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From acute to long-term alterations in pain processing and modulation after spinal cord injury: mechanisms related to chronification of central neuropathic pain

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Abstract

A severe and debilitating consequence of a spinal cord injury (SCI) is central neuropathic pain (CNP). Our aim was to investigate the processes leading to CNP emergence and chronification by analyzing causal relationship over time between spinothalamic function, pain excitability, and pain inhibition after SCI. This longitudinal follow-up study included 53 patients with acute SCI and 20 healthy controls. Spinothalamic, pain excitability, and intrasegmental and extrasegmental pain inhibition indices were repeatedly evaluated at 1.5, 3, and 6 months post-SCI. Between- and within-group analyses were conducted among those patients who eventually developed CNP and those who did not. Healthy controls were evaluated twice for repeatability analysis. Patients who developed CNP, compared with those who did not, exhibited increased thermal thresholds ($P < 0.05$), reduced pain adaptation ($P < 0.01$), and conditioned pain modulation ($P < 0.05$), early post-injury, and the CNP group's manifestations remained worse throughout the follow-up. By contrast, allodynia frequency was initially similar across SCI groups, but gradually increased in the subacute phase onward only among the CNP group ($P < 0.001$), along with CNP emergence. Early worse spinothalamic and pain inhibition preceded CNP and predicted its occurrence, and early worse pain inhibition mediated the link between spinothalamic function and CNP. Crossover associations were observed between early and late pain inhibition and excitability. Inefficient intrasegmental and extrasegmental inhibition, possibly resulting from spinothalamic deafferentation, seems to ignite CNP chronification. Pain excitability probably contributes to CNP maintenance, possibly via further exhaustion of the inhibitory control. Preemptive treatment promoting antinociception early post-SCI may mitigate or prevent CNP.

Keywords: Longitudinal study, Central neuropathic pain, Chronicity, Mechanisms, Extrasegmental, Inhibition, Intrasegmental inhibition, Hyperexcitability

1. Introduction

Central neuropathic pain (CNP), a very debilitating condition that prevails among ~50% of individuals after spinal cord injury (SCI),[7,18,46] is severe, continuous, and interferes with these patients' daily lives and their rehabilitation.[24,52] Central neuropathic pain management is challenging and often unsatisfactory,[2,15,34] probably because the mechanisms leading to its chronicity are not fully elucidated. Especially intriguing is that the initial sensory symptoms post-SCI may spontaneously disappear in one patient but may worsen and develop into CNP in another. Better understanding of these mechanisms is thus essential for providing adequate treatment and quality of life for individuals with SCI.

Central neuropathic pain has been associated with lesions of the spinothalamic tract (STT). Selective damage to the STT or its spinal neurons in animals induces pain behavior.[45,57] Furthermore, individuals with chronic CNP post-SCI exhibit STT damage manifested by decreased/abolished thermal sensibility,[12,17,55] and observed in imaging studies.[13,27] However, STT damage alone, which occurs during SCI, seems insufficient for CNP emergence[9,44]; therefore, additional knowledge regarding its ramifications on the pain system and its contribution to CNP chronification is needed.

Central neuropathic pain has also been associated with neuronal hyperexcitability. Animal models of CNP revealed increased, spontaneous, and evoked neuronal activity as well as increased glial activation in spinal[16,21,39] and supraspinal neurons.[22,45,54] Hyperexcitable neurons were also recorded in patients with CNP,[19,30,37,42] corroborating clinical signs of hyperexcitability, allodynia, and wind-up pain.[13,58] In 2 longitudinal studies, hyperexcitability preceded CNP.[14,58] However, whether pain hyperexcitability results from STT damage or develops independently is presently unknown; furthermore, its

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contribution to CNP emergence and chronification requires further examination.

A third, potentially contributing factor to CNP post-SCI is pain inhibition capacity. Animal models of CNP reveal decreased spinal and supraspinal GABAergic activity and content.[20,36] In patients with CNP, reduced inhibitory control was deduced, based on reduced thalamic inhibitory neurotransmitters and reduced activation of the inhibitory thalamic reticular nucleus.[22,24,29] These findings may correspond to reduced conditioned pain modulation (CPM) in patients with chronic CNP[1,17] and pre-CNP emergence.[18] However, causative interactions of STT damage, pain hyperexcitability, and reduced pain inhibition in patients post-SCI, and their contribution to CNP chronification have not been investigated, to the best of our knowledge.

In considering the challenges of using animal models to mimic CNP, especially the below-level subtype,[28,43] our aim was to conduct a longitudinal study among patients post-SCI and to record, over 6 months, the changes in and the interactions between STT function, excitability level, pain inhibition capacity, and CNP to investigate the causative relationships between them. We hypothesized that CNP emerges and becomes chronic among those patients in whom STT damage leads to early reduced inhibitory control, which in turn leads to increased, longstanding excitability. Because this study was based on repeated measurements, another aim was to evaluate the test–retest repeatability of these outcome measures.

2. Materials and methods

2.1. Subjects

The participants were 71 individuals: 53 with acute SCI (average age 43.2 ± 15 years, 39 males and 14 females) and 20 healthy controls (HCs; 48.2 ± 16.6 years, 15 males and 5 females). Patients with acute SCI were recruited from the Department of Neurological Rehabilitation at Sheba Medical Center, Tel Hashomer, on a voluntary basis. Healthy controls were recruited from among employees of Tel Aviv University and Sheba Medical Center.

Patients with acute SCI were admitted consecutively between 2013 and 2019. The inclusion criteria were as follows: (1) a neurological level of spinal lesion above T10 (to avoid lesions to the conus medullaris and cauda equina) and below C6 (to ensure the use of fingers for testing), (2) SCI period <4 weeks, and (3) age range 18 to 70 years. The exclusion criteria were as follows: (1) chronic pain pre-SCI, (2) acute pain other than from SCI-related postoperative procedures, (3) previous/present wounds in the tested regions, (4) signs of concomitant cerebral damage determined by imaging studies (eg, computerized tomography scan) and clinical evaluation, (5) a history of non-SCI neurological disorders such as multiple sclerosis and Parkinson disease, ascertained by the patient's medical records and clinical evaluation, (6) concurrent severe medical problems such as sepsis, active systemic infection, and active metastatic malignancy ascertained by the patient's medical records and clinical evaluation, (7) diseases causing potential neural damage such as diabetes, (8) pregnancy, and (9) psychiatric/cognitive status that might interfere with the patient's performance in sensory testing (according to psychiatric or occupational therapist evaluation, respectively, using the Montreal Cognitive assessment tool, in case of doubt). Healthy controls had to be in the patients' same age range, be pain-free, and subject to the exclusion criteria #3 to 9.

This study was approved by Sheba Medical Center's institutional review board and Tel Aviv University's ethics committee. Written informed consent was obtained from all subjects, according to the Declaration of Helsinki guidelines, after they received a full explanation of the study protocol and goals.

2.2. Equipment

Heat stimuli were delivered using a computerized thermal stimulator (TSA II, Medoc Ltd, Ramat-Yishai, Israel), with a 3 × 3-cm contact probe. Currents passing through the Peltier element produce temperature changes at rates determined by an active feedback system. As soon as the target temperature is attained, the probe reverts to a preset adaptation temperature by passing an inverse current. The adaptation (baseline) temperature was set to 32°C.

Heat stimuli were also delivered using a 10-L water bath (ChillSafe, ScanVac, Ballerup, Denmark). This circulator bath allows fixed temperatures ranging from 30° to 100°C to be set and maintained (maximum variance ±0.5°C). Water temperature was kept constant at 46°C.

Mechanical stimuli were delivered with Semmes-Weinstein monofilaments (Touch-Test Sensory Evaluator, North Coast Medical, Inc., Morgan Hill, CA). The kit includes 20 monofilaments attached to a plastic holder, ranging between 1.65 and 6.65 calibrated units. Vertical pressure applied with the handle induces a force ranging between 0.008 and 300 g, respectively.

2.3. Study design

The a priori sample size calculation was described in a previous study in which patients with SCI were examined once, in the acute phase.[18] In short, we considered the admission rate of patients with acute SCI, their ability to meet the inclusion/exclusion criteria, the average CNP prevalence rate (about 50%), the expected group mean, and SDs of the main outcome measures (CPM and pain temporal summation) that enable the achievement of 80% power of detecting statistically significant comparisons in a 2-group design study. Owing to the repeated-measure design and risk of dropout, the sample size was further increased by 15%. This sample size was achieved after we excluded participants who withdrew after test 1 (4 due to personal reasons and one transferred to another hospital) and participants with missing data regarding CNP (2 who were unreachable after discharge). We assumed they were missing at random and performed a complete-case analysis.

It should be noted that the present sample included patients reported in the aforementioned previous study[18] as well as additional patients. The previous study followed up the changes over time in CNP characteristics (intensity, quality, location in the body, and aggravating factors, etc.), whereas the current study followed up changes over time in the function of the pain system: pain inhibition and excitability. Furthermore, the previous study analyzed the sensory profile at 1.5 months post-injury, whereas the current study analyzed the sensory profile at 1.5, 3, and 6 months post-SCI. As the aim of the current study was to understand the mechanisms underlying the transition of CNP from acute to chronic, we analyzed only sensory indices that were measured in body regions affected by the SCI, namely, at- and below-injury level.

Figure 1A describes the study's time course for patients with SCI. Three psychophysical evaluations were designed to occur about every 1.5 months, starting as early as possible post-SCI. This design was decided to capture the dynamics of sensory processes post-SCI and so that measurements in the acute and subacute

phases post-SCI will be conducted while the SCI subjects are still hospitalized, when their compliance was maximal. The third measurement of the chronic phase was conducted while some participants were already discharged. The first evaluation (test 1) occurred as soon as subjects were admitted, provided they were in a condition that enabled sensory testing (in terms of their mental state and adjustment to the department) and that they met the inclusion/exclusion criteria (1.5 ± 0.86 months post-SCI). The second (test 2) and third evaluations (test 3) occurred on average at 3 ± 0.97 and 5.1 ± 1.6 months post-SCI, respectively. The follow-up duration was ~6 months.

Because this study relied on repeated measurements over time, it was important to evaluate the repeatability of the sensory indices and to determine whether differences that occur over time can be considered real differences or differences due only to measurement errors. Therefore, in addition to testing patients with SCI, measurements were also conducted twice among HCs (1.5 months apart) and the test–retest repeatability was analyzed.

Figure 1B describes the sites where quantitative sensory testing was performed. Among the patients with SCI, testing was conducted at 2 main body regions: (1) dermatomes at the lesion level (the abdomen or chest area among 84% of the patients; the neck region

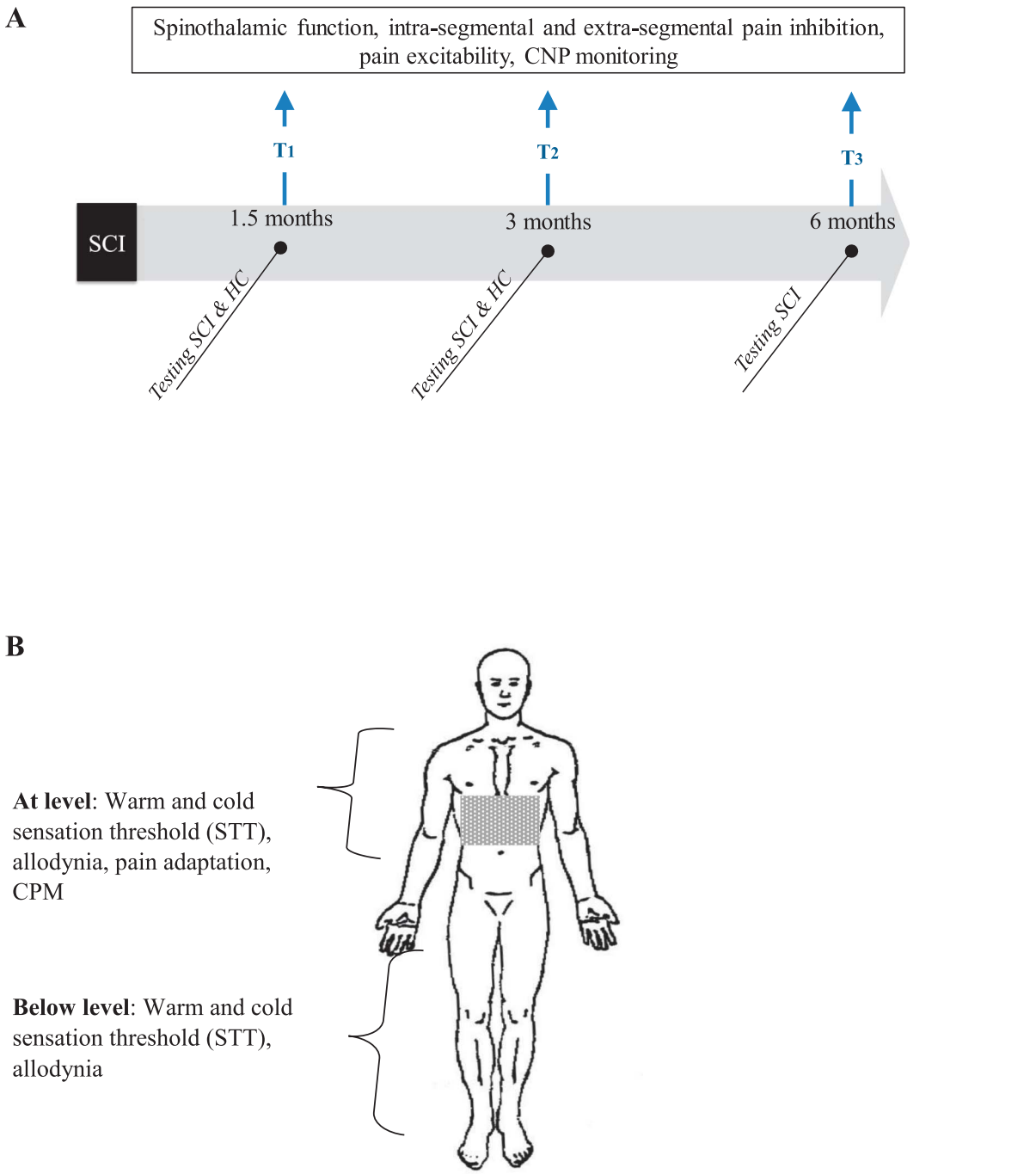

Figure 1. The study's time course (A) and the locations where sensory testing was conducted among people with SCI (B). SCI, spinal cord injury.

among the rest), and (2) dermatomes below the lesion level (mostly the lateral upper part of the shins, about 5 cm below the knee level) among patients with incomplete SCI (n = 42/79%). This region was below the lesion level among all the participants. These testing sites were chosen because they are frequently affected by CNP[13,17] and are therefore susceptible to CNP. The neurological level of injury was determined according to the International Standards for Neurological Classification of SCI (ISNCSCI) part of the neurological examination that was performed at admission, and it was further confirmed during test 1. After confirming the neurological level, the examiner performed the testing at and around the ISNCSCI examination point, randomly, on the right and left sides of the body. In body regions at the lesion level we tested STT function, allodynia—the index of excitability, pain adaptation, and CPM—indices of intrasegmental and extrasegmental pain inhibition. Below the lesion level, we tested STT function and allodynia (as pain inhibition tests are much more time-consuming and require the performance of a stimulus-response function for each testing site, and considering that the entire protocol was already long and tiring for the participants, pain inhibition was not tested in the below-lesion sites). Testing among HCs was conducted on forearms and lateral shins.

Testing took place in a quiet room while participants sat in their wheelchairs/comfortable chairs. First, the subjects were briefly examined to verify the lesion level and then they underwent a training session with the sensory measurements. Testing commenced in a semirandomized order; evaluation of the stimulus–response function for heat pain always preceded pain habituation and CPM tests because stimulation temperatures for these tests had to be extracted from the functions. The evaluations of thermal thresholds and allodynia were randomized, with the former tests within each testing site and subject. Subjects had a several-minute rest between tests. The stimulator probe was moved between stimulation trials.

During hospitalization and throughout the follow-up, the patients with SCI were monitored for CNP development (if the follow-up continued after discharge, it was done via phone and during the patients' outpatient visits). If CNP was diagnosed, the patients completed pain questionnaires and were interviewed about their pain characteristics.[18] Central neuropathic pain was diagnosed according to the International Spinal Cord Injury Pain Classification[6]: spontaneous or evoked burning, stabbing, shooting diffusely located pain, which is perceived more than 3 dermatomes below the dermatome of the neurological level of injury (ie, below-level pain) or within the dermatomes of the neurological level of injury (ie, at-level pain). All relevant data including the clinical examinations and diagnostic tests were examined. Because this definition is of exclusion, care was taken to exclude other pathologies that might underlie pain, including pressure sores, urinary lithiasis, infections, and peripheral neuropathic pain. After the follow-up, the data were compared between patients who did and who did not develop CNP.

2.4. Sensory testing

2.4.1. Spinothalamic tract function

Spinothalamic tract function was evaluated by measuring the thresholds for warm and cold detection. These thresholds were chosen for 3 reasons. First, individuals' performance during the measurement of warm and cold detection thresholds is more repeatable and reliable than that during pain threshold measurement, particularly in regions with sensory alterations. Second, the examiner's sex may affect performance of men during pain threshold measurement, but not during warm and cold detection measurements. Third, anatomical and physiological studies suggest that nociceptive input can ascend not only the STT but also via the dorsal columns, whereas nonnociceptive thermal input ascends only and specifically via the STT.[10,35] Thresholds were measured with the method of limits using the computerized thermal stimulator. Subjects received 4 successive stimuli of gradually increasing or decreasing temperatures, respectively, starting from a baseline of 32°C (at a rate of 2°C/s), with an interstimulus interval of 10 seconds. Subjects were asked to press a switch when a thermal sensation (warm or cold) was first perceived, thus defining the thermal threshold and resetting the probe temperature to baseline values. Warm and cold thresholds were the average of 4 successive stimuli for each sensation separately.[58]

Warm and cold thresholds measured at and below the injury level were averaged. To convert warm and cold sensation thresholds into a single score signifying STT function, the absolute value of the cold threshold was subtracted from the warm threshold, a calculation that considers the distance of each threshold from the baseline temperature: the higher the threshold value, the greater the STT score, hence the damage. For example, warm and cold sensation thresholds of 45°C and 15°C, respectively, provided an STT score of 30°C.[17]

2.4.2. Pain excitability test

Allodynia is pain evoked by a nonnoxious stimulus, a phenomenon that reflects the hyperexcitability of the pain system due to enhanced pro-nociceptive mechanisms.[26] Allodynia was chosen as an index of hyperexcitability because it has been frequently recorded among individuals with CNP.[14,17,58] Mechanical allodynia was examined as described in our previous study[18] by gently dragging a Semmes-Weinstein monofilament no. 4.74 along the subjects' skin at a velocity of 3 cm/ second. If pain sensation was evoked, allodynia was defined as present. The presence of other types of allodynia (eg, due to temperature/ clothing) was recorded based on patient interviews.

2.4.3. Stimulus–response function

A stimulus–response function was created for each subject to extract stimulation temperatures for the 2 pain inhibition measurements. Subjects received a series of thermal stimuli delivered with the thermal stimulator in ascending order and were asked to rate their perceived pain using a numerical rating scale (NRS) with 2 anchor points: 0 (no pain sensation) and 10 (the most intense pain sensation imaginable). The stimuli rose from a baseline of 32°C (a rate of rise of 3°C/second, an interstimulus interval of 25 seconds) to a destination temperature ranging from 41 to 51°C, where it was maintained for 5 seconds and then returned to baseline. The stimulator probe was moved after each stimulus by about 1 to 2 cm to a nonoverlapping but adjacent area within the tested dermatome. From the individual stimulus–response functions, temperatures eliciting NRS values of 3 to 4 and 5 to 6 were extracted for subsequent testing.[17]

2.4.4. Pain inhibition tests

Pain adaptation refers to a gradual pain decrease after repeated/ constant, mildly noxious stimuli of fixed intensity and it reflects antinociceptive mechanisms of intrasegmental inhibition.[4] Pain adaptation was measured because it has been found to be reduced among individuals with chronic or subacute CNP[17,29]; however, its time course post-SCI has not yet been evaluated. As described in our previous study,[18] subjects received a 75-second noxious heat

Table 1

Baseline characteristics of people with spinal cord injury who eventually develop central neuropathic pain compared with those who did not.

	With CNP (n=26)	Without CNP (n=27)	P*
Age (mean±SD, y)	42.6 (15.4)	43.3 (16.3)	0.91
Sex (males/females)	18/8	21/6	0.48
Living with significant other (yes, %)	16 (62%)	18 (67%)	0.70
Employment† (yes, %)	23 (88%)	24 (89%)	0.96
Injury type (%)			0.69
Tetraplegia	11 (42%)	10 (37%)	
Paraplegia	15 (58%)	17 (63%)	
Cause of injury (%)			0.47
Motor vehicle accident	9 (35%)	8 (30%)	
Surgical procedures‡	7 (27%)	9 (33%)	
Fall from height	7 (27%)	4 (15%)	
Spinal stroke	2 (8%)	5 (19%)	
Other	1 (4%)	1 (4%)	
Impairment scale (%)			0.67
A	6 (23%)	6 (22%)	
B	1 (4%)	5 (19%)	
C	10 (38%)	7 (26%)	
D	9 (35%)	9 (33%)	
Medications (%)			0.31
Anticoagulants	20 (77%)	25 (93%)	
Gastrointestinal problems	18 (69%)	21 (78%)	
Opioids	14 (54%)	11 (41%)	
NSAIDs	11 (42%)	7 (26%)	
Antidepressants	10 (38%)	8 (30%)	

CNP, central neuropathic pain; NSAIDs, nonsteroidal anti-inflammatory drugs; SCI, spinal cord injury.
* *P* values of parametric and nonparametric tests.
† Employment values refer to the period before injury. Impairment: A, sensory and motor complete; B, sensory incomplete; C, motor incomplete; D, motor incomplete (at least half of key muscle functions have grade ≥ 3).
‡ Procedures including removal of a benign tumor (n = 11) or removal of a disk protrusion (n = 5).

stimulus of 3 to 4 on the NRS (individually adjusted) and were asked to rate the amount of perceived pain (using NRS) every 15 seconds (at 0, 15, 30, 45, 60, and 75 seconds) while they were not informed of the time that had elapsed. The magnitude of pain adaptation was calculated by subtracting the first NRS rating from the last one.

Conditioned pain modulation refers to the diffuse noxious inhibitory control loop wherein pain in one body region is inhibited by pain in another remote region and it reflects antinociceptive mechanisms of extrasegmental inhibition.[56] Conditioned pain modulation was measured because it was found to be reduced among individuals with chronic or subacute CNP[1,17]; however, its time course post-SCI has not yet been evaluated. Subjects received a heat test stimulus (TS) of 5 to 6 on the NRS (individually adjusted) applied at the injury level for 5 seconds and evaluated its perceived intensity twice: when administered alone and while the subject's contralateral hand was immersed in hot water (46°C) for 30 seconds (TS was applied in the last 5 seconds of immersion). The CPM magnitude was calculated by subtracting the first NRS rating of the TS from the second one.[17]

2.5. Statistical analysis

Data were processed with IBM SPSS statistics software (version 25). Normal distribution was evaluated using the Kolmogorov–

Table 2

Test–retest repeatability of the main outcome measures among healthy controls.

Variable	Test 1 (mean ± SD)	Test 2 (mean ± SD)	ICC (95% CI)	P for ICC	SEM
STT (°C)	3.45 ± 2.38	3.47 ± 2.16	0.98 (0.856-0.997)	<0.0001	0.28
Adaptation (VAS)	−3.21 ± 1.1	−3.28 ± 1.8	0.46 (0.023-0.744)	<0.05	0.56
CPM (VAS)	−3.07 ± 1.6	−3.21 ± 0.4	0.53 (0.085-0.812)	<0.05	1.13

CI, confidence interval; CPM, conditioned pain modulation; ICC, interclass correlation coefficient; STT, spinothalamic tract function; SEM, standard error of test–retest; VAS, visual analogue scale.

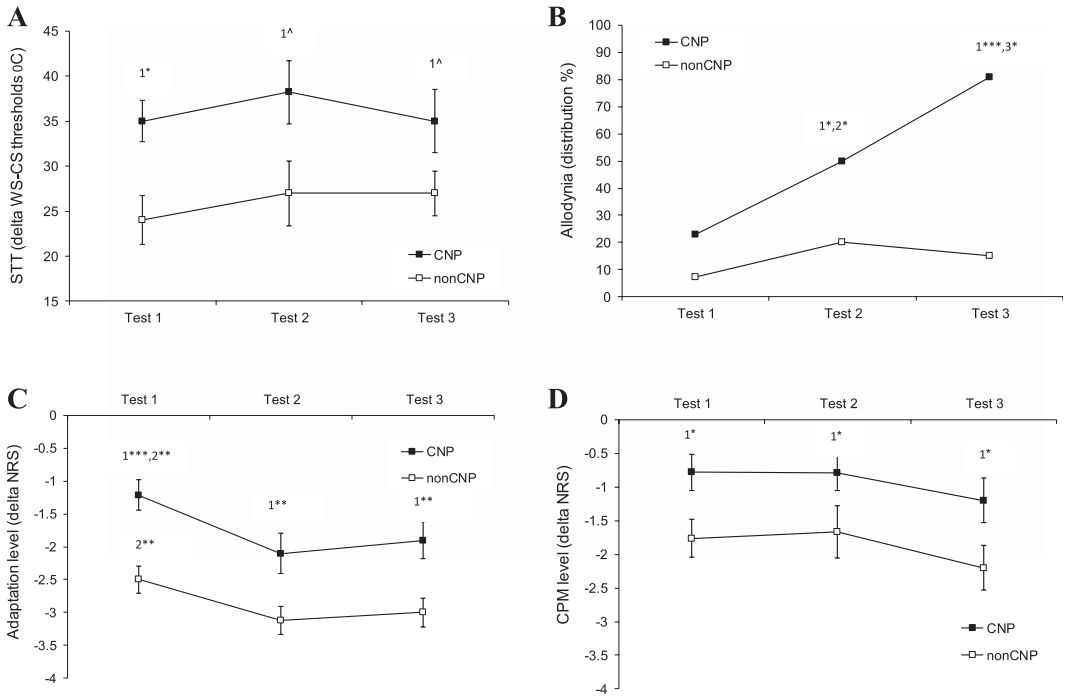

Figure 2. Results of sensory testing among CNP and non-CNP groups across 3 time points: 1.5 months (test 1), 3 months (test 2), and 6 months post-SCI (test 3). (A) Spinothalamic (STT) function, (B) allodynia, (C) pain adaptation, and (D) conditioned pain modulation (CPM). Corrected post-hoc tests: 1 = comparisons between groups within each testing time, 2 = comparisons between test 1 and test 2 within each group, 3 = comparisons between test 2 and test 3 within each group (**$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, #$P = 0.054$, ^$P = 0.08$). Values denote group mean±SE. CNP, central neuropathic pain; STT, spinothalamic tract.

Smirnov test. Parametric and nonparametric models were used to compare patients who did and those who did not eventually develop CNP using demographics, SCI-related variables, and sensory testing results. The models included the main effects of time (tests 1, 2, and 3) and group (CNP and non-CNP) as well as interactions and post-hoc, corrected comparisons (2-tailed *t*-tests for the continuous variables and McNemar tests for the dichotomous variables).

Linear and logistic regression analyses were used to examine the associations between the different variables in the hypothesized model. Specifically, multivariable logistic regressions were calculated to assess the contribution of STT function, pain inhibition (pain adaptation and CPM), and pain excitability (allodynia) measured in tests 1 and test 2, to CNP measured in test 3. This method was chosen because it allows one to study the simultaneous effect of multiple factors on the dependent variable. The SCI severity (according to the ISNCSCI) and the injury level were added as covariates.

Logistic and linear regressions were also used to search the variables in test 1 that predict pain inhibition or pain excitability in test 2. These regressions were performed while controlling for the value of the dependent variable that was measured in test 1. We also examined whether pain inhibition or pain excitability mediated the link between STT and CNP (because the STT status is determined during SCI). Regression analyses and Sobel–Goodman calculations were used for this purpose; the STT score, pain adaptation, CPM, and allodynia measured in test 1 (at which time all patients were still pain-free) and the CNP measured in test 3 were entered into the calculations, and 95% confidence intervals were constructed via bootstrapping (1000 samples, bias-corrected and accelerated). We tested the following paths: $STT_1 \rightarrow CPM_1 \rightarrow CNP_3$, $STT_1 \rightarrow$pain adaptation$_1 \rightarrow CNP_3$, and $STT_1 \rightarrow$allodynia$_1 \rightarrow CNP_3$. As CPM and pain adaptation are 2 aspects of pain inhibition, with a weak-moderate correlation and a similar scale (0-10), we also averaged them into a single variable ("pain inhibition") and tested its mediation effect in the $STT1 \rightarrow$pain inhibition$_1 \rightarrow CNP_3$ path. Mediation occurs if 4 conditions are met: the independent variable significantly affects the mediator, as well as the dependent variable separately; the mediator has a significant effect on the dependent variable; and the effect of the independent variable on the dependent variable decreases when the mediator is added to the model. The Sobel–Goodman test calculates whether the indirect effect of the independent variable (STT_1) on the dependent variable (CNP_3) via the mediator (CPM_1, pain adaptation$_1$ or allodynia$_1$) significantly differs from zero by using the raw (unstandardized) regression coefficient of the different associations and their standard error.[38]

The test–retest repeatability of outcome measures was tested among HCs by calculating interclass correlation (ICC) estimates and their 95% confidence intervals based on an absolute-agreement, 2-way mixed-effects model. Then, the standard error of measurement (SEM) was calculated with the following equation: $SEM = SD \times \sqrt{(1\text{-ICC})}$. Although both the ICC and SEM are reliability coefficients, SEM quantifies error in the same units as the original measurement.

For all analyses, *P*-values <0.05 were considered statistically significant.

3. Results

3.1. The study groups and central neuropathic pain prevalence

Twenty-three patients developed CNP in test 2 (3 months post-SCI), and 3 additional patients developed CNP in test 3 (5-6 months post-SCI), representing 49% of the entire cohort. Among these 26 patients with CNP, pain was localized below-level in 6 (23.1%), at-level in 6 (23.1%), and at-and-below-level among the remaining 14 (53.8%). Central neuropathic pain at 6 months was

Table 3

Logistic regressions assessing the prediction of central neuropathic pain by spinothalamic tract function, pain inhibition, and pain excitability indices measured in test 1 and test 2.

Predictors	OR	95% CI	*P*	%Correct
Test 1				85.7%
STT	1.16	1.024-1.282	<0.01	
$Adaptation_1$	4.71	1.885-11.772	<0.001	
CPM	1.96	1.010-3.825	<0.05	
Allodynia	0.89	0.043-18.655	0.94	
Test 2				68.1%
STT	1.08	1.013-1.164	<0.05	
$Adaptation_1$	3.52	0.865-12.350	<0.05	
CPM	1.16	0.714-1.888	0.54	
Allodynia	3.53	0.791-15.821	0.07	

CPM, conditioned pain modulation; CI, confidence interval; OR, odds ratio of logistic regression; STT, spinothalamic tract function.

moderate in intensity (5.2 ± 1.8 NRS units) and diffusely localized; however, it mainly occupied the lower limbs. A detailed description of the CNP among most of these patients is presented in our previous publication.[17] Of note, 10 patients out of the CNP group complained of paresthesias in test 1, compared with 3 in the non-CNP group (38.5 vs 11.1%, respectively, z = −2.7, $P < 0.01$).

Table 1 presents the baseline (acute phase) characteristics of patients with SCI who did and who did not develop CNP in test 3 (the CNP and non-CNP groups). The 2 groups did not differ in any of the demographic or SCI-related variables (eg, the time since injury and the cause of injury) or in the baseline medication intake that included anticoagulants (20 and 25, for CNP and non-CNP groups, respectively, z = −1.37, $P = 0.11$); medications for gastrointestinal problems (18 and 21, respectively, z = −0.23, $P = 0.48$); opioids (14 and 11, respectively, z = −1.24, $P = 0.34$); nonsteroidal anti-inflammatory drugs (11 and 7, respectively, z = −1.77, $P = 0.21$); antidepressants (10 and 8, respectively, z = −0.71, $P = 0.49$); and benzodiazepines (7 and 6, respectively, z = −0.23, $P = 0.69$).

3.2. The test–retest repeatability of the main outcome measures

Table 2 presents the ICC and SEM values of STT function, pain adaptation, and CPM measured among HCs in tests 1 and 2 (allodynia was absent among them). The measurements of STT function (ie, warm and cold sensations) had excellent reliability, whereas the measurement of CPM and pain adaptation had poor-to-moderate reliability. Out of the 2 dynamic pain measurements, pain habituation was more stable than was CPM, as manifested in the SEM values.

3.3. The spinothalamic tract function

Figure 2A presents the changes over time in the STT score (the delta of cold and warm sensation thresholds) among the 2 SCI groups: those who did, and those who did not develop CNP in test 3. Repeated-measures analysis of variance (ANOVA) revealed no main effect of time on the STT score ($F(2,92) = 0.58$, $P = 0.45$) nor a significant group × time interaction ($F(2,92) = 0.057$, $P = 0.86$). However, the main effect of the group on the STT score was significant ($F(1,46) = 4.44$, $P > 0.05$). Post-hoc tests revealed that the STT score of the CNP group was significantly higher than that of the non-CNP group in test 1 (t = −2.15, $P < 0.05$), with borderline effects in test 2 (t = −1.86, $P = 0.054$) and test 3 (t = −1.53, $P = 0.08$), suggesting that the STT function was worse among the CNP group in the acute phase. Both groups had a worse STT function than the HCs did ($P < 0.0001$ for both groups and for all time points) (the normal values in **Table 2**).

Warm and cold sensation thresholds showed similar patterns. Repeated-measures ANOVA revealed no main effect of time on warm sensation threshold ($F(2,92) = 1.43$, $P = 0.25$) or on cold sensation threshold ($F(2,92) = 1.47$, $P = 0.24$), and no significant group × time interactions. However, the main effect of the group was significant both for warm sensation ($F(1,46) = 5.178$, $P < 0.05$) and cold sensation thresholds ($F(1,46) = 10.43$, $P < 0.01$). Warm sensation thresholds of the CNP group were higher than those of the non-CNP group in test 1 (46.44 ± 3.63 vs 43.84 ± 4.56, respectively, t = −2.0, $P < 0.05$), but not significantly so in test 2 or 3. Cold sensation thresholds of the CNP group were significantly higher than those of the non-CNP group in all the tests: test 1 (11.37 ± 4.9 vs 19.04 ± 5.1, respectively, t = 4.26, $P < 0.001$), test 2 (9.47 ± 8.19 vs 17.9 ± 8.53, respectively, t = 3.03, $P < 0.01$), and test 3 (12.02 ± 8.2 vs 18.8 ± 8.3, respectively, t = 2.1, $P < 0.05$).

3.4. Allodynia

Figure 2B presents the changes in allodynia frequency over time for the 2 SCI groups. Generalized estimating equations analysis revealed the significant effect of time (Wald $\chi^2(2) = 17.8$, $P < 0.0001$) and group (Wald $\chi^2(1) = 10.9$, $P < 0.01$) on allodynia frequency. The group*time interaction was borderline (Wald $\chi^2(2) = 5.6$, $P = 0.06$). Allodynia frequency increased gradually from test 1 to test 2 and then to test 3 among the CNP group (23%, 50%, and 81%, respectively, $Q(2) = 15.8$, $P < 0.0001$), but it did not change over time among the non-CNP group (7.4%, 20%, and 15%, respectively, $Q(2) = 3.5$, $P = 0.17$). Post-hoc tests revealed that although allodynia frequency did not differ between groups in test 1 (Z = −1.5, $P = 0.11$), it was significantly greater among the CNP than the non-CNP group in test 2 (Z = −2.4, $P < 0.05$) and test 3 (Z = −4.58, $P < 0.0001$).

3.5. Pain adaptation

Figure 2C presents the changes in pain adaptation magnitude over time for the 2 SCI groups. Repeated-measures ANOVA revealed the main effect of time, ($F(2,100) = 12.8$, $P < 0.0001$) and of group ($F(1,50) = 13.2$, $P < 0.001$) on the pain adaptation magnitude but a nonsignificant time × group interaction ($F(2, 100) = 0.25$, $P = 0.77$). Post-hoc tests revealed that both the CNP and non-CNP groups exhibited a significant improvement in pain adaptation magnitude from test 1 to test 2 (t = 2.8, $P < 0.001$ and t = 3.3, $P < 0.0001$, respectively), beyond the SEM of HCs (**Table 2**) and then, it remained stable among them. Post-hoc tests also revealed that the pain adaptation magnitude was significantly lower among the CNP than the non-CNP group in all 3 tests (t = −4.1, $P < 0.0001$; t = −2.5, $P < 0.01$; and t = −2.9, $P < 0.01$ in test 1, 2, and 3, respectively), suggesting that the decreased intrasegmental pain inhibition exhibited by the CNP group, compared with the non-CNP group, persisted across time. The values of the non-CNP group were similar to those of HCs (the normal values in **Table 2**).

Table 4

Linear and logistic regressions showing the associations over time among spinothalamic tract function, pain inhibition, and pain excitability.

Prediction of $inhibition_2$		B(SE)	95% CI	*P*	*R*
Predictor	**Dependent**				
$Allodynia_1$	$Adaptation_2$	1.20 (0.47)	0.249-2.156	<0.05	0.56
STT_1		−0.001 (0.01)	−0.036-0.034	0.75	
$Allodynia_1$	CPM_2	1.11 (0.64)	−0.044-2.182	0.052	0.29
STT_1		0.06 (0.02)	−0.003-0.083	0.81	
Prediction of $excitability_2$		**OR**	**95% CI**	***P***	**% Correct**
Predictor	**Dependent**				
$Adaptation_1$	$Allodynia_2$	1.63	0.981-2.711	<0.05	69.8%
CPM_1		1.34	0.839-2.216	0.19	
STT_1		0.98	0.918-1.068	0.71	
Prediction of same		**B(SE)/OR**	**95% CI**	***P***	**R/% correct**
Predictor	**Dependent**				
STT_1	STT_2	0.84 (0.11)	0.605-1.08	<0.0001	0.72
$Adaptation_1$	$Adaptation_2$	0.52 (0.12)	0.248-0.785	<0.0001	0.48
CPM_1	CPM_2	0.19 (0.16)	−0.121-0.510	0.23	0.17
$Allodynia_1$	$Allodynia_2$	7.25	1.278-41.130	<0.05	71.4%

B, unstandardized beta of linear regression; CI, confidence interval; CNP, Central neuropathic pain; OR, odds ratio of logistic regression; R for linear regressions, % correct for logarithmic regressions; STT, spinothalamic tract function; CPM, conditioned pain modulation; 1, measured at test 1; 2, measured at test 2.

3.6. Conditioned pain modulation

Figure 2D presents the changes in CPM magnitude over time for the 2 SCI groups. Repeated-measures ANOVA revealed no main effect of time ($F(2,98) = 0.55$, $P = 0.57$) on CPM magnitude, nor a significant group × time interaction ($F(2,98) = 0.23$, $P = 0.78$). However, the main effect of the group on the CPM magnitude was significant ($F(1,48) = 5.6$, $P < 0.05$). Post-hoc tests revealed that the CPM magnitude among the CNP group was significantly lower than among the non-CNP group in tests 1, 2, and 3 ($t = -2.5$, -1.62, and -1.67, respectively, $P < 0.05$ for all). This finding suggests that the decreased extrasegmental pain inhibition exhibited by the CNP group, compared with the non-CNP group, persisted across time. Both groups had worse CPM values than did HCs at all the time points ($P < 0.01$ for both), except the non-CNP group in test 3, whose CPM level was only slightly different from that of the HCs ($P = 0.06$) (the normal values in **Table 2**).

3.7. Regression and mediation analyses to test the hypothesized model

Table 3 presents the results of the multivariable logistic regressions aimed to test which variable measured in test 1 (the acute phase) and test 2 (the subacute phase) could significantly predict CNP_3 (at 6 months, the chronic phase). CNP_3 was significantly predicted by STT_1, pain $adaptation_1$, and CPM_1. Pain adaptation was the strongest predictor with an odds ratio of 4.71, followed by CPM and STT, with odds ratios of 1.96 and 1.16, respectively, which, combined, accounted for 85.7% of cases correctly identified as having CNP. Allodynia at test 1 could not predict CNP. In test 2, CNP_3 was significantly predicted by STT_2 and pain $adaptation_2$ although with lower odds ratios than in test 1. The prediction of CNP by $allodynia_2$ was borderline with an odds ratio of 3.53 (it should be noted that $allodynia_2$ and pain $adptation_2$ showed some dependency in that patients with allodynia had lower pain adaptation magnitudes than did those without allodynia $P < 0.05$, which may account for the borderline effect of $allodynia_2$. The likelihood ratio of $allodynia_2$ was 6.15, $P < 0.01$). Neither injury-related variables, demographics (eg, age and sex), nor allodynia measured in tests 1 or 2 could predict CNP_3.

Table 4 presents the results of the linear and logistic regressions aimed to test the associations between STT function, pain inhibition, and pain excitability measured in tests 1 and 2. Pain $adaptation_2$ and CPM_2 were predicted by pain excitability ($allodynia_1$) in test 1; the effect on CPM was borderline (upper panel). Pain excitability in test 2 ($allodynia_2$) was predicted by pain adaptation in test 1 ($adaptation_1$) (middle panel). STT_1, pain $adaptation_1$, and $allodynia_1$ predicted their own values in test 2 (lower panel).

Figure 3 shows the mediation effect of CPM_1 and of the combined pain $inhibition_1$ in the link between STT_1 and CNP_3. Mediation is evident in the smaller β coefficient of the association between STT_1 and CNP_3 when CPM_1 or pain $inhibition_1$ is also a predictor of CNP_3 compared with the association of STT_1 alone and CNP_3 (the coefficients are in parentheses, respectively). The reduction in the β coefficient and its significance suggest that the mediation is partial. Thus, more impaired STT conduction significantly worsened CPM (a = 0.059 [0.024]; $P < 0.01$; 95% confidence interval [CI]: 0.01-0.084) and CPM significantly increased CNP prevalence (b = 0.562 (0.340); $P < 0.05$; 95% CI: 0.137-1.435). A significant direct effect of STT on CNP remained after the mediator CPM was modeled (c = 0.128 (0.05); $P < 0.01$; 95% CI: 0.038-0.425/0.146 (0.081); $P < 0.05$; 95% CI: 0.057-0.393) (**Figure 3**, upper panel). Similarly, more impaired STT conduction significantly worsened "pain inhibition" index (a = 0.029 (0.014); $P < 0.05$; 95% CI: 0.001-0.053), which significantly increased CNP prevalence (b = 1.841 (0.529); $P < 0.001$; 95% CI: 0.926-4.288). A significant direct effect of STT on CNP remained after the mediator "pain inhibition" was modeled (c = 0.130 (0.059); $P < 0.05$; 95% CI: 0.006-0.523/0.146 (0.081); $P < 0.05$; 95% CI: 0.057-0.393) (**Figure 3**, lower panel). The Sobel–Goodman test confirmed the mediation's significance for

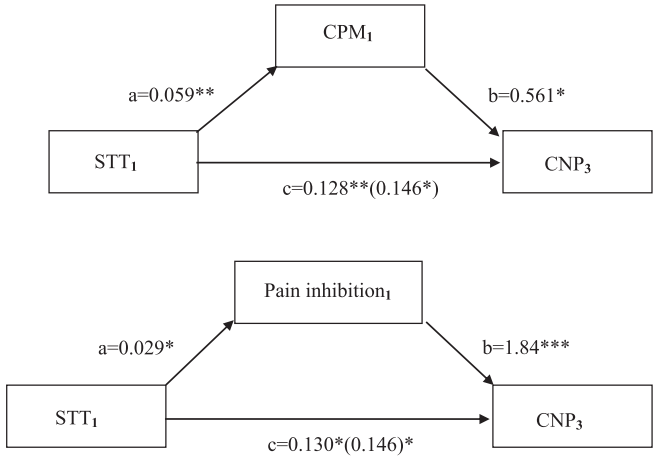

Figure 3. Condition pain modulation (CPM) was a significant mediator in the link between spinothalamic (STT) function and central neuropathic pain (CNP) (upper panel). In the lower panel, one can see the mediation of the combined "pain inhibition" variable (average of CPM and pain adaptation) in the STT-CPM link. The values presented are the unstandardized regression coefficients, the values in the parentheses are the coefficients before CPM or "pain inhibition" was entered into the model, and the asterisks represent the significance level of these coefficients (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). STT, spinothalamic tract.

CPM (t = 2.00, SE = 0.0037, $P = 0.045$) and for the pain inhibition variable (t = 2.34, SE = 0.023, $P = 0.018$). The Sobel–Goodman test revealed that pain adaptation$_1$ (t = 1.75, SE = 0.01, $P = 0.078$) and allodynia$_1$ (t = 1.10, SE = 0.058, $P = 0.266$) did not significantly mediate the STT$_1$-CNP$_3$ link.

4. Discussion

The results show that individuals who over time developed CNP, compared with those who did not, exhibited early, worse STT function and pain inhibition before CNP, which remained worse thereafter; extrasegmental pain inhibition mediated the STT-CNP link. Conversely, acute pain excitability level gradually increased with CNP development and remained increased thereafter. Thus, although reduced antinociception seems crucial for CNP emergence and chronification, increased pronociception may contribute to CNP maintenance.

4.1. Spinothalamic tract function after spinal cord injury

Thermal thresholds early post-SCI (pre-CNP) were significantly higher among those who later developed CNP, compared with those who did not. Furthermore, early STT function predicted CNP at 6 months, suggesting that greater STT damage early post-SCI induces a greater risk for CNP. Spinothalamic tract function is consistently altered among people with chronic SCI and CNP, compared with HCs, but not necessarily compared with pain-free SCI peers.[12,13,23,44] However, the results are consistent with studies on SCI patients in the acute phase.[46,58] Likewise, selective damage of the STT in animal models of CNP is directly linked to behavioral and neurophysiological correlates of pain, especially in the acute phase post-SCI.[45] Interestingly, improvement in pinprick sensibility 3-weeks to 12-months post-SCI was reported among those who developed CNP,[23] possibly corresponding to the trend observed here in tests 2 and 3.

Sensory testing of STT function is affected by the body region tested, being at- or below-injury level, or being painful or not, a variability that may underlie previous inconsistent results. In this study, we measured STT function in regions that in test 1 were pain-free but were selected a priori because of their high susceptibility to CNP[9,17,18,58] and indeed, CNP developed in these regions. Nevertheless, the existence of surviving thermosensitive nociceptive afferents within the STT pathways was reported to characterize SCI individuals with CNP vs those without CNP.[47] Likely, STT damage by itself is insufficient for CNP, but it can propagate additional effects that may be crucial in CNP mechanisms as discussed below.

4.2. Pain excitability after spinal cord injury

Individuals with chronic CNP due to SCI exhibit pain hyperexcitability, manifested in a high frequency of allodynia and wind-up pain[13,17] that corresponds to CNP severity.[5,13,17,44] However, whether hyperexcitability contributes to CNP development, or results from it, can only be determined by a longitudinal follow-up. This study indicates that allodynia in the acute phase (test 1) existed only among a minority of those who eventually developed CNP, and it could not predict CNP. Nevertheless, by tests 2 and 3, when most participants already had CNP, allodynia's frequency increased more than two-to-four fold, respectively, and was associated with CNP.

The gradual buildup of pain hyperexcitability towards CNP emergence observed here corresponds to our previous report on another cohort[58] except that early, below-level allodynia was more frequent in that study than in this one, probably due to the inclusion of patients with incomplete injury only. Finnerup et al.[14] also reported increased frequency of below-level sensory unpleasantness among people with incomplete injury who developed below-level CNP 12 months later. The at-level measurements performed in this study may have lowered the overall recorded allodynia frequency, but it enabled the testing of patients with complete and incomplete injuries, thus allowing for the generalization of results regardless of CNP location. Interestingly, animal models of post-SCI pain developed allodynia two to three weeks after injury,[3,11,16,41,48] corresponding to the delayed hyperexcitability observed herein. As these animals did not present hyperexcitability pre-SCI, it was likely an acquired rather than inherent trait. Nevertheless, the inability of early hyperexcitability to predict CNP in this study and the lack of its association with STT suggest that although hyperexcitability probably results from SCI and contributes to CNP severity and maintenance (for a review, see Ref. 21), another factor seems more crucial in the early propagation of CNP, and it may also promote hyperexcitability.

4.3. Pain inhibition after spinal cord injury

Antinociceptive indices have hardly been tested among individuals with SCI and CNP. Above-level pain adaptation and CPM were impaired among people with CNP in the chronic[17] and subacute states[1] and correlated with CNP severity. In another study, the temporal summation/pain adaptation ratio from admission to discharge correlated with CNP severity.[40] Recently, we reported that pain adaptation and CPM were impaired as early as 1.5 months post-SCI among people who developed CNP at 8 and 24 months.[18] The present, longitudinal study enabled us to show that these antinociceptive indices remained impaired among the CNP group throughout the six-month follow-up: namely, before, during, and after CNP emergence. Furthermore, we have shown that contrary to the pronociceptive indices, early reduced antinociceptive indices predicted CNP and, combined, mediated the STT-CNP link, suggesting that intrasegmental and

extrasegmental antinociceptive processes play a crucial role in CNP emergence. It should be noted that although pain adaptation in both the acute and subacute phases predicted CNP, CPM predicted CNP only in the acute phase. Furthermore, only early pain adaptation predicted subacute excitability. Thus, intrasegmental pain inhibition may have a larger role in pain chronification.

We cannot determine whether the inefficient antinociceptive processing among patients who eventually developed CNP was acquired due to STT damage, or whether it was inherited and existed pre-SCI; however, there is evidence to support the former idea. Pain modulation structures are triggered by ascending STT[32]; therefore, its deafferentation during SCI may rapidly weaken the antinociceptive capacity as found in this study. Interestingly, the fact that CPM was a significant and stronger mediator than pain adaptation in the STT-CPM link whereas pain adaptation was a stronger predictor of CNP may imply that although both aspects of descending control are important to CNP, perhaps extrasegmental inhibition is more dependent on ascending nociceptive input.

In animal models of post-SCI pain, selective STT damage induced an impaired function of supraspinal nuclei involved in descending pain modulation.[33,36,45] Such damage produced an initial reduction in thalamic–cortical connectivity (which may reflect early reduction in inhibitory control) that was followed by increased connectivity, which corresponded to delayed hyperexcitability.[41] Furthermore, alterations in inhibitory neurotransmitters' content and receptor expression occurred at Day 1 post-SCI compared to pre-SCI level, and to control- and/or sham-operated animals.[8,21,25] These studies suggest that a reduction in inhibitory control was acquired after SCI and support the temporal pattern of events in this study. Brain imaging studies reported maladaptive metabolism, structural changes, and connectivity in pain modulation structures among people with chronic CNP, compared to controls, which correlated with pain severity.[19,27,31,37,49,50,53] Without dismissing the possibility that pain inhibition capacity may also be inherent, these reports, along with our results, support the notion that pain inhibition capacity deteriorated (further) due to STT damage, and contributed to delayed-onset hyperexcitability and CNP.

4.4. A suggested model for CNP emergence and chronification

Based on the current and previous findings, we suggest a model for the CNP mechanism described in **Figure 4**. We suggest that an SCI (1) that affects the STT (2) to a certain, critical degree, ignites a pathological chain of events early post-SCI. These events start from the reduction in ascending nociceptive information via the STT to the inhibitory brain stem and thalamic nuclei and lead to a rapid reduction in inhibitory control over residual nociceptive neurons (3) which, in turn, drives the development of their spontaneous, pathological activity, that is, spontaneous pain (4) and a gradual increase in their responsiveness, that is, hyperexcitability (5) which further enhances and maintains CNP. This process probably occurs through neuronal–glial interactions and altered intracellular signaling pathways that contribute to maladaptive reorganization and CNP chronicity (for review, see Refs. 21, 32, 43). The reciprocal associations between pain inhibition and pain excitability (c-e and f-g) may reflect the feedback loop between pronociceptive and antinociceptive elements. This loop is normally balanced but after SCI, reduced inhibition may lead to increased excitability that drains the inhibitory capacity even further; both contribute to CNP maintenance and magnitude. The results suggest that STT damage is crucial in the early propagation of impaired inhibitory

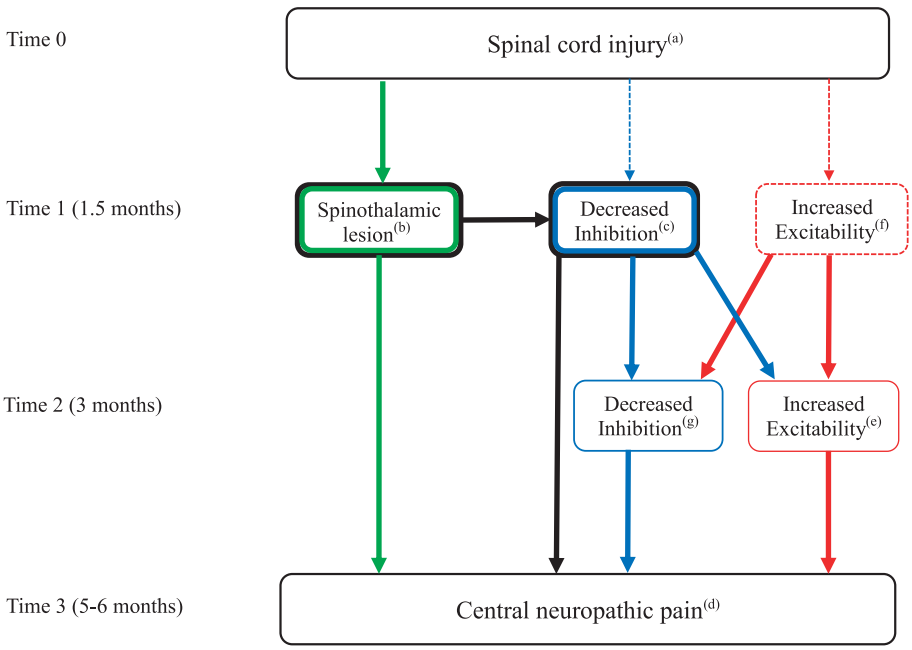

Figure 4. A proposed mechanism underlying CNP. The colored lines are based on multivariable regression analyses. The green path represents the effects of spinothalamic damage, the blue path represents the effects of inefficient pain inhibition, and the red path represents the effect of pain hyperexcitability. The black arrows represent the significant mediation effect wherein the STT_1-CNP_3 link was significantly mediated by CPM and by the pain inhibition variable (CPM and pain adaptation combined). Solid shapes represent significant group differences (CNP vs non-CNP) for each variable in each time point, and dashed shapes represent nonsignificant group differences. It should be noted that the blue arrow between (c) and (e) is correct for pain adaptation but not for CPM. CPM, conditioned pain modulation; CNP, central neuropathic pain; STT, spinothalamic tract.

control; however, its significance declines thereafter, when the consequences of inefficient top-down control take place.

Our study has notable strengths. First, repeated measurements, starting before CNP and throughout its emergence, enabled us to draw conclusions regarding causal relations, rarely described in human subjects. Second, several strong predictors for CNP before its emergence were identified. These predictors can be used to screen patients at risk and then provide preemptive treatment or test its effectiveness. Third, repeatability analysis of the sensory indices enabled us to ascertain changes over time that were beyond the errors of measurements. Nevertheless, there are several potential limitations. First, sensory testing reflects pronociceptive and antinociceptive processes but cannot confirm them. Second, although injury severity and level were covariates in the analyses and therefore the results can be generalized to the SCI population, future studies might investigate possible variations among phenotype subdivisions[51] and include patients with upper cervical and lumbar SCIs. Third, although required due to a binary mediator, the use of the Sobel method imposed an evaluation of indirect effects separately for each mediator rather than simultaneously for all the mediators.

To summarize, STT damage and early, insufficient intrasegmental and extrasegmental pain inhibition capacity may be a core mechanism in the propagation of pain hyperexcitability and of CNP post-SCI. Therefore, antinociceptive indices measured early post-SCI may be used as biomarkers to identify the risk of CNP. Furthermore, preemptive administration of medications, aimed to improve top-down inhibition (eg, pregabalin and selective serotonin/norepinephrine reuptake inhibitors) early post-SCI to patients at risk may restore the pronociceptive/antinociceptive balance and may mitigate or prevent CNP.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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