Conditioned Pain Modulation Decreases Over Time in Patients With Neuropathic Pain Following a Spinal Cord Injury

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Abstract

Background. Neuropathic pain is a major problem following spinal cord injury (SCI). Central mechanisms involved in the modulation of nociceptive signals have been shown to be altered at the chronic stage, and it has been hypothesized that they might play a role in the development of chronic pain. *Objective.* This prospective longitudinal study aimed to describe the evolution of pain modulation mechanisms over time after SCI, and to explore the relationships with the presence of clinical (neuropathic and musculoskeletal) pain. *Methods.* Patients with an SCI were assessed on admission (n = 35; average of 38 days postinjury) and discharge (n = 25; average of 131 days postinjury) using the International Spinal Cord Injury Pain Basic Data Set. Conditioned pain modulation was assessed using the cold pressor test (10 °C; 120 s) as the conditioning stimulus and tonic heat pain, applied above the level of injury, as the test stimulus (120 s). Heat pain threshold was also assessed. *Results.* A marked decrease in the efficacy of conditioned pain modulation was observed over time, with 30.2% of inhibition at admission and only 12.9% at discharge on average (*P* = .010). This decrease was observed only in patients already suffering from neuropathic pain at admission and was not explained by a general increase in sensitivity to thermal nociceptive stimuli. *Conclusion.* These results suggest that the presence of neuropathic pain leads to a decrease in conditioned pain modulation over time, rather than supporting the hypothesis that inefficient conditioned pain modulation mechanisms are leading to the development of neuropathic pain.

Introduction

Studies on pain after spinal cord injury (SCI) have reported widely variable estimates of its prevalence, with a meta-analysis proposing an overall prevalence rate between 44% and 67% depending on the strictness of the definition of pain cases.[1] Regardless, there is a consensus on the fact that pain has substantial impact on the life of persons with SCI and on the limited effectiveness of existing treatments.[2-5] Therefore, there is an urgent need for research aiming to provide a better understanding of the underlying mechanisms in order to guide intervention.

Research using sensory testing has revealed changes in the processing of nociceptive input below, at, and above the level of injury in individuals with neuropathic pain following SCI.[6-19] While the large majority of these studies have been conducted at the chronic stage, comparing individuals with or without neuropathic pain related to SCI, a few longitudinal studies have looked at changes over time since injury. A study performed in the first 6 months postinjury showed

that individuals who eventually developed neuropathic pain had higher thermal thresholds than those who did not.[17] Moreover, the same individuals displayed high rates of allodynia and hyperpathia, which gradually increased with time until neuropathic pain developed.[17] Another prospective study identified early sensory hypersensitivity (particularly cold-evoked dysesthesia present at 1 month postinjury) as a predictor for the development of below-level neuropathic

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pain at 12 months.[15] Together, these results suggest that neuronal hyperexcitability, as reflected by sensory hypersensitivity, can precede the development of neuropathic pain and might therefore predict the risk of developing pain.

Recently, a potential role of deficient descending inhibitory controls has also been proposed. In humans, descending inhibitory controls are typically assessed using a conditioned pain modulation (CPM) paradigm that measures how a nociceptive stimulation can cancel out another nociceptive stimulation occurring on a distant body site.[20] Among individuals who have sustained a SCI, those with chronic (>6 months) neuropathic pain have been reported to have decreased CPM compared to those without neuropathic pain. Importantly, this deficit was observed although the test stimulus was applied on an intact dermatome (ie, above the level of the lesion and away from the body sites in which clinical pain was reported). The dysfunction of CPM was shown to be associated with the number of painful body regions.[11] Another study has been conducted in a sample including people with a more recent SCI (1-70 months post-SCI, with a median of 5 months), also finding a lack of CPM in individuals with neuropathic pain compared with those who are pain free.[6]

The observed alterations in CPM, arising mainly from individuals with SCI and chronic neuropathic pain, are consistent with a large body of literature in which CPM was shown to be impaired in populations with long-standing pain conditions (see Yarnitsky,[20] Lewis et al,[21] and van Wijk and Veldhuijzen[22] for reviews). Interpretation of such changes in CPM efficacy in individuals with chronic pain remains difficult however, as whether changes in CPM efficiency are a causative factor in pain or a consequence of the presence of pain is a matter of debate.[20,21] Most of the studies conducted so far are cross-sectional, and longitudinal studies are needed in order to be able to clarify the chronology of the development of clinical pain and impaired CPM, and thus cause-effect relationships. On the one hand, some studies predicting the risk of developing postsurgical pain based on presurgery CPM support the idea that weak CPM plays a causative role in chronic pain development.[23,24] On the other hand, a study reporting that deficient CPM in patients with painful hip osteoarthritis returns to normal levels after joint replacement suggests that CPM mechanisms can be modified over time depending on the presence or absence of pain.[25] Importantly, these 2 proposed mechanisms are not necessarily mutually exclusive. The aforementioned observations highlight the complexity of the relationship between CPM and clinical pain as well as the need for longitudinal studies. So far, only one longitudinal study performed in individuals with SCI measured CPM.[26] However, while clinical pain was measured over the first 2 years postinjury, CPM was measured only once at 1.5 months post-SCI, and only individuals without neuropathic pain at that time were included. CPM measured above the level of injury were found to be similar across healthy controls, individuals with SCI who developed neuropathic pain over the 2-year period and individuals with SCI who remained pain free. These results do not suggest that altered CPM prior the occurrence of pain play a causal role in the development of pain, but do not explain why individuals with pain following SCI typically show altered CPM compared with those who are pain free.

The primary aim of this study was to describe the evolution of CPM over time after SCI, and to explore the relationships with the presence of clinical pain. Based on recent studies with transversal results showing either normal CPM above the level of lesion in individuals without neuropathic pain early after injury[26] or altered CPM in individuals with neuropathic pain at the chronic stage,[6,11] our working hypothesis was that CPM would decrease (ie, resulting in less inhibition) over time following SCI.

Material and Methods

Thirty-five adults with an acute SCI were recruited from the SCI unit of the Institut de réadaptation en déficience physique de Québec du Centre intégré universitaire en santé et service sociaux de la Capitale-Nationale. The recruitment period extended from April 2012 to June 2016. Inclusion criteria were (1) at least 18 years of age and (2) traumatic or vascular origin, with a rapid and clearly identifiable onset. Exclusion criteria comprised history of neuropathy or chronic pain prior to spinal cord injury, psychiatric disorders, cognitive deficits interfering with the testing (eg, ability to maintain attention during sensory testing and to rate pain intensity) and extensive sensory loss on all dermatomes of both hands. Importantly, individuals were admitted to the study no matter their pain status (ie, presence of neuropathic and or nociceptive musculoskeletal [MSK] pain). However, this pain status at admission was considered in the analysis (see Statistical Analysis section). All individuals provided written informed consent and all procedures described below were in accordance with the Declaration of Helsinki and approved by institutional review board of the Institut de réadaptation en déficience Physique de Québec (reference number: 2011-258). We used the STROBE cohort checklist when writing our report.[27]

Study Design

In the first 3 weeks after being admitted to the rehabilitation center (hereafter referred as Admission), the severity of the SCI and the presence of pain were assessed by one of the physiatrists of the SCI unit. The severity and neurological level of spinal cord injury and the clinical pain were assessed according to International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI)[28] and the International Spinal Cord Injury Pain Basic Data Set,[29] respectively. Heat pain threshold and CPM efficacy were tested in a laboratory located within the rehabilitation facility by a trained researcher. Assessment of

clinical pain, heat pain threshold, and CPM were repeated in the last 2 weeks of intensive functional rehabilitation (hereafter referred as Discharge).

Pain Assessment

The International Spinal Cord Injury Pain Basic Data Set used for the clinical pain assessment is a questionnaire evaluating the painful body sites as well as the type of pain (nociceptive vs neuropathic) and its intensity (rated on a 0-10 numerical rating scale [NRS]) at each site.[29] Although some phenotypical differences have been reported between at-level and below-level pain,[15] both types of pain were classified as neuropathic pain because of the limited sample size and of the fact that at each time point several patients were reporting both types of pain. Nociceptive MSK pain was also used as a separate variable.

Heat Pain Threshold

Heat pain threshold was tested at a body site located above the level of the lesion. In patients with a lesion below T1, tests were made on the volar surface of the forearm (C6 dermatome). For patients with a lesion at T1 or above, a body site located two dermatomes above the spinal level of the lesion was selected (ie, for patients with a lesion at C5, tests were performed on the cheek). However, the site of testing was kept the same for each testing session.

Assessment was conducted according to the recommendations of the German Research Network on Neuropathic Pain[30] using a 3 × 3 cm thermode (TSA II, Medoc, Advanced Medical Systems). The baseline temperature was set at 32 °C and then rose at a rate of 1 °C/s. The patient was instructed to indicate the moment at which the sensation of warmth switched to a painful sensation by pushing a button (or providing a verbal signal if this motor deficits were too severe). Three trials, separated by 30 seconds, were performed at each assessment time, and the heat threshold was defined as the mean temperature for these 3 trials.

Conditioned Pain Modulation

To assess CPM, a continuous heat stimulation was administered with the same thermode for 2 minutes on the same body site used for the sensory testing. The temperature of the heat stimulation was individually set in order to induce a pain perception of ~5/10. During this thermal stimulation (Test stimulus), pain intensity was measured using a 100 mm computerized visual analog scale (left edge = no pain, right edge = worst imaginable pain), except in patients in which upper limb motor impairments prevented its used (in this case, verbal pain ratings were taken every 15 seconds). This Test stimulus was applied twice, with a cold pressor test (CPT) procedure (Conditioning stimulus) between both applications, following a well-established paradigm[31] that has been used successfully in various clinical populations.[32-35]

In agreement with the recommendations on practice of conditioned pain modulation testing,[36] the test stimulus was applied as fast as possible after the conditioning stimulus (<30 s interstimulus interval). The CPT, a strong nociceptive stimulation, consists in immersion of the opposite hand (up to the wrist) for 2 minutes in a bath of cold (10 °C) water, with verbal pain ratings every 15 seconds. The CPM was quantified by comparing the average pain intensity reported during the Test stimulus (2-minute thermode) performed before and after the CPT. For each Test stimulus, the pain rating was the average of either the computerized visual analog scale over 2 minutes, in mm (0-100), or of the verbal pain rating (0-100; in patients with significant upper limb motor impairments). Calculation was performed as follow: CPM = (pain rating post-CPT – pain rating pre-CPT) × 100/pain rating pre-CPT). Therefore, a negative value indicates inhibition, reflecting effective CPM mechanisms.

Statistical Analysis

A Priori Analyses. In order to describe the evolution in the type of pain (MSK vs Neuropathic) over time (Admission vs Discharge), McNemar chi-square tests were performed. Moreover, to investigate the evolution of pain over time, non parametric analyses of variance (nonparametric for longitudinal data, nparLD[37]) with one factor (Admission vs Discharge) were performed on different variables measuring clinical pain (either MSK or neuropathic), sensitivity to thermal nociceptive stimuli (heat pain threshold, pain rating during CPT) and CPM. nparLD is robust method for designs with small and inequivalent samples which is not affected by missing values and outliers and do not require normality of distributions and homoscedasticity.[37] Association between pain at admission and at discharge was also assessed with Tau coefficient (Kendall correlation).

A Posteriori Analyses. As results suggested different pain modulation profiles over time for individuals with MSK and neuropathic pain, additional a posteriori analyses were performed using nparLD to test the effect of Group and Time (Admission vs Discharge) on CPM. Note that in order to investigate the effect of early pain on the evolution of pain modulation and sensitivity, groups were created based on the pain status (>1/10) at Admission: Neuropathic pain only, MSK pain only and Neuropathic + MSK pain. Because sensitivity to thermal nociceptive stimuli could potentially affect CPM, similar analyses were performed on pain ratings during test and conditioning stimuli during the CPM procedure, as well as on heat pain thresholds.

Statistical analyses were performed with R (v.3.5.2) using nparLD and Kendall packages.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Table 1. Demographic and Clinical Characteristics.

Subject	Sex	Age, y	AIA	SCI level	Days since injury (Admi)	Days between Assess	Pain MSK (0-10 NRS) Admi	Pain MSK (0-10 NRS) Disch	Neuro. Pain (0-10 NRS) Admi	Neuro. Pain (0-10 NRS) Disch	Type of Neuro. Pain Admi	Type of Neuro. Pain Disch
Neuropathic pain only at admission												
1	M	74	D	C5	26	18	0	0	4	4	a	a
2	M	63	D	C2	19	55	0	0	4	0	a	—
3	M	55	C	T11	45	77	0	0	7	4	a + b	a + b
4	F	30	A	T6	34	84	1	2	9	4	a	a + b
5	M	57	D	C7	36	—	0	—	5	—	a + b	—
Musculoskeletal pain only at admission												
6	M	51	D	C3	25	69	4	0	1	1	b	b
7	M	24	A	T5	23	69	8	7	1	0	b	—
8	M	18	B	L2	23	73	6	0	0	0	—	—
9	F	35	B	C7	55	110	3	8	0	6	—	a
10	M	50	A	T4	44	131	4	7	0	7	—	b
11	M	34	D	C5	43	180	3	2	0	0	—	—
12	M	54	A	T2	32	191	3	5	0	0	—	—
13	M	20	D	T5	38	—	4	—	0	—	—	—
14	M	60	B	T12	35	—	3	—	0	—	—	—
15	M	31	B	T10	37	—	4	—	0	—	b	b
16	M	44	A	T11	31	—	6	—	0	—	—	—
Neuropathic + Musculoskeletal pain at admission												
17	M	30	D	L3	24	19	6	5	5	3	a	a
18	F	41	D	D11	27	34	4	6	7	4	a + b	a + b
19	M	54	D	C4	50	51	3	3	6	7	a	a
20	M	19	B	T7	54	78	3	—	3	0	b	—
21	F	36	A	T11	24	82	2	0	2	9	a	b
22	M	47	D	C3	37	84	3	4	3	4	a + b	b
23	M	33	A	T12	19	90	3	0	3	8	a	a
24	M	33	B	C5	42	99	4.5	0	4.5	5	a + b	a
25	M	33	B	L3	29	108	7	0	3	0	b	b
26	F	37	B	L3	26	119	5	5	5	5	a	a
27	M	54	A	C5	59	125	6	2	6	4	a	a
28	F	50	A	C6	68	129	4	0	4	0	a	—
29	M	42	D	C5	53	148	—	2	0	3	—	a
30	M	30	C	T6	33	148	7	0	7	3	a	b
31	F	18	B	C5	70	—	5	—	5	—	a	—
32	M	57	D	L2	57	—	3	—	3	—	a	—
33	M	41	C	T11	41	—	3	—	4	—	b	—
34	M	28	A	T1	31	—	5	—	4	—	a	—
35	M	47	D	L2	28	—	10	—	10	—	a	—

Abbreviations: Admi., admission; AIS, American Spinal Cord Injury Association Scale; C, cervical; Disch., discharge; F, female; L, lumbar; M, male; Neuro., neuropathic; NLI, neurological level of injury; NRS, numerical rating scale; SCI, spinal cord injury; T, thoracic; a, at-lesion pain; b, below-lesion pain; a + b, at- and below-lesion pain.

Results

Sample Description

Of the 139 patients admitted to the SCI unit with a traumatic injury between April 2012 and June 2016, 55 did not met the inclusion criteria or were not contacted within the prescribed delay and 30 declined to participate. Of the 54 who met the inclusion criteria and agreed to participate to the study, 35 had a complete dataset (including CPM) at Admission to rehabilitation and are included in the present article.

Twenty-five of these patients were also assessed at Discharge. Reasons for dropping out included: death (n = 1); very short stay in rehabilitation (n = 2); inability to assess before discharge (n = 5; eg, because discharge occurred too rapidly or because the research coordinator was on vacation); technical problem with the equipment (n = 1); hypersensitivity to cold that developed over time (n = 1). The demographic and clinical characteristics of the patients are summarized in Table 1, medication in Table 2 and location of pain is shown in Figure 1.

Table 2. Medication at Admission and Discharge.

Medication	Admission (N = 35), % (n)	Discharge (N = 25), % (n)
ANAL	85 (30)	76 (19)
NSAI	28 (10)	44 (11)
OPIOID	94 (33)	64 (16)
BENZO	48 (17)	28 (7)
T-AD	20 (7)	16 (4)
MR	14 (5)	4 (1)
AC	80 (28)	72 (18)
Non-T-AD	17 (6)	12 (3)
NMDA-a	31 (11)	32 (8)

Abbreviations: ANAL, analgesics; NSAID, nonsteroidal anti-inflammatory drugs; Benzo, benzodiazepine; T-AD, tricyclic antidepressant; MR, muscle relaxant; AC, anticonvulsant; Non-T-AD, non–tricyclic antidepressant; NMDA-a, NMDA antagonist.
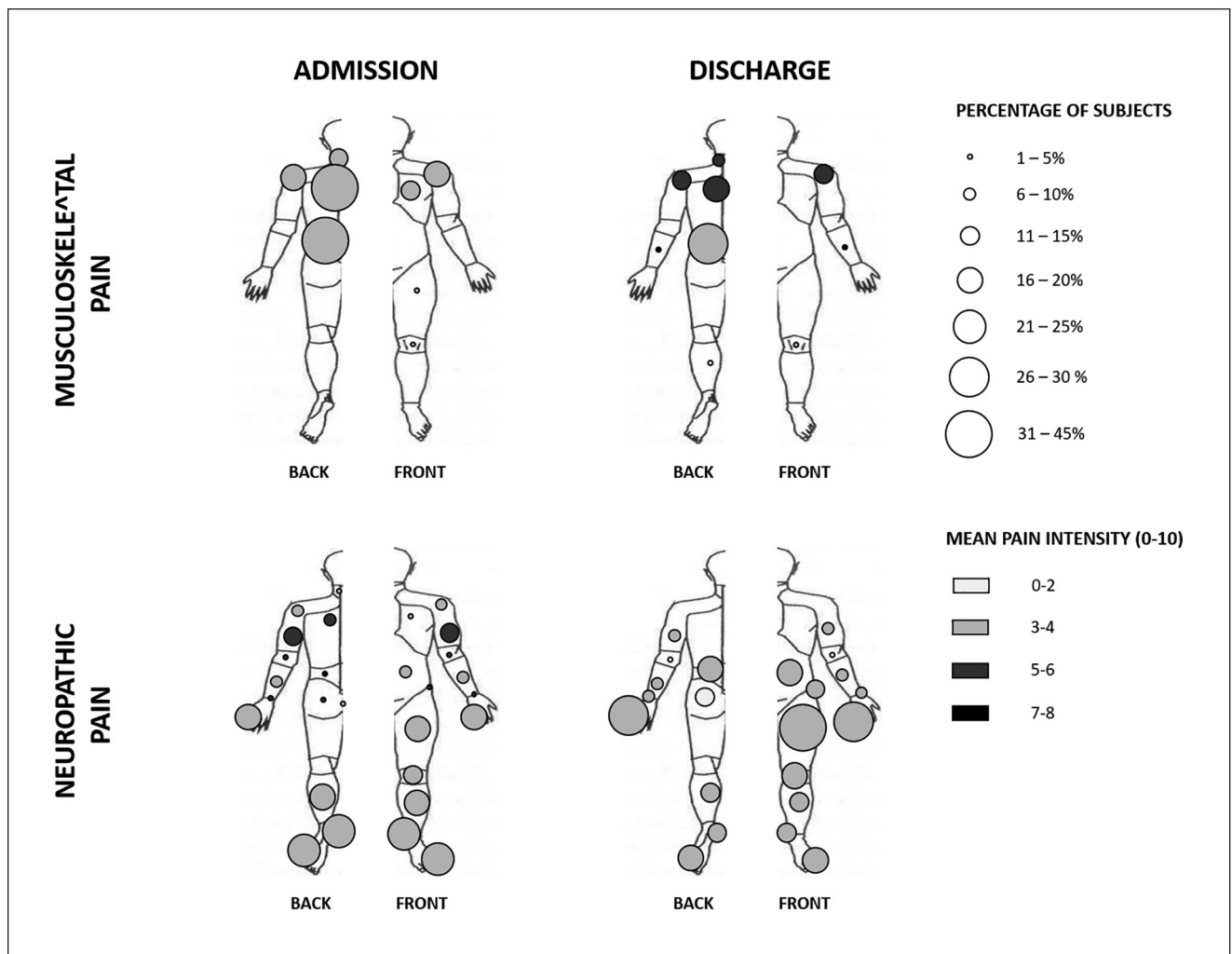
Figure 1. Location of musculoskeletal and neuropathic pain at admission and discharge.

Evolution of Pain and Pain Modulation Over the Course of Rehabilitation

Among the 25 patients with neuropathic pain measures available at Admission and Discharge: 17 patients had neuropathic pain >1/10 at Admission and 16 patients had pain at Discharge. As previously reported in the months following SCI, at-level neuropathic pain was the most prevalent type of neuropathic pain.[15,38,39] Among the 24 patients with MSK pain measures available at admission and discharge: 19 patients had MSK pain >1/10 at Admission, and 13 patients had pain at Discharge.

More specifically, 47% of participants who reported MSK pain at Admission no longer had MSK pain at Discharge while 25% of participants who had MSK pain at Discharge did not have MSK pain at Admission, meaning that MSK pain was more likely to be present at Admission ($\chi_1 = 4.9$; $P = .026$). In contrast, 23% of the participants who reported neuropathic pain at Admission did not have any at Discharge while 37% who reported neuropathic pain at Discharge did not report at Admission, indicating that the presence of neuropathic pain did not depend of the time of measure ($\chi_1 = 0.14$; $P = .70$).

Regarding pain intensity, no significant change was observed over time for neuropathic pain (Admission: 3.3/10 $\pm$ 2.8; Discharge: 3.2/10 $\pm$ 2.8; analysis of variance-type statistic $(ATS)_1 = 0.01$; $P = .91$) but a significant decrease was observed for MSK pain (Admission: 3.8/10 $\pm$ 2.4; Discharge: 2.4/10 $\pm$ 2.7; $ATS_1 = 5.9$; $P = .015$). The intensity of neither type of pain at Admission was predictive of the intensity of pain at Discharge ($P \geq .29$), with important interindividual variability in patterns of evolution.

Table 3 shows individual data for outcomes of the laboratory pain assessment at each time point. To assess whether the pain evoked by thermal nociceptive stimuli evolved over time, comparisons between Admission and Discharge were performed. No significant changes were observed for either the heat pain thresholds (Admission: 44.9 $\pm$ 3.87 °C; Discharge: 46.2 $\pm$ 2.81 °C; $ATS_1 = 0.20$, $P = .28$) or the pain reported during the CPT (Admission: 71.6 $\pm$ 20.5; Discharge: 71.8 $\pm$ 7.9; $ATS_1 = 1.58$, $P = .21$). Altogether, these results suggest that there was no general change in sensitivity to thermal nociceptive stimuli developing over time above the lesion level.

To assess the evolution of descending inhibitory controls, CPM was also compared between Admission and Discharge. Importantly, no differences were observed between time points on either the temperature for the Test stimulus employed or on the pain rating during the first Test stimulus or during the Conditioning stimulus (all P values >.799), ensuring that the measurements at both time points were comparable. As illustrated on Figure 2, a marked decrease in the efficacy of CPM was observed over time, with −30.4% $\pm$ 28.4% of inhibition at Admission and only −12.9% $\pm$ 23.2% at Discharge on average ($ATS_1 = 7.62$; $P = .005$). This decrease in efficacy of CPM was not associated with either the number of days between injury and the Admission assessment, or the number of days between assessments (all P values >.42).

Relationship Between the Presence of Pain and CPM

CPM measured at Admission was significantly associated with the *intensity* of neuropathic pain at Admission ($\tau = −0.22$, $P = .013$, see Figure 3). Surprisingly, however, a higher level of neuropathic pain at Admission were associated with more effective CPM (ie, more inhibition). CPM at Admission was not predictive of the intensity of neuropathic pain at Discharge ($P = .94$), and was not associated to the presence of MSK pain at any time points (both $Ps > .72$). These results do not suggest that CPM measured at Admission to rehabilitation is predictive of the evolution of pain, but rather that the type of pain (MSK vs neuropathic) present at this time might influence the CPM and its evolution over time.

Therefore, a posteriori analyses were performed in order to further examine the relationship between the type of pain at Admission and pain modulation over time. To do so, the total sample was subdivided into 3 Groups according the type of Pain at Admission (>1/10) (MSK only, Neuropathic pain only, or Neuropathic + MSK pain). The MSK, Neuropathic, and Neuropathic + MSK pain groups, respectively, included 11, 5, and 18 participants.

Figure 4 depicts the mean and standard error of the mean for CPM (Figure 4A), pain ratings during the conditioning stimulus (CPT; Figure 4B), and heat pain thresholds (Figure 4C). For the CPM, a significant interaction between Time and Group was observed ($ATS_{1.4} = 4.57$, $P = .020$). At Admission, the MSK group had significantly less effective CPM than the 2 other groups with Neuropathic pain (both $Ps < .05$). The Neuropathic + MSK and Neuropathic pain group did not differ significantly from each other ($P = .22$). At Discharge, the Neuropathic + MSK pain group had less effective CPM than MSK ($P < .05$). However, there was no significant difference between the MSK and Neuropathic pain ($P = .78$) and between the Neuropathic and Neuropathic + MSK pain ($P = .22$) groups. Moreover, the CPM decreased over time (from Admission to Discharge) for individuals with Neuropathic pain (Neuropathic + MSK pain: $P = .006$; Neuropathic pain: $P = .06$) while CPM stayed stable in the participants with only MSK ($P = .60$).

For pain ratings during the conditioning stimulus (CPT, temperature identical across participants), a significant effect of Group was observed ($ATS_{1.5} = 15.21$, $P < .001$).

Table 3. Outcomes of the Laboratory Pain Assessment.

| Subject | Heat pain threshold | | Test heat temperature | | CPT pain rating | | Conditioned pain modulation | |
	Admi.	Disch.	Admi.	Disch.	Admi.	Disch.	Admi.	Disch.
Neuropathic pain only at admission								
1	38.7	49.4	47.0	47.5	—	—	−56.7	17.6
2	39.6	40.2	46.5	47.0	88.0	90.0	−59.2	−24.1
3	49.0	48.6	48.0	48.0	90.0	99.0	−24.6	−21.4
4	48.2	45.9	46.5	46.0	92.0	99.0	−38.0	−46.7
5	47.8	—	46.0	—	87.0	—	−82.9	—
Musculoskeletal pain only at admission								
6	46.8	42.3	47.5	47.0	51.0	73.8	0.0	−13.2
7	44.2	42.1	48.0	48.0	89.0	88.3	−7.7	−28.7
8	47.3	49.4	48.0	49.0	25.0	63.8	−77.4	−55.5
9	41.9	44.7	48.6	47.6	19.0	27.5	8.4	−38.1
10	43.6	49.0	46.8	47.0	93.0	85.6	−4.9	4.0
11	48.1	49.1	49.1	49.0	70.0	64.4	−43.8	−38.2
12	35.3	48.5	46.0	47.0	84.0	55.0	−13.3	−16.6
13	47.7	—	47.7	—	76.0	—	13.9	—
14	45.2	—	46.7	—	85.0	—	−31.1	—
15	49.6	—	48.0	—	49.0	—	−14.6	—
16	46.1	—	47.0	—	81.0	—	1.4	—
Neuropathic + Musculoskeletal pain at admission								
17	50.0	48.4	48.7	48.7	70.0	57.5	−33.6	−3.8
18	44.2	44.2	47.4	46.9	64.0	64.3	−73.7	−33.3
19	40.3	47.8	47.0	48.0	79.0	76.7	−38.2	−21.1
20	46.4	44.9	47.9	46.3	56.9	82.6	8.0	20.9
21	42.0	48.4	46.0	45.0	90.0	68.8	−62.9	−32.7
22	50.0	47.1	48.0	47.7	79.0	76.0	−26.2	0
23	45.7	48.8	47.9	47.5	75.0	54.0	4.6	−11.1
24	49.7	48.1	48.5	48.5	68.0	37.5	−9.9	−19.0
25	49.5	46.1	47.0	—	76.0	76.3	−20.4	−18.3
26	42.3	41.8	46.5	46.5	79.0	86.6	−100.0	−4.9
27	44.6	41.4	46.5	46.5	62.0	65.0	−15.9	46.2
28	47.0	46.2	47.0	47.0	96.0	93.8	−14.7	1.2
29	43.8	46.4	48.0	48.5	44.0	71.3	−27.3	−0.7
30	45.3	45.2	47.5	47.5	79.0	66.3	−31.8	15.6
31	40.7	—	45.5	—	66.9	—	−64.8	—
32	45.6	—	47.0	—	99.0	—	−38.9	—
33	46.8	—	47.5	—	83.0	—	−50.9	—
34	49.0	—	47.0	—	94.0	—	−37.2	—
35	41.1	—	46.8	—	87.0	—	−34.1	—

Abbreviations: Admi., admission; CPT, cold pressor test; Disch., discharge.

Post hoc analyses revealed that the Neuropathic pain group had higher pain ratings during CPT than the Neuropathic + MSK pain ($P = .001$) and the MSK ($P = .001$) groups while the Neuropathic + MSK and the MSK groups did not differ from each other ($P = .16$). The interaction between Group and Time was significant ($ATS_{1.7} = 1.71$, $P = .02$). Post hoc analyses revealed that the Neuropathic pain group had higher pain ratings during CPT at both Admission (vs MSK: $P = .03$; vs Neuropathic + MSK: $P = .07$) and Discharge (vs MSK: $P = .02$; vs Neuropathic + MSK: $P = .03$). Moreover, the pain ratings increased over time (from Admission to Discharge) for the Neuropathic Group ($P = .03$) and stayed stable for the MSK ($P = .67$) and the Neuropathic + MSK pain ($P = .23$) groups.

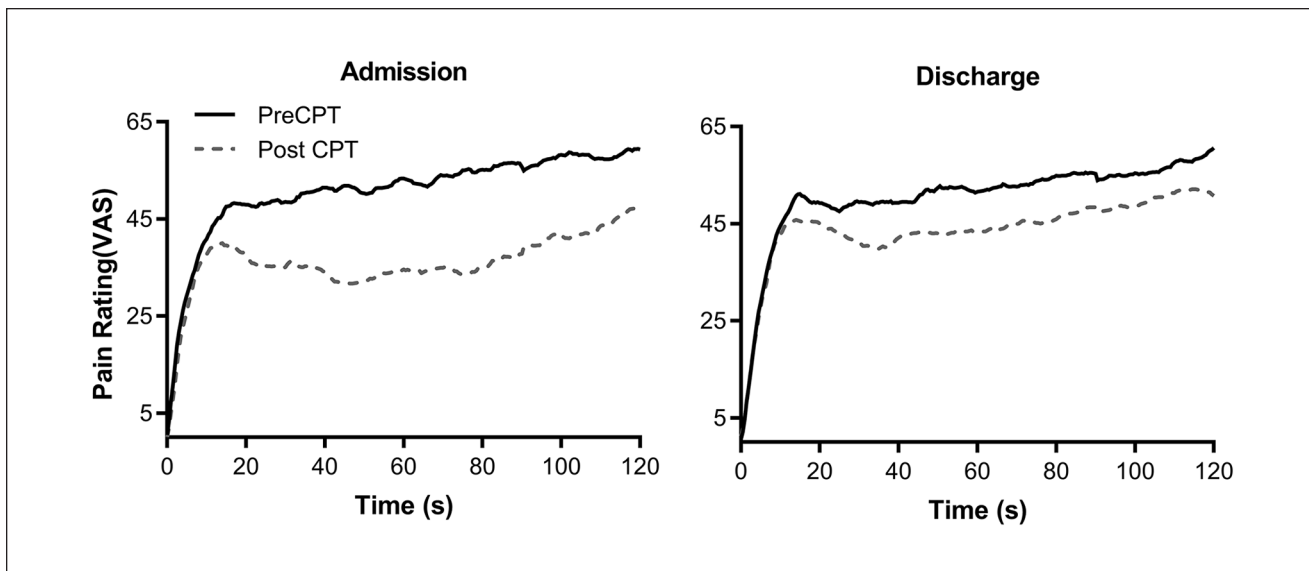No significant effects were observed for the heat pain thresholds (all $Ps > .27$).

Figure 2. Change in efficacy of conditioned pain modulation (CPM). Curves represent the group average pain rating over time during the 2 minutes of application of the Test stimulus prior (full line) and after (dashed line) the cold pressor test (CPT; Conditioning stimulus) at Admission (left panel) and Discharge (right panel). It can be seen that on average, the pain intensity reported during the pre-CPT test is similar at both time points. However, the pain intensity reported during the post-CPT Test stimulus differs, the larger decrease at Admission indicating more effective CPM. CPM was calculated for each participant at each assessment period as follow CPM = (pain rating post-CPT − pain rating pre-CPT) × 100/ pain rating pre-CPT). Therefore, it reflects the % of decrease in rating averaged over the 2-minute period, a negative value reflecting inhibition, that is, effective CPM mechanisms.
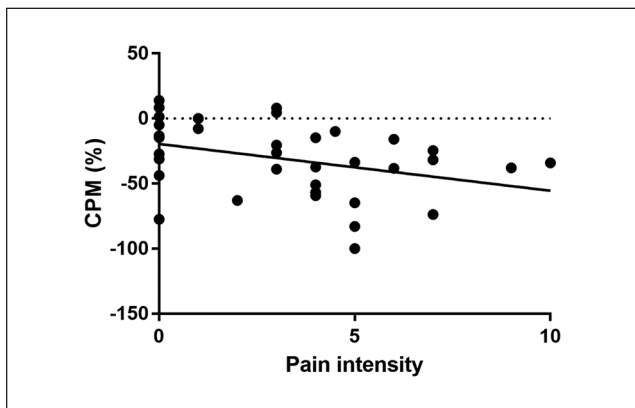
Figure 3. Relationship between condition pain modulation (CPM) measured at Admission and the intensity of neuropathic pain at Admission. CPM is expressed as a % of change relative to the preconditioning test, a negative value indicating inhibition, that is, effective CPM mechanisms. Neuropathic pain was rated on a 0-to-10 numerical rating scale, as part of the International Spinal Cord Injury Pain Basic Data Set (worst neuropathic pain problem).

Discussion

The aims of the present study were to describe the evolution of CPM over time after SCI and to explore the relationships with the presence of clinical pain. In the sample recruited in the present study, a large majority of patients were reporting both MSK and neuropathic pain during the course of their rehabilitation. While the occurrence of MSK pain decreased over time (with a significant decrease in intensity), no such improvement was observed for neuropathic pain. By the conclusion of rehabilitation, 64% of patients reported neuropathic pain >1/10. Of the 16 patients that reported neuropathic pain at Discharge, 13 already exhibited neuropathic pain at Admission, that is, in the first 2 months postinjury. This differential pattern of evolution between MSK and neuropathic pain in the first 6 to 12 months postinjury is consistent with previous studies,[15,38-40] supporting the external validity of the results despite the limited sample size.

While previous studies have reported altered CPM in patients with chronic neuropathic pain after SCI,[6,11] this is the first showing a gradual reduction over time. This reduction appears to occur without a general increase in sensitivity to nociceptive stimuli above the lesion level, as no global change (ie, at the whole group level) was observed for either the heat pain thresholds or the pain reported during test or the conditioning stimulus of the CPM assessment procedure. This strongly suggests that CPM changes reflect changes in endogenous pain modulation and do not result from altered response to the Test or Conditioning stimuli themselves. Subgroups analyses showed an increase in pain ratings during the CPT (from Admission to Discharge) for the Neuropathic group only. However, higher pain level
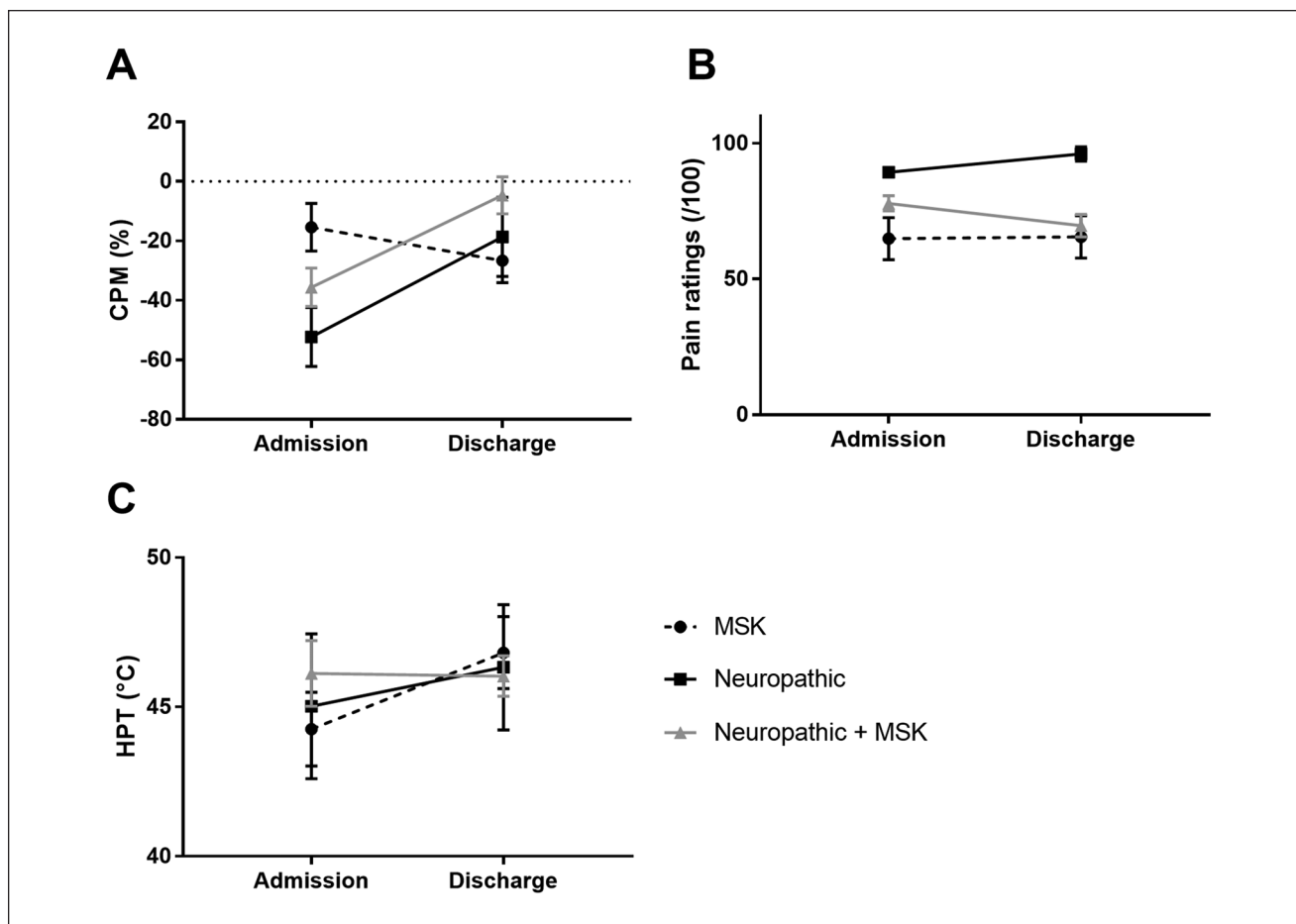
Figure 4. (A) Evolution of condition pain modulation (CPM) between Admission and Discharge, according to the pain status at Admission (Neuropathic pain only, MSK pain only, and Neuropathic + MSK). CPM is expressed as a % of change relative to the preconditioning test, a negative value indicating inhibition, i.e. effective CPM mechanisms. (B) Pain ratings (/100) at Admission and Discharge during the Cold pressor test (CPT), that is, the conditioning stimulus. Pain intensity was measured using a 100 mm computerized visual analog scale (left edge = no pain, right edge = worst imaginable pain). (C) Heat pain threshold (HPT, in °C) at Admission and Discharge during the cold pressor test (CPT), that is, the conditioning stimulus.

associated to the conditioning stimuli would be expected to cause an increase in inhibition, and not a decrease.[41] Therefore, this potential bias would tend to decrease the effect that was observed over time in CPM, rather than explaining it.

CPM is a well-described phenomenon and is generally considered as human behavioral correlate of "diffuse noxious inhibitory controls," the lower brainstem-mediated inhibitory mechanism directly observed in animal studies.[42-44] However, the underlying mechanisms in humans are not fully elucidated. Human lesion studies showed that the circuitry responsible for conditioned pain modulation lies within the caudal brainstem,[45,46] with recent brain imaging results suggesting the involvement of the caudalis subdivision of the spinal trigeminal nucleus, the region of the subnucleus reticularis dorsalis and the dorsolateral pons in the region of the parabrachial nucleus.[47] The evolution of

endogenous descending modulation and relationship with clinical neuropathic pain observed in the present study suggest that impaired CPM is NOT a cause of neuropathic pain after spinal cord injury, which is consistent with previous finding showing that CPM assessed above the level of injury at 1.5 months postlesion (in the absence of neuropathic pain) does not predict long-term emergence or severity of neuropathic pain.[26] In fact, CPM was initially *positively* correlated with neuropathic pain at Admission (ie, higher ratings associated with greater capacity to modulate). While unexpected, this is not entirely contrary to existing evidence. Most notably, a recent study in patients with complex regional pain syndrome for less than 1 year demonstrated *greater* CPM compared with healthy controls.[48] This could be explained by neuropathic pain symptoms initially and defensively boosting or engaging CPM, momentarily increasing antinociceptive functions (eg, descending

control). Greater CPM associated with neuropathic pain at Admission cannot, however, be maintained in light of persistent symptoms (ie, at Discharge), eventually leading to reductions in CPM. Moreover, CPM at Admission was not predictive of the presence of pain at Discharge. This relationship would be expected if reduced CPM was the mechanism underlying the development of neuropathic pain (as has been postulated for postsurgical chronic pain[23,24]). A longitudinal study including more measurement times (for both pain and CPM) would be needed to confirm the hypothesis that the duration of neuropathic pain plays an important role in driving changes in CPM. It could also allow to determine whether at-level and below-level neuropathic pain have similar impact on CPM, something that was not possible in the present study due to the small number of patients (n = 2) having significant below-level pain without any at-level pain.

While conducting a longitudinal study in the months following SCI certainly provide valuable insights, there are limitations in our design that needs to be taken into consideration. First, the sample size is limited (35 patients at Admission and 25 at Discharge) and the population is clinically heterogeneous. However, our sample was quite comparable to that of a published longitudinal study.[17] While the limited sample size raises the possibility of type II errors, especially for the subgroup analyzes, the risk of type I error appears limited, as the pattern of results was very consistent across participants (76.5% of individuals with neuropathic pain at Admission showed a decrease in CPM efficacy over time). Moreover, nparLD is a robust statistical method for small samples.[37] However, a replication of the results in a larger sample would be warranted. Second, the measurement times were based on admission to and discharge from rehabilitation, and therefore the time since the lesion was variable across patients. This could contribute to explain that no association were found between measure at Admission and at Discharge. However, no significant relationship was found between the magnitude of the CPM change over time and either the number of days between injury and the Admission assessment, or the number of days between both assessments. Third, no screening tools were used for neuropathic pain, for instance the DN4, in addition to the International Spinal Cord Injury Pain Basic Data Set. However, the assessment was conducted by two experienced physiatrists practicing exclusively in patients with spinal cord injury, and therefore very knowledgeable of the characteristics of neuropathic pain. A last important factor that might have contributed to the decrease in CPM is the use of analgesics. CPM has been shown to be blocked by naloxone, suggesting an important role of opioids in the CPM mechanism.[49] Opioid-treated patients have been shown to have less efficient CPM than non-opioid-treated patients on average.[50,51] However, in opioid-users, daily opioid dose and duration was not associated with CPM at

group level[50,51] (but a negative effect of these 2 factors was observed in men only,[51] which represents the large majority of our sample). However, to the best of our knowledge, no longitudinal study has been performed in opioid users so far, and the administration of opioid in controls was rather reported to enhance CPM.[52] As the large majority of patients (94%) were receiving opioids at admission to rehabilitation, as well as several other medications (see Table 2), it was not feasible to assess the potential contribution of medication to the change in CPM. Achieving this would require a much larger sample size and more variability in the use of medication across participants, which probably explain why this is rarely done in the literature. Indeed, other drugs have been shown to affect CPM, such as ketamine[53] and alpha2 agonists.[54] This limitation is inherent to all physiological studies performed early after SCI, as medication use cannot be prevented for ethical reasons. However, it is important to note that most patients with MSK pain received opioids and did not exhibit a decrease in CPM over time. Because of factors such as medication and other factors related to the SCI (autonomic changes, need to alter the protocol to accommodate heterogenous lesions, etc), a direct comparison with data from healthy subjects was not deemed relevant and we favored focusing on within-subject comparisons over time. Nevertheless, it can be noted that published studies using the same CPM protocol reported average CPM values between −18.8% and −25.1%.[34,55-57] This suggest that the SCI itself does not dramatically alter the effectiveness of conditioned pain modulation mechanisms when assessed above the level of injury.

In conclusion, our study does not support the hypothesis that inefficient conditioned pain modulation mechanisms are leading to the development of neuropathic pain symptoms after SCI, but rather suggest that the presence of neuropathic pain leads to a decrease in conditioned pain modulation over time. However, this does not exclude the possibility that altered conditioned pain modulation can in turn contribute to the chronicity of neuropathic pain or could be a therapeutic target in the case of chronic neuropathic pain.

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