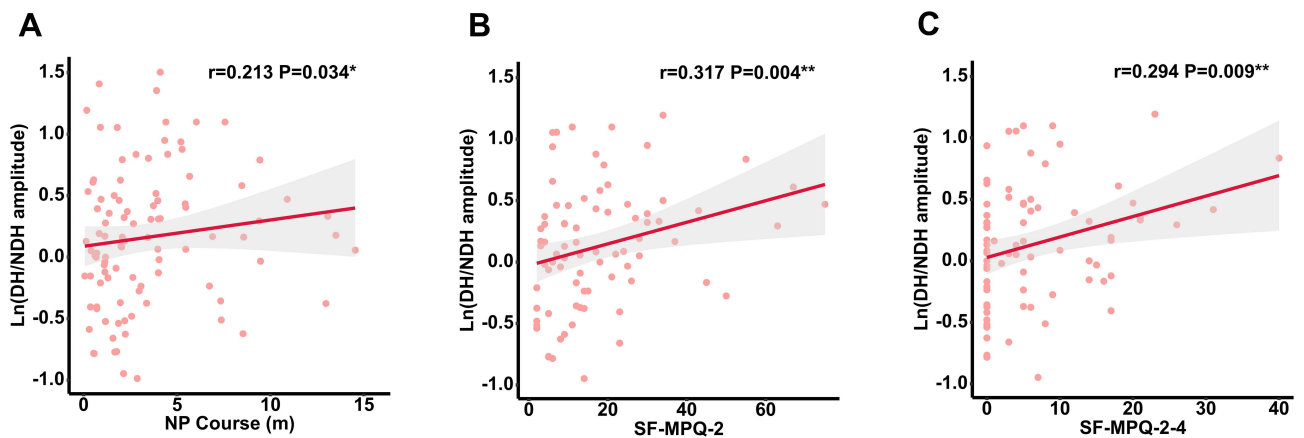


Figure 3 Correlation Between Hemispheric CSE Asymmetry and NP Duration and Severity Scores. **(A)** Correlation of hemispheric CSE asymmetry degree with NP course. A notable positive correlation was identified between the $\ln(\text{DH}/\text{NDH}$ amplitude) and NP duration ($r=0.213$). **(B)** Correlation of hemispheric CSE asymmetry degree with SF-MPQ-2 scores. A notable positive correlation was found between the $\ln(\text{DH}/\text{NDH}$ amplitude) and the SF-MPQ-2 score ($r=0.317$). **(C)** Correlation of hemispheric CSE asymmetry degree with SF-MPQ-2-4 scores. A notable positive correlation was noted between the $\ln(\text{DH}/\text{NDH}$ amplitude) and SF-MPQ-2-4 ($r=0.294$). * $P < 0.05$, ** $P < 0.01$. **Abbreviations:** NP, neuropathic pain; DH, dominant hemisphere; NDH, non-dominant hemisphere; CSE, corticospinal excitability; SF-MPQ-2, short-form McGill pain questionnaire-2; SF-MPQ-2-4, subscale 4 of SF-MPQ-2.

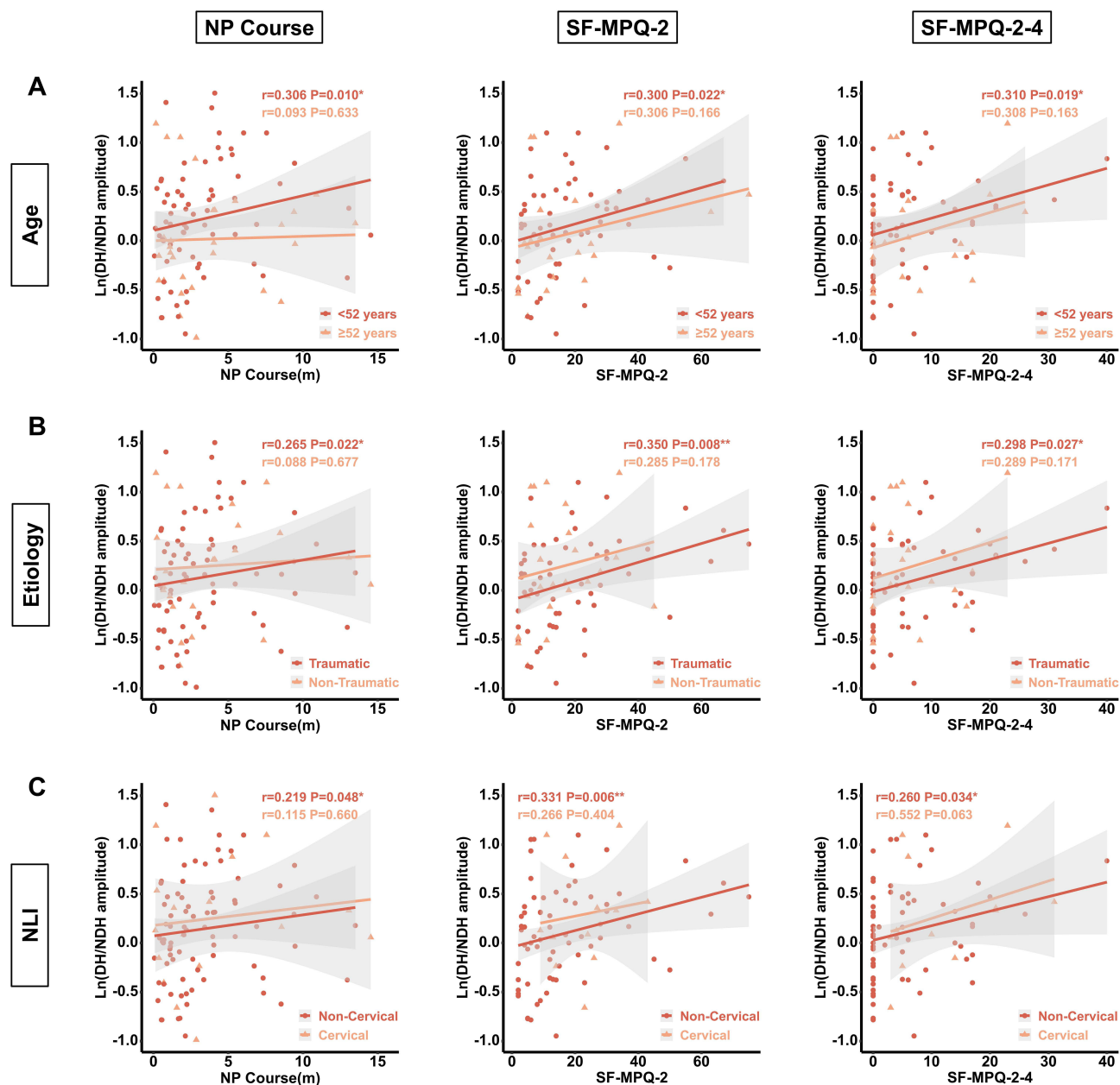


Figure 4 Correlation Between Hemispheric CSE Asymmetry and NP Course and Severity Scores in SCI Subgroups. **(A)** Correlation of hemispheric CSE asymmetry degree with NP course and severity scores in patients under 52 years of age. The $\ln(\text{DH}/\text{NDH}$ amplitude) showed a significant positive correlation with NP course ($r = 0.306$), SF-MPQ-2 ($r = 0.300$), and SF-MPQ-2-4 ($r = 0.310$). For patients aged 52 and above, there was no significant correlation between $\ln(\text{DH}/\text{NDH}$ amplitude) and NP course ($r = 0.093$), SF-MPQ-2 ($r = 0.306$), or SF-MPQ-2-4 ($r = 0.308$). **(B)** Correlation of hemispheric CSE asymmetry degree with NP course and severity scores in the traumatic SCI group. A significant positive correlation was observed between the $\ln(\text{DH}/\text{NDH}$ amplitude) and NP course ($r = 0.265$), SF-MPQ-2 ($r = 0.350$), and SF-MPQ-2-4 ($r = 0.298$). In the non-traumatic SCI group, no significant correlation was found between the $\ln(\text{DH}/\text{NDH}$ amplitude) and NP course ($r = 0.088$), SF-MPQ-2 ($r = 0.285$), or SF-MPQ-2-4 ($r = 0.289$). **(C)** Correlation of hemispheric CSE asymmetry degree with NP course and severity in the cervical injury group. The $\ln(\text{DH}/\text{NDH}$ amplitude) showed no significant correlation with NP course ($r = 0.115$), SF-MPQ-2 ($r = 0.266$), or SF-MPQ-2-4 ($r = 0.552$). In the non-cervical injury group, $\ln(\text{DH}/\text{NDH}$ amplitude) showed a significant positive correlation with NP course ($r = 0.219$), SF-MPQ-2 ($r = 0.331$), and SF-MPQ-2-4 ($r = 0.260$). * $P < 0.05$, ** $P < 0.01$.

Abbreviations: SCI, spinal cord injury; NP, neuropathic pain; DH, dominant hemisphere; NDH, non-dominant hemisphere; CSE, corticospinal excitability; SF-MPQ-2, short-form McGill pain questionnaire-2; SF-MPQ-2-4, subscale 4 of SF-MPQ-2.

Etiology Subgroup Analysis

The $\ln(\text{DH}/\text{NDH}$ amplitude) and NP course were significantly positively correlated in the traumatic SCI subgroup ($r=0.265$, $P=0.022$) but not in the non-traumatic SCI subgroup. In the traumatic SCI subgroup, $\ln(\text{DH}/\text{NDH}$ amplitude) showed a significant positive correlation with SF-MPQ-2 ($r = 0.350$, $P = 0.008$) and SF-MPQ-2-4 ($r = 0.298$, $P = 0.027$), whereas no such correlation was observed in the non-traumatic SCI subgroup (Figure 4B).

NLI Subgroup Analysis

A positive correlation was identified between ln(DH/NDH amplitude) and NP course ($r = 0.219$, $P = 0.048$), SF-MPQ-2 ($r = 0.331$, $P = 0.006$), and SF-MPQ-2-4 ($r = 0.260$, $P = 0.034$) in patients with non-cervical SCI. However, these correlations were not observed in the cervical SCI subgroup (Figure 4C).

Contribution of Hemispheric M1 Hand Area CSE Asymmetry to NP Severity

Univariate and multivariate linear regression analyses were performed using SF-MPQ-2 and SF-MPQ-2-4 scores as dependent variables to mitigate potential confounding factors. Univariate analysis revealed that hemispheric M1 hand area CSE asymmetry, NP course, and NLI significantly contributed to both outcomes ($P < 0.10$). However, multivariate analysis indicated that only hemispheric CSE asymmetry contributed significantly to both SF-MPQ-2 scores (unstandardized $\beta = 7.085$, $P = 0.049$) and SF-MPQ-2-4 scores (unstandardized $\beta = 3.828$, $P = 0.045$) (Table 3).

Additional univariate and multivariate linear regression analyses focused on NP patients younger than 52 years with traumatic SCI occurring outside the cervical region. Univariate analysis within this specific subgroup disclosed a substantial association between the extent of hemispheric CSE asymmetry and scores of the SF-MPQ-2 (unstandardized $\beta = 11.187$, $P = 0.014$) and SF-MPQ-2-4 (unstandardized $\beta = 5.787$, $P = 0.014$) (Table 4). Compared to the broader analyses, the unstandardized β values demonstrated an increase of 2.618 for SF-MPQ-2 and by 1.097 for SF-MPQ-2-4, respectively.

Discussion

The study found that patients with bilateral NP after SCI showed reduced MEP amplitudes in the M1 hand areas compared to NNP patients, especially in the NDH. Additionally, increased hemispheric CSE asymmetry in NP patients correlated positively with NP severity, duration, and emotional disturbances. Multiple regression analysis identified hemispheric CSE asymmetry as an independent factor associated with NP severity and emotional disturbances, particularly in younger (under 52 years) traumatic non-cervical SCI patients. The results indicate that hemispheric CSE asymmetry could be a biomarker for SCI-NP, advocating for high-frequency rTMS targeting of bilateral M1 hand areas, particularly the NDH, as a therapeutic approach.

Our study established a significant link between bilateral M1 hand areas and SCI-NP. Patients with B-MEP exhibited a higher incidence of NP (73.55%) compared to those without (NB-MEP, 49.25%), suggesting a strong association between M1 activity and NP onset ($P < 0.001$). Notably, a greater reduction in CSE was observed in the NDH among NP patients, suggesting that reduced NDH CSE plays a pivotal role in NP development. This finding aligns with Jutzeler et al, who reported that post-SCI NP development was linked to increased gray matter volume in the NDH M1, hypothesizing that this enhanced cortical connectivity may exacerbate pain transmission.³³ Similarly, Galhardoni et al reported that patients with persistent idiopathic facial pain (PIFP) exhibited decreased MEP amplitudes and reduced short-interval intracortical inhibition (SICI) in both hemispheres, as noted by Schwenkreis et al found diminished intracortical inhibition (ICI) in both hemispheres in type I CRPS patients.^{34,35} Our study similarly found prolonged bilateral MEP latencies in patients with SCI-NP, suggesting that bilateral M1 alterations are physiologically linked to SCI-NP.

To account for inter-patient variability, we standardized MEP amplitudes across both hemispheres and introduced a metric for hemispheric CSE asymmetry. This metric was significantly higher in NP patients compared to NNP patients and positively correlated with both the duration and severity of NP. The results suggest that hemispheric CSE asymmetry may be a dependable biomarker for evaluating NP severity in SCI patients. Previous research indicated that high-frequency rTMS targeting the left M1 hand area offered analgesic effects, albeit with limited efficacy.^{15,16} The current study revealed reduced bilateral MEP amplitudes in SCI-NP patients and a positive correlation between hemispheric CSE asymmetry and SF-MPQ-2 scores. This indicates that diminished hemispheric CSE asymmetry could be associated with decreased NP intensity, emphasizing the potential of high-frequency rTMS targeting bilateral M1 hand areas, especially the NDH, as an innovative treatment for SCI-NP.

Table 3 Linear Regression Analysis of SF-MPQ-2 and SF-MPQ-2-4

Variable	NP Patients	Univariate Analysis (SF-MPQ-2)		Multivariate Analysis (SF-MPQ-2)		Univariate Analysis (SF-MPQ-2-4)		Multivariate Analysis (SF-MPQ-2-4)	
		Unstandardized β (95% CI)	P	Unstandardized β (95% CI)	P	Unstandardized β (95% CI)	P	Unstandardized β (95% CI)	P
Age in Years, median (QR)	46.50 (35.00, 53.00)	0.020 (-0.229, 0.270)	0.872	–		0.010 (-0.123, 0.143)	0.879	–	
Gender [N (%)]									
Female	29 (25.44)	–		–		–		–	
Male	85 (74.56)	-2.348 (-9.761, 5.064)	0.530			-2.291 (-6.225, 1.643)	0.250		
Etiology [N (%)]									
Non-Traumatic	32 (28.07)	–		–		–		–	
Traumatic	82 (71.93)	3.390 (-3.548, 10.328)	0.334			0.281 (-3.443, 4.006)	0.881		
Hemispheric CSE Asymmetry Degree (Mean \pm SD)	0.16 \pm 0.56	8.569 (1.802, 15.337)	0.014	7.085 (0.020, 14.149)	0.049	4.690 (1.032, 8.348)	0.013	3.828 (0.088, 7.568)	0.045
NP Course, median (QR)	2.18 (0.88, 4.16)	1.126 (0.132, 2.120)	0.027	0.735 (-0.357, 1.827)	0.184	0.488 (-0.050, 1.025)	0.075	0.266 (-0.308, 0.840)	0.358
NLI [N (%)]									
C	21 (18.42)	–		–		–		–	
T	69 (60.53)	-8.000 (-17.527, 1.527)	0.099	-4.669 (-14.597, 5.259)	0.352	-7.204 (-12.159, -2.250)	0.005	-5.770 (-10.975, -0.566)	0.030
L	21 (18.42)	-3.083 (-13.983, 7.817)	0.575	-1.341 (-12.690, 10.009)	0.815	-5.717 (-11.376, -0.058)	0.048	-5.114 (-11.062, 0.834)	0.091
S	3 (2.63)	0.667 (-22.132, 23.466)	0.954	-2.516 (-25.607, 20.574)	0.829	-3.667 (-15.503, 8.170)	0.539	-5.324 (-17.427, 6.779)	0.384
AIS grade [N (%)]									
A	52 (45.61)	–		–		–		–	
B	7 (6.14)	-1.632 (-15.818, 12.555)	0.820			-0.622 (-8.270, 7.027)	0.872		
C	19 (16.67)	-4.832 (-13.925, 4.262)	0.294			-0.488 (-5.402, 4.425)	0.844		
D	36 (31.58)	4.468 (-2.815, 11.752)	0.226			2.545 (-1.399, 6.489)	0.203		

Notes: Continuous variables are presented as mean \pm standard deviation (SD) for normally distributed data or as median and quartile range (QR) for non-normally distributed data. Categorical variables are expressed as counts and percentages. Bold text indicates $P < 0.1$ for univariate analyses and $P < 0.05$ for multivariate analyses.

Abbreviations: NP, neuropathic pain; SF-MPQ-2, short-form McGill pain questionnaire-2; SF-MPQ-2-4, subscale 4 of SF-MPQ-2; CSE, corticospinal excitability; NLI, neurological level of injury; AIS, American Spinal Injury Association (ASIA) impairment scale.

Table 4 Linear Regression Analysis of SF-MPQ-2 and SF-MPQ-2-4 in NP Patients Under 52 Years of Age, Traumatic, and Non-Cervical Injury After SCI

Variable	NP Patients	Univariate Analysis (SF-MPQ-2)		Univariate Analysis (SF-MPQ-2-4)	
		Unstandardized β (95% CI)	P	Unstandardized β (95% CI)	P
Age in Years, median (QR)	37.50 (33.00, 47.00)	0.165 (-0.307, 0.638)	0.484	-0.064 (-0.304, 0.177)	0.595
Gender [N (%)]					
Female	11 (19.64)	–			
Male	45 (80.36)	4.543 (-6.174, 15.260)	0.397	2.647 (-2.717, 8.011)	0.325
Hemispheric CSE Asymmetry Degree (Mean \pm SD)	0.19 \pm 0.58	11.187 (2.343, 20.031)	0.014	5.787 (1.259, 10.315)	0.014
NP Course, median (QR)	2.18 (0.91, 4.24)	0.387 (-1.322, 2.096)	0.650	0.536 (-0.316, 1.389)	0.211
AIS grade [N (%)]					
A	35 (62.50)	–			
B	4 (7.14)	1.148 (-17.212, 19.508)	0.900	1.897 (-7.403, 11.198)	0.682
C	9 (16.07)	-2.280 (-15.076, 10.515)	0.721	0.374 (-6.121, 6.868)	0.908
D	8 (14.29)	7.648 (-4.496, 19.792)	0.211	3.231 (-2.936, 9.397)	0.296

Notes: Continuous variables are presented as mean \pm standard deviation (SD) for normally distributed data or as median and quartile range (QR) for data that are not normally distributed. Categorical variables are expressed as counts and percentages. Bold text indicates $P < 0.1$ for univariate analyses and $P < 0.05$ for multivariate analyses. **Abbreviations:** NP, neuropathic pain; SF-MPQ-2, short-form McGill pain questionnaire-2; SF-MPQ-2-4, subscale 4 of SF-MPQ-2; CSE, corticospinal excitability; AIS, American Spinal Injury Association (ASIA) impairment scale.

Current rTMS guidelines do not agree on the best M1 stimulation target for NP treatment.⁸ Some studies suggest targeting the cortical representation of the painful area, while others recommend the M1 hand area for its accessibility and broader analgesic effects.^{36,37} Our findings support the latter, showing significant changes in CSE and hemispheric asymmetry in the M1 hand area, even in SCI patients with lower limb NP. The M1 hand area likely plays a systemic role in pain modulation due to its extensive cortical and subcortical connections.³⁸ Clinically, it is more accessible for targeting than lower-limb motor areas, making it a practical option for rTMS interventions.¹³

The revised pain definition by the International Association for the Study of Pain (IASP) highlights that neuropathic pain (NP) impacts both sensory and emotional aspects.³⁹ The SF-MPQ-2, a prevalent tool in NP research, evaluates these dimensions comprehensively, offering more robust insights than single-dimension tools like the Numeric Rating Scale (NRS).³⁰ Our study found a significant positive correlation between SF-MPQ-2 scores and hemispheric CSE asymmetry, with the affective subscale (SF-MPQ-2-4) showing the strongest correlation. This highlights the profound emotional burden that NP imposes on patients. This finding supports previous research indicating that NP impairs emotional regulation and stress coping, contributing to anxiety and depression.⁴⁰ Emotional disturbances may worsen chronic pain via noradrenergic system dysfunction.⁴¹ Anxiety and depression prevalence in NP patients can reach 65.6% and 73.7%, respectively, significantly impacting their quality of life.⁴² The well-documented reciprocal relationship between chronic pain and emotional disorders highlights that emotional distress often intensifies pain perception, further harming emotional well-being.⁴³ This emphasizes the need for early intervention addressing both the physical and emotional aspects of NP. High-frequency rTMS targeting the M1 area has been shown to alleviate both NP and co-occurring depression, reinforcing the need for integrated treatment strategies that address both aspects of SCI-NP.⁴⁴

In our subgroup analysis, we found that younger patients (under 52 years), those with traumatic SCI, and those with non-cervical SCI exhibited more pronounced positive correlations between hemispheric CSE asymmetry and NP characteristics. This supports previous research indicating that cortical excitability and neuroplasticity decline with age, which may reduce the effectiveness of plasticity-based interventions such as rTMS in older adults.^{45,46} Moreover, the stronger correlation observed in traumatic SCI patients compared to non-traumatic SCI patients may reflect more predictable recovery patterns and consistent NP mechanisms in traumatic injuries. Notably, we observed a significant correlation between hemispheric CSE asymmetry and NP parameters in patients with non-cervical SCI, but no such relationship was found in those with cervical SCI. Direct damage to the CST in the M1 hand area in cervical SCI may compromise MEP pathway integrity, affecting the reliability of CSE measurements. Further subgroup analysis of younger, traumatic non-cervical SCI patients revealed a stronger correlation between hemispheric CSE asymmetry and

both NP severity and emotional disturbances. These results suggest that hemispheric CSE asymmetry may be a particularly robust biomarker for assessing NP in this specific patient population, emphasizing the importance of considering injury location and patient demographics when developing personalized treatment strategies.

Previous studies have explored cortical excitability changes in patients with CNP. Hosomi et al investigated 21 patients with chronic post-stroke CNP and 8 healthy controls, finding higher RMT values in patients but no significant difference in MEP amplitudes.⁴⁷ Similarly, Barbosa et al examined 93 stroke and 70 neuromyelitis optica (NMO) patients, including 74 with CNP, and found lower MEP amplitudes in brain injury-related CNP compared to non-neuropathic pain and no-pain groups.¹⁹ These findings indicate that changes in cortical excitability could serve as neurophysiological markers for the development of CNP. However, their findings are primarily based on stroke populations, limiting generalizability to SCI patients. Our study included 625 SCI patients and 131 healthy controls, representing the largest SCI patient population studied to date. Unlike Barbosa et al's focus on NMO, our study covered a broader range of etiologies, including trauma, offering more clinical relevance.⁴⁸ Additionally, our analysis was more comprehensive, incorporating stratified analyses based on age, etiology, and neurological level of injury (NLI). Given that SCI can lead to cortical excitability changes, we investigated differences in cortical excitability among NP, NNP, and healthy control groups, controlling for SCI-induced alterations.⁴⁹ To address individual variability in SCI outcomes, we further compared excitability between hemispheres.⁵⁰ This is the first study to conduct such analyses in SCI patients with NP.

This study has certain limitations. While 625 patients were enrolled, only about a quarter had complete and analyzable MEP data for both M1 hand areas. Larger sample sizes of SCI patients with NP and NNP are needed to validate the findings on hemispheric CSE asymmetry. Prospective cohort studies are essential to further explore the relationship between CSE asymmetry and NP severity. Our findings indicate that bilateral high-frequency rTMS applied to M1 hand area may reduce neuropathic pain by correcting imbalances in CSE. Future double-blind randomized controlled trials (RCTs) should compare unilateral and bilateral approaches, using CSE measurements to personalize treatment parameters (eg, targeting specific brain hemispheres or adjusting stimulation frequency). Although MEP measurements assessed hemispheric excitability asymmetry, methods like paired-pulse TMS (ppTMS) and functional near-infrared spectroscopy (fNIRS) could offer a more comprehensive evaluation of cortical excitability changes.^{15,51}

Conclusions

In summary, this study demonstrates that SCI patients with bilateral NP exhibit reduced CSE in the NDH M1 hand area. Hemispheric CSE asymmetry is linked to pain severity and emotional disturbances in NP patients, suggesting it may serve as a candidate biomarker for objective NP assessment. The observed CSE changes in both M1 hand areas also indicate that these regions could be effective therapeutic targets for high-frequency stimulation in SCI patients with NP. Timely identification and intervention for NP, along with suitable psychological support, may alleviate pain and enhance quality of life in specific patient groups. These findings propose new avenues for NP assessment and treatment, with promising clinical implications.

Abbreviations

SCI, spinal cord injury; NP, neuropathic pain; NNP, no neuropathic pain; IASP, International Association for the Study of Pain; TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; M1, primary motor cortex; CSE, corticospinal excitability; CST, corticospinal tract; MEP, motor evoked potential; DH, dominant hemisphere; NDH, non-dominant hemisphere; SF-MPQ-2, short-form McGill pain questionnaire-2; AIS, American Spinal Injury Association (ASIA) impairment scale; NLI, neurological level of injury; CMCT, central motor conduction time; ICI, cortical intracortical inhibition; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation; RMT, resting motor threshold; SD, standard deviation; QR, quartile range; ROC, receiver operating characteristic; PIFP, persistent idiopathic facial pain; CRPS, complex regional pain syndrome; CNP, central neuropathic pain; ppTMS, paired-pulse TMS; fNIRS, functional near-infrared spectroscopy; NRS, Numeric Rating Scale; NMO, neuromyelitis optica.

Data Sharing Statement

For additional details, please reach out to the corresponding author. The datasets analyzed in this study can be obtained from the corresponding author upon reasonable request.

Ethics Statement

The present study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University of Chinese People's Liberation Army (No. KY20222096-C-1) and registered in the Chinese Clinical Trial Registry (ChiCTR2300073824). Due to the retrospective nature of this study, informed consent was waived as it would not adversely affect the rights and welfare of the subjects, and it was objectively impossible to obtain informed consent from the subjects.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com). We thank the Home for Researchers (www.home-for-researchers.com) for their help with language.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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