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# Identifying discomplete spinal lesions: New evidence from pain-autonomic interaction in spinal cord injury

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Summary (25 words max): This study highlights the value of pain-autonomic interaction to assess residual spinothalamic tract function and its relation to neuropathic pain after spinal cord injury.

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**Abstract**

The clinical evaluation of spinal afferents is an important diagnostic and prognostic marker for neurological and functional recovery after spinal cord injury (SCI). Particularly important regarding neuropathic pain following SCI is the function of the spinothalamic tract (STT) conveying nociceptive and temperature information. Here, we investigated the added value of neurophysiological methods revealing discomplete STT lesions, i.e., residual axonal sparing in clinically complete STT lesions. Specifically, clinical pinprick testing and thermal thresholds were compared to objective contact heat-evoked potentials (CHEPs) and a novel measure of pain-autonomic interaction employing heat-induced sympathetic skin responses (SSR). The test stimuli (i.e., contact heat, pinprick) were applied below the lesion level in 32 subjects with thoracic SCI while corresponding heat-evoked responses (i.e., CHEPs and SSR) were recorded above the lesion (i.e., scalp and hand, respectively). Readouts of STT function were related to neuropathic pain characteristics. In subjects with abolished pinprick sensation, measures of thermosensation (10%), CHEPs (33%) and SSR (48%) revealed residual STT function. Importantly, SSRs can be used as an objective readout and when abolished, no other proxy indicated residual STT function. No relation was found between STT function readouts and spontaneous neuropathic pain intensity and extent. However, subjects with clinically preserved STT function presented more often with allodynia (54%) than subjects with discomplete (13%) or complete STT lesions (18%). In individuals with absent pinprick sensation, discomplete STT lesions can be revealed employing pain-autonomic measures. The improved sensitivity to discern STT lesion completeness might support revealing the interference with neuropathic pain following SCI.

## Introduction

Spinal cord injury (SCI) results in disrupted sensorimotor communication through the site of neuronal damage. The standard neurological classification of an SCI encompasses sensory and motor testing, and defines a clinically complete SCI by the absence of sensorimotor function in the most sacral segments of the spinal cord [1]. Early studies from the 1980s reported preserved supraspinal motor control in subjects with such clinically complete SCI, and shaped the terminology of “discomplete” lesions [2-4]. The term "discomplete lesion" was defined as neurophysiological evidence of residual axonal sparing in clinically complete lesions [3, 5]. Further studies revealed a notable amount of subjects with discomplete SCI, and the terminology was extended to the sensory system assessed with magnetic resonance imaging or electrophysiology [6-9]. The identification of residual subclinical neuronal function offered a possible explanation for the prevalence of excessive spasticity [10] and potentially also of neuropathic pain (NP) after SCI [11]. For the development of NP, residual function of the spinothalamic tract (STT) might be of particular importance. Multiple studies indicated that lesions of spinothalamic projections are necessary, however not sufficient, for the development of NP [12, 13]. Strikingly, STT damage did not predict NP after SCI [14], but residual STT function contributed to severe NP [11, 15]. Additionally, partial integrity of pain pathways measured by laser-evoked potentials, increase the probability of developing stimulus-evoked pain, i.e., allodynia and hyperalgesia [16].

The neurological assessment of an SCI contains pinprick testing as a proxy for STT function [1]. This clinical bedside testing can be complemented with thermal stimulation, in particular cold and warm detection thresholds, to test STT integrity [17-20]. In addition to bedside examination tools used in the clinical work-up of spinal lesions, electrophysiological methods including pain-related evoked potentials provide objective evidence of preserved somatosensory function [21, 22]. In particular, contact heat-evoked potentials (CHEPs) provided additional value revealing residual STT function compared to pinprick testing in subjects with spinal disorders [23, 24]. In general, contact heat or laser stimuli activate thermo-nociceptive primary afferents projecting to the fast-conducting STT [25]. The synchronized afferent volleys are relayed though thalamic nuclei and further processed

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within the insular and anterior cingulate cortex [26, 27] ultimately being recordable as pain-related evoked potentials. Beyond this activation pattern, nociceptive stimuli activate the central autonomic network comprised of multi-synaptic spinal pathways to brainstem regions including the reticular formation, nucleus tractus solitarii, parabrachial nucleus, and ventrolateral medulla [28]. Further, the activation of the medial thalamic nuclei is conveyed to several brain regions including the amygdala and hypothalamus [28]. The activation of the central autonomic network by painful stimuli results in sympathetic activity, e.g., increased vascular and sudomotor function [28, 29]. The fact that thermo-nociceptive stimuli are processed in manifold ways along the nociceptive neuraxis and thereby evoke different somatosensory and autonomic responses, may be leveraged as part of the assessment of the functional integrity in spinal lesions. Therefore, the primary objective was to investigate measures of pain-autonomic interaction, i.e., heat-induced sympathetic skin responses (SSRs), as a readout for residual STT function in subjects with SCI. Our hypothesis was that the measure of heat-induced SSR has an additional value by unmasking discomplete STT lesions compared to conventional clinical testing, i.e., pinprick and thermal thresholds, and CHEPs. The secondary objective was to investigate how residual STT function relates to the presence and clinical phenotype of NP after SCI. We hypothesized that subjects spared STT function after SCI are more likely to report spontaneous NP and allodynia.

## Methods

### Subjects

This study was carried out in 34 subjects with chronic thoracic SCI. Subjects were recruited through the Swiss Spinal Cord Injury Cohort Study (SwiSCI) database and a local outpatient registry at Balgrist University Hospital in Zurich, Switzerland. Inclusion criteria comprised of i) SCI for at least one year, ii) neurological level of injury between T1-T12. Exclusion criteria were as follows: i) neurological disorders other than SCI, ii) psychiatric or cognitive status interfering with the study.

**Study design**

The study was designed as a 1-visit, cross-sectional study. All subjects provided written informed consent, and all procedures were in accordance with the Declaration of Helsinki. The study was approved by the local ethics board 'Kantonale Ethikkommission Zürich, KEK' (ref.number: EK-04/2006, PB_2016-02051, cinicaltrial.gov: NCT02138344). Subjects filled out the German version of the Pain Catastrophizing Scale (PCS) [30] and the Beck Depression Inventory-II (BDI-II) [31] in order to assess the possible confounding effects of pain catastrophizing and mood on pain experience [32]. A clinical assessment and pain phenotyping as well as the neurophysiological testing (see Figure 1) were done in a supine position in a quiet room with ambient temperature and minimized external confounders for steady electrophysiological recordings.

**Clinical assessment and pain phenotyping**

Subjects underwent a standard neurological assessment (International Standards for Neurological Classification of Spinal Cord Injury, ISNCSCI) where sensorimotor complete SCI (American Spinal Injury Association impairment scale; AIS A) is defined as absent sacral sparing (S4-5 dermatomes), and sensory and/or motor function is preserved in incomplete SCI (AIS B-D) [1]. Pinprick testing on the right mid-thigh (L2 dermatome), an area below the lesion, was used as a proxy for STT integrity. Next to pinprick, thermosensation was tested using cold and warm detection thresholds (CDT, WDT) in accordance with the German Research Network on Neuropathic Pain (DFNS) protocol [33]. A contact heat stimulator (PATHWAY Pain & Sensory Evaluation System, Medoc Ltd., Ramat Yishai, Israel) using a thermode with a 3x3cm contact surface and a heating and cooling rate of 1°C/s was applied with safety cut-offs at 0 and 50°C [18].

The pain phenotyping included a central NP assessment according to the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG) guidelines [34, 35]. The NP subtype was classified as at-level or below-level according to the International Spinal Cord Injury Pain criteria [36]. Presence of allodynia was tested with 25°C and 40°C thermorollers (Somedic, Hörby, Sweden), a brush, and the International Spinal Cord Injury Pain Data Set (ISCPDS) questionnaire [35]. Based on previous literature, pain extent was reported as the number of 13 body regions being affected by NP [18, 35] and with

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pain drawings using two DIN-A4 papers with standardized body charts (frontal/dorsal view) [37]. Shaded body areas of perceived NP at the moment were assessed by a) verbal descriptors, b) pain intensity (numeric rating scale, NRS; '0' = no pain, '10' = worst pain imaginable), and c) type of NP (evoked or spontaneous). Only NP intensities of ≥3 NRS were take into account for further analyses. The shaded pixels were analyzed as percentage of total body area.

**Contact heat-evoked potentials**

CHEPs recordings were performed based on a previously published set-up [23, 24, 38-41]. Briefly, 20 heat stimuli to the right mid-thigh, i.e., below the lesion level (see Figure 1), were applied after a familiarization on the left forearm. The heat stimuli had a baseline and destination temperature of 42°C and 52°C, respectively [23, 24, 38, 41]. Within the inter-stimulus interval of 15–19 sec, the thermode positioning was slightly changed to avoid peripheral adaptation [42]. Subjects were instructed to rate the pain intensity of the applied heat stimulus on the NRS after an auditory signal. CHEPs were recorded at the vertex (Cz, referenced to the earlobes) using a customized LabVIEW program (V2.04 CHEP, ALEA Solutions, Zurich, Switzerland) with a recording time of 10 seconds including a one-second pre-trigger window. The signals were acquired at 2000 Hz using a preamplifier (20000x, ALEA Solutions, Zurich, Switzerland) and band-pass filtered in the range of 0.5-30 Hz. During offline analysis, individual trials were inspected by two examiners for artefacts (e.g., coughing, blinking and spasticity). The resulting 15 artifact-free trials were averaged to determine N2 latencies and N2P2 amplitudes.

**Pain-autonomic interaction: Sympathetic skin responses**

While CHEPs were recorded as cortical responses to noxious heat stimuli, sympathetic sudomotor activity elicited by the same noxious stimulus, i.e., heat-induced SSRs, were simultaneously measured as a readout for pain-autonomic interaction (see Figure 1). SSRs were recorded with self-adhesive recording electrodes (AMBU BlueSensor NF-50-K/W, Ambu, Denmark) at the left hand. The signals were acquired with the same setup as described above for CHEPs albeit using a moving average filter of 50 samples for the recorded signal. Quantitative analysis of the SSR trials included the latency and peak-to-

peak amplitude. In order to ensure intact sympathetic innervation of the recorded hand, heat stimuli were also applied above the lesion level, i.e., at the volar forearm.

### Data classification and statistics

The four proxies of STT function, i.e., pinprick-, thermosensation, CHEPs and SSR, were grouped into "abolished" and "preserved" function. Preserved function was assumed if i) the pinprick score was a 1 (impaired) or 2 (normal) [1], ii) any thermal thresholds could be measured, iii) any CHEP was recordable, even with delayed latency or small amplitude, and iv) two or more out of five heat stimuli resulted in SSRs [43-45].

Further, we introduced three classifications of STT lesion completeness: 1) "Incomplete" and 2) "complete" STT lesions based on subjective clinical pinprick- and thermosensation being preserved or abolished, respectively. 3) "Discomplete" lesions classified by preserved objective CHEPs and/or SSRs readouts in "complete" STT lesions (abolished clinical measures) [3, 5-8].

Statistical analyses were performed using R Studio (version 4.0.4). Normal distribution was tested using the Shapiro-Wilk tests and histograms. As most parameters were non-normally distributed, the data is reported as median and inter-quartile range ($25^{th}$-$75^{th}$ percentile). Chi-square and Kruskal-Wallis tests were performed to compare pain parameters between three STT lesion classifications, with $p<0.05$ considered as statistically significant.

## Results

### Subject characteristics

Thirty-two out of the 34 SCI subjects were included in the study. Reasons for dropout were a small fiber neuropathy detected during the study measures (n=1) and an inability to follow experimental instructions (n=1). Demographics and clinical subject characteristics are listed in Table 1. The subjects (5 females, 27 males) had a median age of 57.5 years (53.7-62.3 years) and a time since injury of 14.5 years (8.3-24.2 years). Half of the subjects were classified as sensorimotor complete (AIS A). NP below the level of injury was reported in 18 subjects (intensity: 5.8 NRS [3.5-7.0], extent: 5.5 regions [4.0-7.0 regions] or 11.5% [5.3 – 35.8%] of total body area, see Table 2 for NP characteristics). The median PCS


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score of 10.0 points [3.0 – 15.75 points] and BDI-II score of 7.0 points [3.0 – 10.5 points] reflected clinically relevant catastrophizing [30] in only one subject (32 points) and no moderate or severe depression in the total study cohort. Further, the PCS and BDI-II scores were neither related to the presence of spontaneous NP (p=0.931, p=0.193, respectively) nor to the presence of evoked NP (p=0.394, p=0.089, respectively).The current pain medication included anti-epileptic drugs (n=8), non-steroidal anti-inflammatory drugs (n=5), antidepressants (n=4) and cannabinoids (n=1).

**STT function – from clinical to electrophysiological assessments**

Based on the pinprick score (ISNCSCI examination) of the thigh, 21 subjects (66%) presented with abolished and 11 (34%) with preserved STT function. Thermosensation (CDT and WDT) was abolished in 20 (62%) and preserved in 12 subjects (38%). The latter group showed a CDT of 28.4°C (20.5-30.2°C) and a WDT of 37.3°C (35.6-42.6°C). Electrophysiological testing revealed 16 subjects with recordable CHEPs (50%) and abolished ones in the other half. Compared to normative data, the SCI subjects presented with increased CHEP latencies (N2 latency: 356 (350-442) ms) and lower pain ratings (3.5 (1.8-6.6) NRS), while CHEP amplitudes (N2P2 amplitude: 21.6 (17.1-27.9) µV) were within normal range [41]. Interestingly, SSRs were recorded in more than half of the subjects (66%, 21/32) after contact heat stimulation of the thigh. All analyzed SSRs (amplitude: 1212 (904-1836) µV; latency: 1.92 (1.85-2.04 s)) were time-locked to the stimulus.

Intact nociceptive processing above the level of injury was guaranteed in all subjects as they showed preserved CHEPs and palmar SSRs after stimulation of the volar forearm. This also confirmed the integrity of efferent sympathetic pathways to the hands (recording site).

A summary of pinprick sensation and electrophysiological outcomes is shown in Figure 2. All subjects with normal pinprick sensation presented with recordable CHEPs and SSRs, in line with preserved STT function. Out of the six subjects with impaired pinprick sensation, CHEPs were recorded in four (67%) and SSR in all subjects (100%). Most importantly, in the 21 subjects with absent pinprick sensation, thermosensation was preserved in two (10%), whereas CHEPs were recorded in seven (33%) and SSR in ten subjects (48%). Additionally, heat-induced SSRs as a readout for pain-autonomic interaction was more sensitive for

preserved STT function compared to CHEPs (abolished CHEPs, but preserved SSR, n=5). Ultimately, when SSRs were abolished, none of the other proxies indicated preserved STT function. Representative examples of CHEPs and SSRs recordings are shown in Figure 3.

### Completeness of STT lesion and neuropathic pain

Sensorimotor complete (AIS A) subjects presented with more severe STT damage (9 complete, 6 discomplete, 1 incomplete STT lesion) than sensorimotor incomplete subjects (AIS C: 2 complete, 3 discomplete, 0 incomplete; AIS D: 0 complete, 4 discomplete, 7 incomplete STT lesions).

Figure 4 depicts a flow chart including both clinical and both electrophysiological proxies for the classification of STT lesion completeness. Based on clinical measures of pinprick- and thermosensation, 13 subjects had an incomplete and 19 subjects had a complete STT lesion. Strikingly, eight of the subjects with a clinically complete STT lesion presented with recordable CHEPs and/or SSRs, and were therefore defined as having a discomplete lesion. The electrophysiological parameters for the three STT lesion classifications are displayed in Table 3.

The NP phenotype for the three different STT lesion classifications can be seen in Table 4. The presence of spontaneous NP was equally distributed over the three groups; 62% of subjects with incomplete, 50% with discomplete, and 55% with complete STT lesions (p=0.866). Furthermore, no group differences were seen for NP intensity (p=0.784), extent (p=0.401), nor psychological readouts (PCS, p=0.644; BDI, p=0.876). Allodynia was most prevalent in subjects with incomplete STT lesions (54%), compared to subjects with discomplete or complete STT lesions (13% and 18%, respectively, p=0.072).

## Discussion

This study highlights the additional value of pain-autonomic interaction measures in the assessment of residual STT function in SCI subjects. The objective neurophysiological recordings of CHEPs and heat-induced SSRs revealed discomplete STT lesions in subjects with abolished sensation measured by conventional clinical sensory testing. The concurrent recording of SSR, in addition to cortical responses to heat stimuli, further improves the detection of residual STT function. Additionally, our results reveal an

association of STT function with the presence of allodynia, while spontaneous NP was not related to the degree of STT lesion completeness.

### The value of pain-autonomic interaction measures detecting discomplete spinal lesions

Awad and colleagues revealed discomplete lesions in around 50% of sensorimotor complete subjects using both innocuous tactile and sharp nociceptive stimuli [7]. In comparison, our study revealed 42% discomplete lesions in subjects without clinically preserved pinprick sensation. While pinprick testing assesses mechano-nociceptive processing along the neuraxis including peripheral Aδ fibers and the STT [46], our other proxies rely on thermo-nociceptive processing. We particularly focused on the thermo-nociceptive system with the spinothalamic and spinoreticular tract as main ascending systems within the anterolateral system of the spinal cord [47]. In accordance with several studies [17, 23, 24], subjects with absent pinprick sensation or thermal thresholds showed subclinical preservation of STT function assessed by CHEPs (7/21 and 8/21, respectively). On average, the preserved CHEPs had prolonged latencies compared to normative data, indicating damage to the nociceptive neuraxis [41, 48]. Further, we showed that the preserved STT integrity in discomplete STT lesions was associated with longer CHEPs N2 latencies and lower SSR peak-to-peak amplitudes compared to incomplete STT lesions. This finding highlights altered electrophysiological recordings in subjects with partial damage of the STT, i.e., discomplete lesion.

Next to CHEPs, measures of heat-induced SSR even increased the number of detectable discomplete lesions (8/19). The recording of palmar SSRs in all subjects when stimuli were applied above the lesion level, assures the integrity of the pain-autonomic interaction including intact efferent sympathetic innervation of the palmar eccrine sweat glands. This is of particular importance when interpreting the SSR recording and using it as a proxy for afferent nociceptive processing. However, in comparison to previous literature, the preserved SSRs in our study sample had prolonged latencies possibly attributable to impaired afferent conduction in line with damage to the nociceptive neuraxis [48].

Preservation of CHEPs and SSR despite loss of the respective perceptual correlates suggests a dissociation of spared nociceptive signaling from subjective pain perception.

Indeed, there is evidence that sympathetic responses are more related to stimulus intensity than subjective pain perception [49]. Our results support this dissociation of spared nociception from pain perception with subjects showing no pinprick and thermal sensation, but recordable SSRs [6]. For example, a potential confounding effect of stimulation awareness on SSR recordings can especially be neglected in subjects without perceived heat pain (n=8).

The comparison of the objective proxies for STT function revealed that roughly one-third of the subjects with abolished CHEPs had preserved SSRs (5/16). This difference might be explained by the fact that thermo-nociceptive stimuli are processed in different pathways along the nociceptive neuraxis. While the generation of cortical evoked potentials after radiant heat stimulation relies in particular on thermo-nociceptive Aδ fibers and fast-conducting fibers of the lateral STT, i.e., neospinothalamic tract, SSR can be elicited by a variety of afferent signaling, e.g., electrical, heat, cold [16, 50]. Specifically, the spino-reticular-thalamic system is assumed to be involved in alertness and arousal in response to nociceptive stimuli. Slower conducting multi-synaptic pathways, i.e., paleospinothalamic tract, might be responsible for SSRs when fast-conducting fibers in the lateral STT are damaged (abolished CHEPs) [25, 47]. Another possible explanation for improved sensitivity, might be that CHEPs are reported to be dependent on highly synchronized afferent volleys [23, 24], while SSR might be elicited via less intact fibers since already minor arousing stimuli are captured with autonomic recordings [51].

In conclusion, measures of pain-autonomic interaction can complement CHEPs for the assessment of spinal lesions possibly by taking advantage of assessing the phylogenetically older spino-reticulo-thalamic pathway.

**Association of residual STT function with neuropathic pain**

The association of STT function with NP is heavily discussed in the field of central NP. Previous studies reported that STT damage is a necessary condition for NP development, however, the NP development cannot be sufficiently explained by STT damage only [12, 13]. It has been shown that SCI subjects with and without NP had similar loss of STT function at and below the level of injury [15], and impairment or loss of STT function is not a significant NP predictor [12, 14]. Our findings on the lack of a difference in spontaneous NP, i.e.,

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presence, intensity and extent, between the three different STT lesion classifications (incomplete, discomplete, complete) are in accordance with these studies. Next to the impact of STT functional integrity, the presence and severity of ongoing central NP have previously been discussed with mechanisms such as hyperexcitability and disinhibition within the central nervous system [14, 15, 52, 53]. These mechanisms, as potentially reflected in increased wind-up and lack of conditioned pain modulation, might further improve the mechanistic exploration of the effects caused by the structural STT damage, eventually resulting in spontaneous NP. While no additional readouts on mechanistic changes were performed in the current study, a recent study found a significant mediation effect of conditioned pain modulation in the link between STT damage and central NP [54]. This study by Defrin and colleagues further highlighted the value of assessing anti-nociceptive indices (such as conditioned pain modulation) in predicting NP [54]. Furthermore, the highly debated imbalance theory claims that STT dysfunction in conjunction with preservation of the dorsal columns is responsible for NP development [15].

With regard to evoked pain, we found that only 38% (8/21) of our subjects with residual STT function, i.e., incomplete or discomplete, reported allodynia, indicating that STT preservation is not sufficient for the development of allodynia. However, preserved STT integrity may be a requirement for the development of evoked pain, whereas patients with a profound deafferentation had spontaneous pain exclusively [11, 16, 55]. It has been hypothesized that subjects with large lesions - affecting the whole STT system – are less prone to imbalanced spino-thalamic subsystems, i.e., medial/lateral system, which potentially would increase the likelihood of observing hyperalgesia/allodynia [16]. Interestingly, 80% of our SCI subjects with allodynia (8/10) showed preserved STT function based on neurophysiological testing. However, only one of these subjects belonged to the discomplete STT group, whereas the other subjects had an incomplete STT lesion apparent from the clinical testing.

Further, while pain catastrophizing and depression scores were previously reported to be associated with more severe chronic pain [56-58], our psychological measures were not related to NP intensity and extent. This is possibly attributed to the floor effect seen in the two psychological scales. Therefore, the relationship between STT integrity and NP

characteristics can be interpreted without any potential confounding of pain catastrophizing and depressive states.

### Limitations

There are several limitations of this study. The small sample size hinders more sophisticated statistical analyses of the findings on STT function and its relation to NP characteristics. Also, no further questionnaires, e.g., Neuropathic Pain Symptoms Inventory (NPSI) [59, 60], were performed to cover pain qualities and refine associations of STT integrity with distinct NP characteristics. Further, the electrophysiological recordings were based on a thermal stimulation only, but additional stimulation modalities (cold and mechano-nociceptive stimuli) would exhaustively assess all aspects of the STT. Furthermore, only one body region was examined, while covering multiple sites, e.g., at-level regions, might be interesting regarding zones of partial preservation or overlap with pain symptoms. Moreover, the link of STT damage to the presence and characteristics of NP was not further investigated on a more mechanistic level. For example, to assess neuronal hyperexcitability and deficient pain modulatory capacity, more elaborated test batteries, including wind-up and conditioned pain modulation paradigms, could further elucidate the link between STT integrity and NP.

### Conclusion and clinical relevance

In conclusion, we provide evidence that neurophysiological readouts such as CHEPs and heat-induced SSRs provide information regarding STT integrity beyond the clinical examination of pinprick and thermal thresholds. Our findings might be of particular interest with respect to the interpretation of pinprick scores during standard neurological examination of an SCI. In SCI subjects with absent pinprick sensation, 30-50% can still be assumed to present with discomplete spinal lesion, i.e., neurophysiological evidence of subclinical afferent sparing, having implications for clinical research study designs. Further, in SCI subjects with impaired/diminished pinprick sensation, residual STT function can be assumed by means of recordable SSRs in all subjects.

With regard to NP, the findings on STT integrity might have implications for the understanding of evoked NP, however, the direct relation to spontaneous NP warrants further investigations including studies targeting the mechanisms underlying chronic NP.

## Author contribution

J.R. and M.H. conceived the original idea. R.L. carried out the experiment. R.L. and M.H. performed the analysis. J.R. and A.C. supervised the findings of the work. All authors discussed the results and contributed to the final manuscript.

## Conflict of interest statement

The authors declare that there are no conflicts of interest regarding this work.

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**Table 1: Demographics and clinical characteristics of subjects with spinal cord injury (SCI).** Abbreviations: AIS, American Spinal Cord Injury Association Impairment Scale; F, female, M, male; NLI, neurological level of injury; NT, non-traumatic; Th, thoracic; T, traumatic.

| Subject ID | Age [yr.] | Gender | AIS (A-D) | NLI | Etiology (T/NT) | Time since injury [yr.] |
|---|---|---|---|---|---|---|
| 1 | 52 | F | A | Th10 | T | 23 |
| 2 | 55 | M | A | Th1 | T | 12 |
| 3 | 53 | M | A | Th5 | T | 20 |
| 4 | 75 | F | A | Th10 | NT | 14 |
| 5 | 58 | M | A | Th11 | NT | 24 |
| 6 | 62 | M | C | Th11 | T | 9 |
| 7 | 36 | M | A | Th11 | T | 7 |
| 8 | 75 | M | D | Th10 | NT | 14 |
| 9 | 62 | M | A | Th11 | T | 36 |
| 10 | 66 | M | D | Th3 | T | 19 |
| 11 | 57 | M | A | Th2 | T | 4 |
| 12 | 61 | M | D | Th8 | NT | 11 |
| 13 | 63 | M | A | Th12 | T | 17 |
| 14 | 62 | M | D | Th1 | T | 36 |
| 15 | 50 | M | D | Th3 | NT | 21 |
| 16 | 54 | M | C | Th10 | T | 13 |
| 17 | 59 | M | C | Th12 | T | 38 |
| 18 | 54 | F | D | Th5 | NT | 6 |
| 19 | 67 | M | C | Th4 | NT | 3 |
| 20 | 35 | M | A | Th7 | T | 15 |
| 21 | 65 | M | D | Th10 | NT | 7 |
| 22 | 55 | M | D | Th8 | T | 17 |
| 23 | 34 | M | D | Th12 | T | 6 |
| 24 | 57 | F | A | Th6 | T | 41 |
| 25 | 58 | M | A | Th5 | T | 34 |
| 26 | 65 | M | A | Th4 | T | 36 |
| 27 | 45 | F | A | Th9 | T | 25 |
| 28 | 68 | M | A | Th12 | NT | 3 |
| 20 | 56 | M | D | Th10 | T | 30 |
| 30 | 56 | M | A | Th11 | T | 9 |
| 31 | 35 | M | C | Th11 | T | 15 |
| 32 | 59 | M | D | Th9 | T | 7 |



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**Table 2: Pain characteristics of spinal cord injured (SCI) subjects with neuropathic pain (NP).** The pain phenotype segregated into spontaneous at- and below-level NP with intensity and extent. Additionally, the presence of thermal/mechanical allodynia and the intake of pain medication are reported. Abbreviation: NRS, numeric rating scale.

| Subject ID | Below-level NP | Pain intensity [NRS] | Pain extent [%] | Pain extent [# regions] | At-level NP | Allodynia | Pain medication |
|---|---|---|---|---|---|---|---|
| 1 | Yes | 3 | 12 | 7 | Yes | Yes | - |
| 2 | Yes | 4 | 2 | 1 | - | - | Yes |
| 3 | Yes | 3 | 7 | 5 | - | - | - |
| 4 | Yes | 9 | 50 | 8 | Yes | - | Yes |
| 5 | Yes | 5.5 | 38 | 7 | Yes | - | Yes |
| 6 | Yes | 8 | 13 | 2 | Yes | Yes | Yes |
| 7 | Yes | 3.5 | 38 | 6 | Yes | - | Yes |
| 8 | Yes | 7 | 36 | 7 | Yes | Yes | Yes |
| 9 | Yes | 3.5 | 34 | 6 | Yes | Yes | - |
| 10 | Yes | 8 | 3 | 3 | - | - | - |
| 11 | Yes | 6 | 16 | 4 | Yes | - | Yes |
| 12 | Yes | 3 | 11 | 7 | - | Yes | - |
| 13 | Yes | 7 | 10 | 7 | - | Yes | - |
| 14 | Yes | 4 | 5 | 4 | - | Yes | - |
| 15 | Yes | 7 | 6 | 4 | - | Yes | - |
| 16 | Yes | 7 | 39 | 7 | Yes | - | Yes |
| 17 | Yes | 9 | 3 | 5 | - | Yes | - |
| 18 | Yes | 3 | 5 | 5 | - | Yes | Yes |



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**Table 3: Parameters of contact heat-evoked potentials (CHEPs) and sympathetic skin response (SSR) after contact heat stimulation at the thigh shown for the three STT lesion classifications.** Parameters are reported as median ± IQR. Mann-Whitney U tests were performed to compare incomplete and discomplete STT lesions. Statistical significance at $p < 0.05$ is shown in bold. Abbreviations: NRS, numeric rating scale; STT, spinothalamic tract.

| | **Incomplete STT lesion** | **Discomplete STT lesion** | **Complete STT lesion** | **p value** |
|---|---|---|---|---|
| Contact heat pain rating [NRS] | 3.7 (2.6-6.7) | - | - | - |
| CHEPs N2P2 amplitude [µV] | 20.5 (10.4-27.7) | 18.6 (11.4-23.3) | - | 0.971 |
| CHEPs N2 latency [ms] | 352 (321-356) | 452 (441-489) | - | **0.012** |
| SSR peak-to-peak amplitude [µV] | 1761 (1157-1985) | 906 (604-1242) | - | **0.037** |
| SSR latency [s] | 1.92 (1.82-2.04) | 1.95 (1.92-1.99) | - | 0.5 |



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**Table 4: Spinothalamic tract (STT) lesion severity and pain characteristics.** According to clinical and electrophysiological measures, the STT lesion completeness could be classified into three groups: incomplete, discomplete and complete. Parameters are reported as percentage or median ± IQR. Abbreviation: NRS, numeric rating scale.

| STT lesion | Spontaneous neuropathic pain | Pain extent [# of body areas] | Pain intensity [NRS] | Allodynia |
|---|---|---|---|---|
| **Incomplete** (n=13) | 8 (=62%) | 6.5 [5.0-7.0] | 4.8 [3.4-7.0] | 7 (=54%) |
| **Discomplete** (n=8) | 4 (=50%) | 4.5 [3.8-5.5] | 7.0 [6.0-7.2] | 1 (=13%) |
| **Complete** (n=11) | 6 (=55%) | 5.0 [2.5-6.8] | 5.0 [3.6-7.5] | 2 (=18%) |



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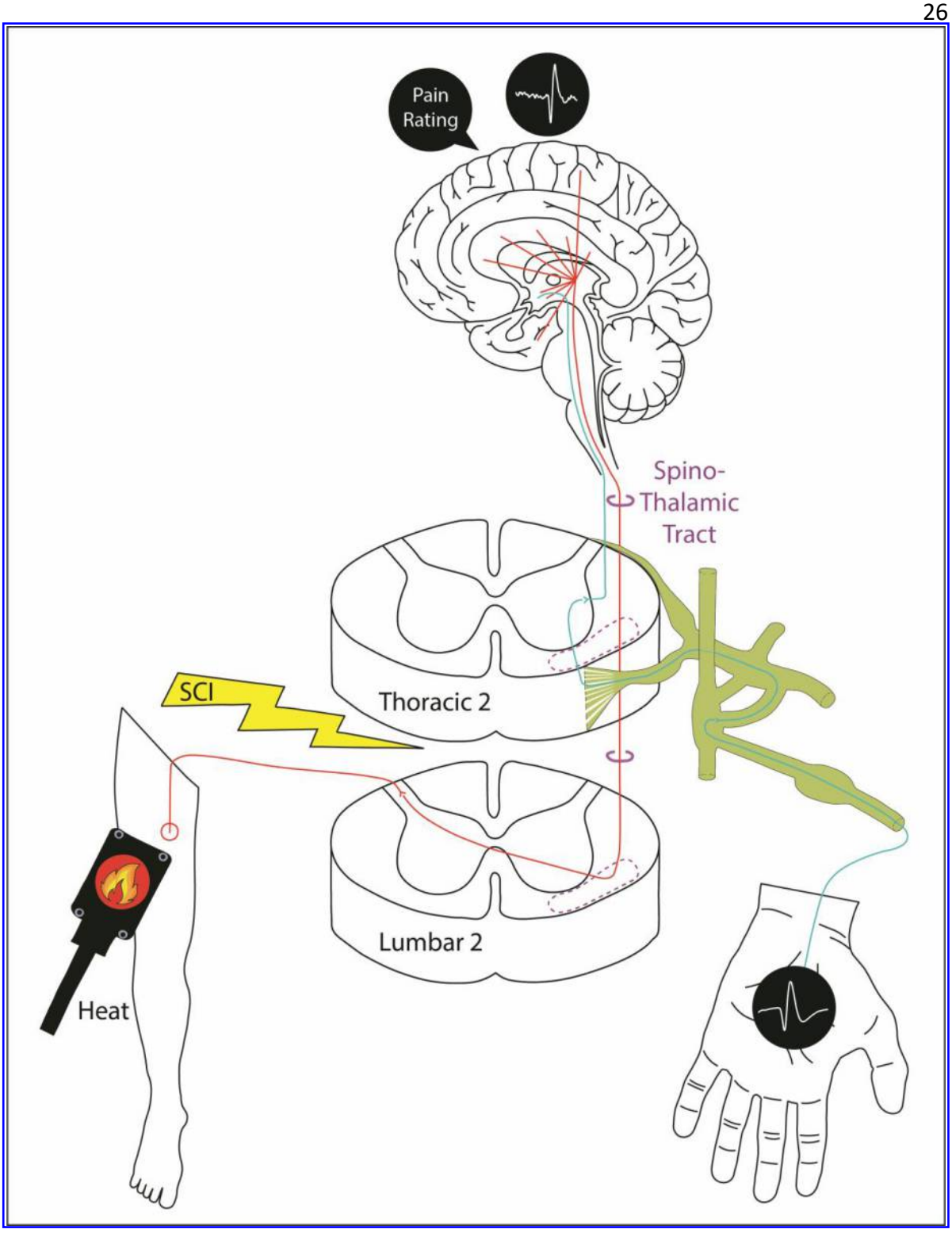


**Figure 1: Schematic drawing of neuroanatomical pathways of electrophysiological readouts to noxious heat application below a spinal cord injury.** Contact heat stimuli were applied to the right thigh. The peripheral nociceptive neurons synapse to the second-order neurons of the nociceptive neuraxis (red) at the corresponding L2 and adjacent spinal levels (Lissauer's tract, not shown). These neurons cross the midline of the spinal

cord and comprise the STT (purple). Activation of thalamic nuceli is relayed to multiple brain regions of the pain matrix as well as autonomic centers, e.g., hypothalamus. Pain rating was noted as a subjective readout, while CHEPs and SSRs were recorded as objective readouts of the noxious heat stimuli. Autonomic efferent control (blue) includes spinal sympathetic preganglionic neurons (high thoracic level), the paravertebral chain and postganglionic neurons innervating the specific effector organ, i.e., eccrine sweat glands of the hand. Abbreviations: CHEPs, contact heat-evoked potentials; SCI, spinal cord injury; SSRs, sympathetic skin responses; STT, spinothalamic tract.

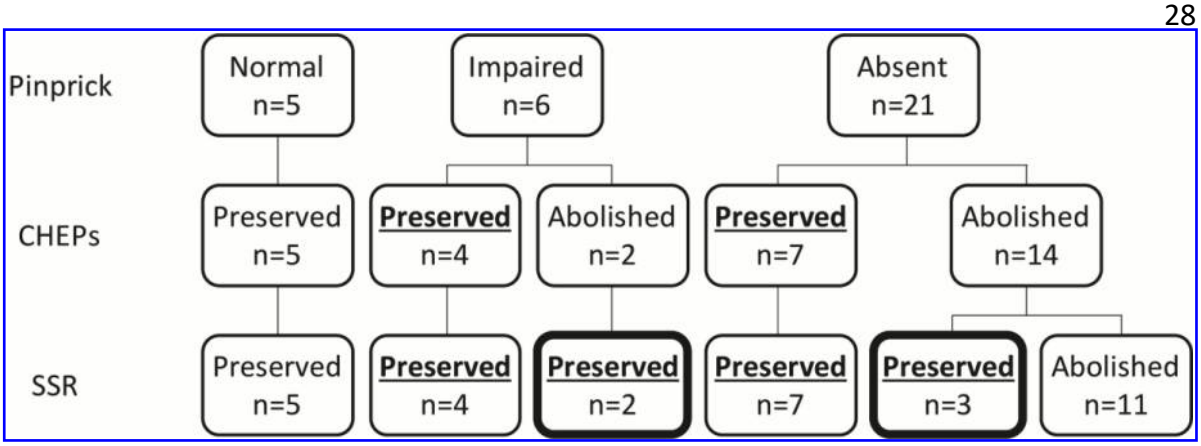


**Figure 2: Flow chart of pinprick sensation (subjective) and electrophysiological (objective) readouts of spinothalamic tract (STT) function (n=32).** Summary of pinprick testing (pinprick score: normal = 2, impaired = 1, absent = 0) and recordable CHEPs as well as concomitant pain-autonomic interaction, i.e., SSR. Improved assessment of residual STT function employing SSR are highlighted in bold. Abbreviations: CHEPs, contact heat-evoked potentials; SSR, sympathetic skin response.



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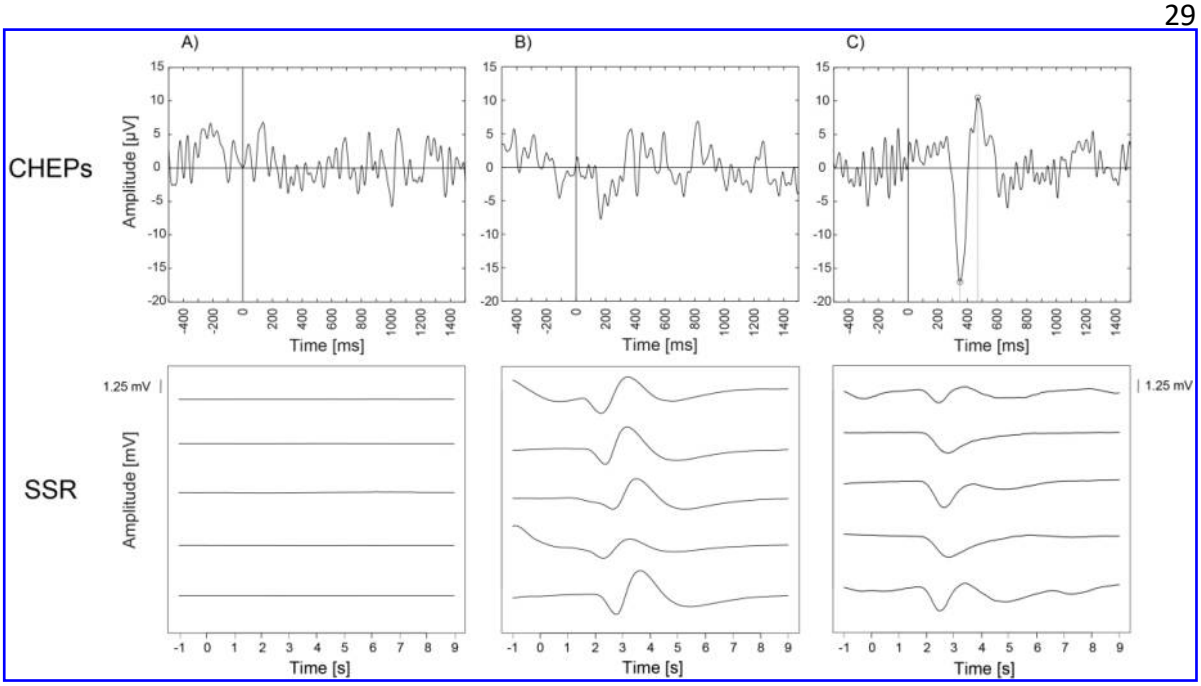


**Figure 3: Representative examples of contact heat-evoked potentials (CHEPs) and simultaneous palmar sympathetic skin response (SSR) recordings in paraplegic subjects.** A) Abolished CHEPs and SSR accompanied by a pinprick score of 0 and a contact heat pain rating of NRS 0. B) Pinprick score of 0, contact heat pain rating of 0 NRS, abolished CHEPs but preserved SSR. C) CHEPs and SSR preserved, accompanied by a pinrick score of 2 and a contact heat pain rating of 3.9 NRS. Abbreviation: NRS, numeric rating scale.



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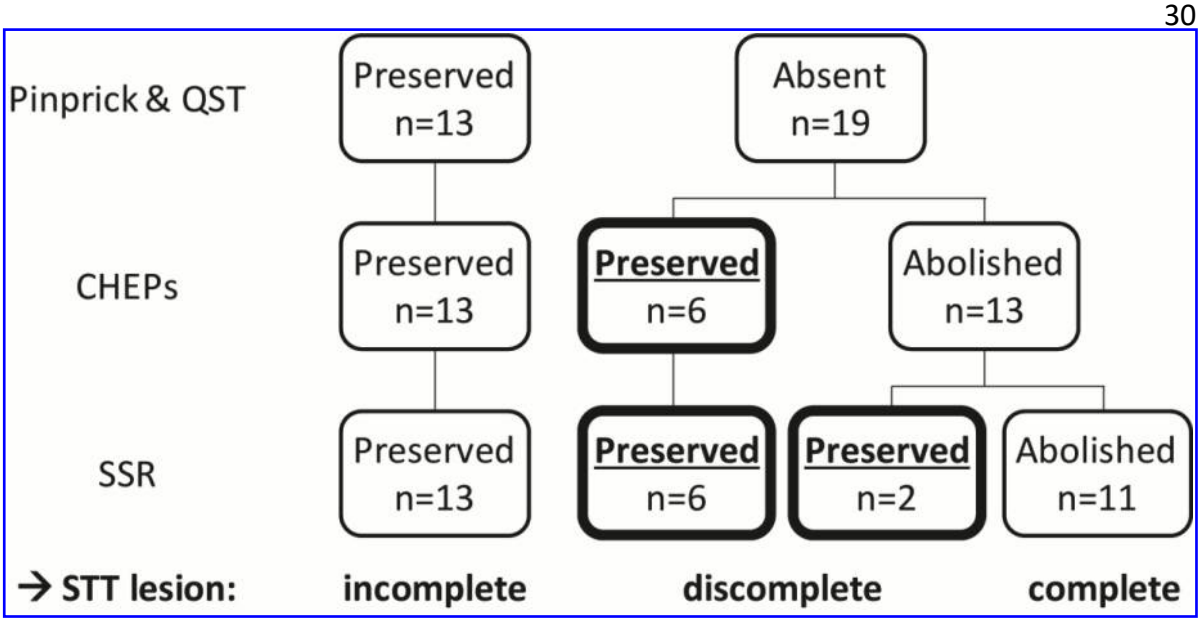


**Figure 4: Flow chart for the classification of STT (spinothalamic tract) lesions into incomplete, discomplete and complete subgroups via clinical assessments of STT function (pinprick and thermosensation).** Discordant findings between clinical and electrophysiological measures are highlighted in bold. A total of eight SCI subjects presented with a discomplete STT lesion. Abbreviations: CHEPs, contact heat-evoked potentials; QST, quantitative sensory testing; SSR, sympathetic skin response.



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