Decreased Spinothalamic and Dorsal Column Medial Lemniscus-Mediated Function Is Associated with Neuropathic Pain after Spinal Cord Injury

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Abstract

Neuropathic pain (NP) after spinal cord injury (SCI) can significantly and negatively affect quality of life and is often refractory to currently available treatments. In order to find more effective therapeutic avenues, it would be helpful to identify the primary underlying pathophysiological mechanisms in each individual. The aim of the present study was to assess the relationship between the presence and severity of NP after SCI and measures of somatosensory function mediated via the dorsal column medial lemniscal (DCML) pathway and the spinothalamic tract (STT). Vibratory, mechanical, thermal, and pain thresholds measured in areas at and below the neurological level of injury (LOI) in persons with SCI and NP (SCI-NP, $n=47$) and in persons with SCI without NP (SCI-noNP, $n=18$) were normalized to data obtained from able-bodied pain-free control subjects (A-B, $n=30$). STT-mediated function at and below the LOI was significantly impaired in both SCI groups compared with A-B controls ($p<0.001$), but not significantly different between the two SCI groups (NP vs. no-NP). In contrast, the SCI-NP group had significantly greater impairment of DCML-mediated function at the LOI, as reflected by greater vibratory detection deficits ($z = -3.89 \pm 0.5$), compared with the SCI-noNP group ($z = -1.95 \pm 0.7$, $p=0.034$). Within the SCI-NP group, NP severity was significantly associated with increased thermal sensitivity below the LOI ($r=0.50$, $p=0.038$). Our results suggest that both impaired STT and DCML-mediated function are necessary for the development of NP after SCI. However, within the SCI-NP group, greater NP severity was associated with greater sensitivity to thermal stimuli below the LOI. This finding concurs with other studies suggesting that STT damage with some sparing is associated with NP.

Key words: NP; pain measurement; pain threshold; sensory thresholds; SCI

Introduction

AFTER A SPINAL CORD INJURY (SCI) most individuals develop chronic pain, which can be debilitating and decrease a person's life satisfaction and quality of life.^{1,2} The pain conditions associated with SCI are usually classified into musculoskeletal, visceral, and neuropathic categories at and/or below the level of injury.³ Neuropathic pain (NP) types associated with SCI are especially refractory to currently available treatments.^{4–6} Therefore, if the primary pain-generating mechanisms in a person could be identified, it could potentially result in better pain management, by tailoring treatments to underlying mechanisms. Unfortunately, the identification of specific underlying mechanisms of NP after SCI

has been difficult, as the relationship among these mechanisms and clinical signs and symptoms has not been clearly defined.

One approach used to further mechanism-based clinical research includes the investigation of the relationship between NP and somatosensory status after SCI. These studies have been inconclusive regarding the function of specific sensory pathways and their relationship to NP.^{7–11} Whereas the literature seems to agree that spinothalamic tract (STT) damage is necessary for the development of NP after SCI,^{7–11} the role of the dorsal column medial lemniscal (DCML) pathway is less clear. Beric and colleagues⁷ found a relative preservation of DCML-mediated function in combination with decreased STT function in persons with SCI and NP. In contrast, Eide et al.,⁸ found significantly decreased sensitivity to

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both thermal and mechanical stimuli but did not identify any differences in DCML or STT-mediated modalities between painful and pain-free areas in subjects with SCI and NP. Unfortunately, neither of these studies included SCI subjects without NP as controls, which may have limited the interpretation of these results. There is some support in the literature for a reduced DCML function in NP. For example, an MRI study including >100 patients with syringomyelia with and without NP, demonstrated significantly larger lesions in the dorsolateral quadrants of the spinal cord in those with pain than in pain-free individuals.¹² Recently, Zeilig et al.¹³ conducted longitudinal sensory assessments in persons with SCI over an 18 month period and reported a gradual decrease in sensitivity to thermal stimuli in combination with increased frequencies of allodynia and hyperpathia, in subjects who developed NP. These authors also found more deficits in DCML modalities (touch and graphesthesia) at the baseline assessment in those who subsequently developed pain ($n=13$) than in those who did not develop pain ($n=15$), which bordered on statistical significance ($p=0.052$ and $p=0.051$, respectively). Their findings suggest that neuronal hyperexcitability subsequent to STT damage, possibly coupled with DCML damage, precedes the development of central pain. This is consistent with previous clinical studies that have suggested that, whereas STT damage appears to be necessary for the development of NP after SCI, it is not sufficient by itself.^{9–11} The variability in test sites for sensory testing, levels of injury, and pain distribution is a factor that may explain some of the inconsistencies across studies.

Studies in other central pain conditions also demonstrate the difficulty of linking NP symptoms and signs to their underlying mechanisms. Whereas supraspinal lesions after stroke typically result in varying NP symptoms depending upon injury location, several studies have reported that thalamic lesions are associated with both STT and DCML mediated deficits and extrathalamic lesions mainly with STT-related deficits.^{14–17}

There are also discrepancies in basic research studies with respect to the roles of specific central pathways in the development of NP. Similar to human studies, results from animal studies suggest that STT damage is necessary for post-SCI NP to develop.¹⁸ Most of the discordant results concern the role of the DCML lesions. For example, some animal studies support the idea that large lesions that include both the STT and DCML pathways may be needed for the development of NP after SCI.^{19–21} Although DCML lesions were not intentional in these studies, the insertion of a gelfoam with blood into the spinal cord increased the lesion sizes to include part of the dorsal columns, and these lesions were associated with hyperalgesia to electrocutaneous stimulation. Similarly, Siddall and colleagues²² found that more damage to the central and dorsal regions of the spinal cord was significantly related to increased allodynia in rats. A study by Hoschouer et al.²³ showed that thermal sensitivity was increased in the hind paws irrespective of injury severity, and that severe spinal contusion in mice, with <2% white matter sparing within the STT area of the spinal cord, was associated with shorter latencies of response to light mechanical stimulation (i.e., mechanical allodynia). Other studies have proposed a complex relationship between these two pathways and suggest that nociceptive activity is dependent upon the convergence of afferent input from both the STT and DCML pathways.^{24,25} Similar to clinical studies, however, animal studies are not always comparable, because of methodological differences, with some studies using hyperreflexia as the primary outcome measure of changes in nociception, and others using operant behavioral testing or electrophysiological recordings.

The aim of the present study was to assess the relationship between the presence and severity of NP after SCI and measures of somatosensory function mediated via the DCML and the STT. To our knowledge, this is the first large study to use methods similar to those proposed by the German Research Network on Neuropathic Pain (DFNS) group to compare sensory function after SCI. The DFNS has published standard guidelines for quantifying sensory function data in an injured nervous system relative to normative data, with the purpose of facilitating comparisons among different pain patient populations.^{26,27} This framework makes it possible to compare sensory data between individuals with and without NP regardless of test site location and pain distribution. This data standardization procedure results in quantitative sensory testing (QST) profiles in which z -score values for all tested modalities have standard normal distributions (zero mean and one standard deviation). Z -score values outside two standard deviations (95% confidence interval [CI]) are considered abnormal and represent sensory dysfunction.^{26,27} Because of the conflicting clinical and basic research evidence regarding STT and DCML-mediated function described previously, we proposed two hypotheses: 1) significantly decreased STT-mediated function, in combination with more preserved DCML-mediated function, in areas at and below the level of injury will be associated with both the presence and severity of NP in participants with SCI; and 2) decreases in both STT and DCML-mediated function in areas at and below the level of injury will be significantly associated with both the presence and severity of NP in participants with SCI. To test our hypotheses, we compared thermal and pain detection z -score values (i.e., STT-mediated function) and vibratory and mechanical detection (MD) z -score values (i.e., DCML-mediated function) in persons with and without NP pain after SCI standardized to matched able-bodied control subjects as described by the DFNS.^{26,27}

Methods

SCI participants

Individuals with SCI and NP (SCI-NP) and individuals with SCI with no NP (SCI-noNP) were recruited through advertisements posted at the Miami Department of Veterans Affairs (VA) Medical Center and the University of Miami medical campus, including The Miami Project to Cure Paralysis, and by word of mouth. Potential subjects were screened over the telephone or in person to confirm study eligibility. Participants had to be >18 years of age; be fluent in English; have experienced a traumatic SCI at least 1 year before study participation; have an injury above the conus medullaris; and have no prior history of drug abuse, major psychiatric disorders, cognitive deficits, or signs of brain damage on MRI. A physical examination by a board-certified SCI neurologist was performed to exclude individuals with known damage to the cauda equina, brachial plexus, or peripheral nerve. The International Association for the Study of Pain (IASP) SCI pain taxonomy³ was used, in combination with a pain history assessment and physical examination, to determine the presence/absence of central neuropathic pain. Participants in the neuropathic pain group (SCI-NP) must have experienced neuropathic-like pain for at least the past 3 months and rated their pain on average as ≥ 4 on a 0–10 numerical rating scale (NRS). Based on the IASP taxonomy,³ neuropathic pain was present if participants endorsed the descriptors sharp, shooting, burning, and/or electric in areas of sensory disturbance with increased or decreased sensibility (hyperesthesia, hyperalgesia).³ Participants in the SCI-noNP group were allowed to have non-neuropathic pain described as dull, aching, and cramping, in areas of sensory preservation,³ as long as the pain was rated <4 out of 10 on the NRS.

Able-bodied (A-B) control participants

Healthy A-B participants were recruited in a similar manner as the participants with SCI. They were screened to confirm that they had no current/recent pain or health problems, had no history that may have put them at risk for neurological injuries, and were not regularly taking any prescription or over-the-counter medications (both for chronic pain and other chronic health conditions), other than on an as-needed basis.

Study protocol

The data presented in this article are part of a larger study that was approved by the Institutional Review Boards of the Miami VA Medical Center and the University of Miami-Miller School of Medicine. Subjects who met the initial study inclusion criteria were scheduled for their first study visit. After informed consent was obtained, a neurological examination was conducted for SCI participants, and a second visit was scheduled. During the second visit, demographic and health history questionnaires were administered in an interview format followed by somatosensory testing. All participants were asked to report any medications (for pain or other condition) taken regularly during the past 3 months.

Demographic and injury characteristics of participants

As part of the structured interview, participants were asked to provide information regarding demographic and injury characteristics (e.g., age at time of study, time since injury, sex, and racial and ethnic background).

American Spinal Injury Association (ASIA) Impairment Scale (AIS)

A physical examination was performed to determine neurological level of the injury (LOI). The grading of the severity of the injury was based on the ASIA impairment scale: ASIA A (no motor or sensory function in the sacral segments S4–S5) through ASIA E (normal motor and sensory function).²⁸ According to the International Standards for Neurological Classification of Spinal Cord Injury guidelines, the lowest segment with normal sensation was considered the LOI for the right and left sides. For the present study, a single neurological LOI was selected as the most rostral single level with normal sensation. “At the LOI” was defined as a band of dermatomes including the dermatome of the neurological LOI and three dermatomes below this level, and “below the LOI” was defined as the areas at least four dermatomes below the neurological LOI.²⁸

Pain evaluation

Standard pain history assessment. As part of a standard pain history assessment, participants were asked to indicate the areas where they currently experienced chronic pain and their current pain intensity using Numerical Rating Scale (NRS). Subjects indicated the location of their pain(s) using a pain drawing (Fig. 1) by shading in the location(s) of their pain on two body maps (frontal and dorsal views). The body maps used were previously described by Margolis et al.,²⁹ and recoded into the following eight principal areas: head, neck and shoulders, arms and hands, frontal torso and genitals, back, buttocks, thighs, and legs and feet.³⁰ The locations of pain using this drawing have been shown to be reliable over an 18 month period in persons with SCI and chronic pain.³¹ If a subject experienced more than one pain simultaneously, and these pains were distinguishable from each other, the subject was asked to identify his/her worst pain, which was later classified according to the IASP taxonomy.³

Neuropathic Pain Symptom Inventory (NPSI). The NPSI³² assesses severity of symptoms commonly associated with neuro-

FIG. 1. Pain drawing showing the frequency of “worst” pain location in the SCI-NP participants (people with spinal cord injury and neuropathic pain; $n = 47$).

pathic pain types. It includes severity ratings (from 0 to 10) of multiple descriptive adjectives reflecting five dimensions of neuropathic pain symptomatology: 1) burning superficial spontaneous pain; 2) pressing deep spontaneous pain described as pressure and squeezing pain; 3) paroxysmal pain described as electric shock and stabbing pain; 4) evoked pain described as pain evoked from brushing, pressure or contact with something cold; and 5) paraesthesias/dysesthesias described as tingling and pins and needles.³² A total score is calculated by adding the five subscale scores, with higher scores reflecting more severe neuropathic pain symptoms.

QST

QST was used to assess the functional properties of somatosensory pathways, similar to the methodology previously reported by our group.³³ All QST procedures were performed in a quiet room with an approximate temperature between 21°C and 23°C. Control subjects were seated in a comfortable chair with armrests and a semi-reclining back. Subjects with SCI were tested in their own wheelchair. Standardized test sites were identified based on anatomical landmarks to ensure that the same site could be accurately located in each person. A rating of current pain intensity (on a 0–10 NRS, with 0 = “no pain” and 10 = “most intense pain imaginable”) was recorded just before testing commenced.

An overview of the testing procedures was then read to the subject. For each different modality, specific instructions were read immediately before beginning the test. Measurement of a particular type of threshold was first demonstrated, and at least two practice trials were conducted on the subject’s left cheek to ensure that subjects understood the testing procedures.

After the practice trials were completed, the data collection began for each test modality. Measurements of mechanical detection (MD) thresholds were recorded at each test site first, followed by measurements of vibratory detection (VD) thresholds and thermal thresholds (cool detection thresholds, warm detection thresholds, cold pain thresholds, and hot pain thresholds). Skin surface temperature was measured at each site with a Raytek MiniTemp noncontact thermometer (Raytek Corporation, Santa

Cruz, CA) immediately before thermal threshold measurements commenced, to ensure temperature was within the range of 27–37°C. QST thresholds have been reported to be independent of skin temperature within this range.³⁴ In order to keep skin temperature within this ideal temperature range, skin test sites on distal extremities were covered with blankets between modality testing trials when necessary. Vibrotactile and thermal threshold measurements were obtained with the TSA-II Neurosensory Analyzer and accompanying software (Medoc Ltd., Ramat Yishai, Israel).

For each stimulus type (mechanical, vibration, thermal), the first measurements were taken at the subject's right cheek and testing progressed to more caudal sites. By proceeding in this manner, subjects with SCI could compare the quality of the sensation evoked by each test stimulus in areas at and below the level of injury (LOI) to the quality evoked at the cheek, an area above the LOI where sensation was expected to be within normal limits. For measures obtained with the TSA-II (vibration, thermal detection, and thermal pain thresholds), all SCI and A-B control subjects orally responded when the threshold was reached, and the experimenter immediately pressed a button to stop the stimulus trial and record the threshold. Although this method of response caused an increase in reaction time and, thereby, slightly higher threshold values, it was necessary to accommodate participants with upper limb impairment and was used across all subject groups (SCI and A-B controls) to ensure consistency. Additional steps were taken to minimize potential sources of bias during the testing. First, the same research assistant worked on the computer and pressed the button for all subjects tested, including SCI and healthy controls. This allowed a similar reaction time artifact across all subject groups. Second, the research assistant was blinded to the study hypotheses and had no knowledge of our analysis plan.

Test sites. Standard body sites were chosen for testing in our sample of healthy, A-B control subjects and the SCI-noNP control participants as previously reported.³³ These standard sites were selected to be distributed no more than four dermatomes from another standard test site. SCI-NP subjects were tested at and below the LOI based on each individual's LOI and pain distribution, to include sites where chronic neuropathic pain was present.

DCML mediated function: Mechanical detection (MD). A standard set of Semmes–Weinstein monofilaments (Touch Test™ Sensory Evaluator, North Coast Medical, Inc., Morgan Hill, CA) was used to measure MD. Subjects were instructed to close their eyes during this portion of the testing and to respond with a “yes” if they could feel the test stimulus when it was delivered or with a “no” if they could not feel the stimulus. Four stimulus series were performed at each site according to the method of limits. For each of the two descending series, an average was calculated using the force for the last monofilament that was detected and the force for the first monofilament that was not detected. For each of the two ascending series, an average was calculated using the force for the last monofilament that was not detected and the force for the first monofilament that was detected. “Catch trials” were performed periodically at each site by making the motion of applying a monofilament but without actually touching the skin in order to document the participant's bias. Threshold values obtained at test sites in which a subject reported a sensation during a catch trial were eliminated from analysis. On series during which the lowest force was detected (0.008g), this value was taken as threshold for that series. On series in which the highest force (300g) was not detected, this ceiling value was recorded as threshold. Threshold values for MD at each test site were defined as the arithmetic mean of the values obtained during the four stimulus series.

DCML mediated function: vibratory detection (VD). The handheld VSA-3000 probe of the Medoc system was used to

measure VD thresholds for a 100 Hz stimulus frequency. Subjects were read a standard set of instructions that informed them to indicate as soon as they felt the vibratory sensation. The probe's circular contact tip (1.22 cm²) was held in place by the experimenter during testing so that there was a slight and maintained indentation of ~1–2 mm. Stimulus presentations were programmed with the software accompanying the vibratory equipment to control the rise rate of stimulus amplitude, the number of trials, and the time between each trial. Three trials, separated by ~10 sec each, were conducted using the ascending method of limits: vibratory amplitude began at 0 μ m at a rate of 0.5 μ m/sec and increased until the subject indicated that the stimulus was felt or until the maximum amplitude of 130 μ m was reached. Subjects were asked to indicate the “first moment” that they felt the vibration at the test site. The mean value across the three trials was calculated as the vibratory threshold for each site.

STT-mediated function: cool and warm detection (CD and WD). The method of limits was used to obtain measures of cool and warm detection thresholds. A 1.6 $\times$ 1.6 cm thermode connected to the TSA-II Neurosensory Analyzer was used to deliver thermal stimuli. The experimenter held the thermode firmly against the skin with light pressure during all thermal testing procedures. Each trial began with the thermode temperature set at 32°C. Once the trial began, the temperature decreased (for CD) or increased (for WD) at a rate of 1°C/sec until the subject perceived the stimulus or until the stimulus reached the cutoff value (0°C for CD and 50°C for WD). Each trial was separated by ~10 sec. After four CD trials were completed, four WD trials were conducted in the same manner. The average of threshold temperatures across the four trials was calculated as threshold for each modality and site.

STT-mediated function: cold and hot pain detection (CP and HP). The method of limits was also used to determine CP and HP thresholds using the same equipment and in a similar manner as the CD and WD thresholds. Subjects were read a standard set of instructions that informed them to indicate as soon as the sensation changed from “just being cold to being *painfully* cold” or from “just being hot to being *painfully* hot.” Each trial began at 32°C and was either decreased (CP) or increased (HP) at a rate of 1.5°C/sec until pain threshold was reached or the cutoff value was reached (0°C for CP and 50°C for HP). Each trial was separated from the next by at least 20 sec. The arithmetic mean across three trials at each test site was calculated as the pain detection threshold.

QST data evaluation

Data were entered by one experimenter and checked for accuracy by a different experimenter. QST data were processed and analyzed according to the methods described by the DFNS group.^{26,27} For test sites where no sensation was reported even at the programmed device cut-off values, the ceiling/floor value for that modality was recorded as the threshold.

All QST data were analyzed for their distribution properties. We calculated skewness, kurtosis, Kolmogorov–Smirnov's *d* for raw data, and log-transformed data. The product of the geometric mean of skewness and kurtosis combined and the geometric mean of Kolmogorov–Smirnov's *d* (for continuous test of normality of distribution) was calculated as a compound measure of goodness of normality. When the ratio of the raw data to log-transformed data exceeded a factor of 3, then the log transformation was considered to be more appropriate for the data analysis in order to meet the assumptions of parametric statistical inference procedures.^{26,27}

Z-transformation of QST data

In order to compare the SCI participant's QST data (SCI-NP vs. SCI-noNP participants) independent of the different units of

measurement across QST parameters, and the location tested relative to the person's LOI, pain area, and body region sensitivity, the data were z -transformed and therefore normalized to the A-B data for each QST parameter by using the formula described by Rolke et al.^{26,27}:

$$Z\text{-score} = (X_{\text{single subject}} - \text{Mean}_{\text{A-B controls}}) / \text{SD}_{\text{A-B controls}}$$

This procedure provided a QST profile in which all parameters were presented as standard normal distributions (with the A-B controls having zero mean and one standard deviation) and eliminated differences resulting from test site location.^{26,27} Similar to the Rolke et al.^{26,27} studies, we adjusted the algebraic signs of the z -score values to reflect the person's sensitivity for each sensory test modality. According to this transformation, z -score values >0 indicated a gain of function (i.e., greater sensitivity to the test stimuli) compared with normative data, whereas z -score values <0 indicated a loss of function (i.e., lower sensitivity to the test stimuli). Accordingly, negative z -score values corresponded to increased thresholds. After the z -transformation, it could be determined whether one single subject's data fell within the normative range by comparing that subject's value to the normative group mean with the 95% confidence interval (CI) of a standard normal distribution defined as follows:

$$95\% \text{ CI} = \text{Mean}_{\text{A-B controls}} \pm 1.96\text{SD}_{\text{A-B controls}}$$

For the present investigation, any z -score value that fell between the values $+1.96$ and -1.96 was considered to have "normal" sensory function comparable to 95% of the values of the A-B control subjects (i.e., normative range).

Statistical analysis

In a previous study by our group in persons with NP and SCI, there was a significant degree of multicollinearity ($r > 0.70$) between the CD-WD and the CP-HP z -score values.³³ Therefore, the strength of the relationships between the CD-WD and the CP-HP z -score values in the present study were examined using Pearson product-moment correlations. For any pair of z -score values that had a correlation coefficient >0.70 , the two modalities were combined into a new score by calculating the average of the two z -score values. These averaged values were used in all further statistical analyses. The combination of warm and cold modalities is appropriate based on the physiological properties of sensory channels, as cold and warm stimuli are transmitted via A δ and C fibers. These fibers terminate primarily in laminae I, II, and V and ascend via the STT. Similarly, nociceptive information from cutaneous A δ and C fibers send information via wide dynamic range neurons and nociceptive specific neurons and also ascend within the STT.³⁵

Statistical techniques included ANOVA and/or Kruskal-Wallis tests to compare groups with respect to continuous/discrete ordinal variables and χ^2 analyses to assess associations between nominal variables. Group comparisons on the repeated site measurements were performed by fitting a linear mixed models procedure using the PROC MIXED statement in SAS. Restricted/residual maximum likelihood (REML) estimation and a compound symmetry covariance structure were used to specify models that accounted for QST z -score values in multiple sites within one individual, while taking into consideration the location of test sites relative to level of injury (at or below the level of injury) and the participant's pain status (NP or noNP). Multiple comparisons were adjusted using the Bonferroni correction method unless otherwise stated, and $p < 0.05$ was considered statistically significant. Data analyses were performed by using SAS 9.2 software (SAS Institute, Cary, NC).

Results

Demographic and pain data

Forty-seven individuals with SCI and NP (SCI-NP), 18 persons with SCI without NP (SCI-noNP) and 30 able-bodied (A-B) control subjects met our inclusion criteria and completed the study. The participants' demographic data are shown in Table 1. The groups were not significantly different with respect to sex, age, race and ethnicity, and time since injury (for the SCI groups). A greater proportion of the SCI-noNP group had complete injuries (77.8%) compared with the SCI-NP group (51.1%), but this was not a statistically significant difference.

In order to confirm the difference in pain status on the day of testing, the NPSI and current pain intensity were compared among the groups. The SCI-NP group scored significantly higher on the NPSI and pain intensity (NPSI = 33.0 ± 17.2 , NRS = 4.8 ± 2.7) compared with the SCI-noNP group (NPSI = 6.6 ± 11.2 , NRS = 0.1 ± 0.5 , $p < 0.001$). Most (76%) SCI-NP participants experienced central neuropathic pains below the LOI in addition to other pain types. Other subjects with NP (24%) located in areas within the three dermatomes around the LOI were also likely exhibiting central NP, as subjects with peripheral nerve injuries (i.e., cauda equina, brachial plexus injury) were excluded from the study based on the physical examination. Most of the SCI-NP participants' (43/47 = 91.5%) "worst" pain was classified as neuropathic according to the IASP taxonomy.³ The most common location for the "worst" pain was the legs and feet area (19/47 = 40.4%) and this pain was most commonly described as sharp or burning (22/47 = 46.8%) (Fig. 1). The majority of worst pains were located in areas below the LOI (32/47 = 68.1%).

QST data

The distribution properties of threshold measures for each stimulus modality were assessed in the A-B control subjects to determine

TABLE 1. DEMOGRAPHIC AND INJURY CHARACTERISTICS OF STUDY PARTICIPANTS (N=95)

	SCI-noNP (n=18)	SCI-NP (n=47)	A-B (n=30)	p
Age,^a Mean$\pm$SD	36.78 $\pm$ 11.0	39.8 $\pm$ 12.9	33.4 $\pm$ 8.1	0.060
Time since injury^b (yrs.) Mean$\pm$SD	16.22 $\pm$ 9.4	11.4 $\pm$ 9.5	NA	0.071
Sex,^c n (%)				
Men	14 (77.8)	38 (80.9)	22 (73.3)	0.740
Women	4 (22.2)	9 (19.1)	8 (26.7)	
Ethnicity/race,^c n (%)				
White non-Hispanic	6 (33.3)	17 (36.0)	7 (23.3)	0.188
Hispanic	9 (50.0)	22 (46.8)	16 (53.3)	
African American	3 (16.7)	8 (17.0)	3 (10.0)	
Other	0 (0)	0 (0)	4 (13.3)	
Neurological level of injury,^d n (%)				
ASIA A Complete	14 (77.8)	24 (51.1)	NA	0.090
ASIA B Incomplete	1 (7.1)	7 (14.9)		
ASIA C Incomplete	2 (11.1)	6 (12.8)		
ASIA D Incomplete	0 (0)	10 (21.3)		

^aOne-way ANOVA.

^bWilcoxon-Mann-Whitney test.

^cChi-square test.

^dFisher Exact test.

SCI, spinal cord injury; NP, neuropathic pain; ASIA, American Spinal Injury Association.

whether transformation was needed to better approximate a normal distribution, using the methods described by Rolke et al.²⁷ The skewness, kurtosis, and Kolmogorov-Smirnov *d* statistics for the raw thresholds and for the log-transformed threshold values at each standard test site can be found in the supplementary materials section. The MD, VD, CD, and WD measures had ratios of the raw data to log-transformed data that exceeded 3, suggesting that a log transformation was more appropriate for meeting the assumptions of parametric statistical inference procedures, and therefore for further data analysis. We used the raw data when performing statistical analyses for the CP and HP measures. This is similar to the transformations necessary for the different test modalities reported by the DFNS group,²⁷ and in our previous article.³³

Pearson correlations between the CD-WD and the CP-HP *z*-score values were examined before applying inferential statistical techniques. Similar to the previous findings,³³ there were high and significant correlations between the CD and WD ($r=0.73$, $p=0.001$) and CP and HP ($r=0.71$, $p=0.001$). To account for the covariance between these measures, an average thermal detection (ATD) scale was constructed by calculating the mean of the CD and WD *z*-score values for each test site in each subject. The ATD scale had excellent internal consistency (Cronbach's $\alpha=0.85$), supporting the use of the combined scale over the individual variables. Likewise, the CP and HP *z*-score values were averaged into an average pain detection (APD) scale, which had a high internal consistency (Cronbach's $\alpha=0.73$). The ADT and APD were used for further analysis. Somatosensory function *z*-score values at and below the LOI for the SCI participants are summarized in Table 2.

STT mediated function: ATD. The mean ATD *z*-score values for the SCI participants were outside the A-B control range and significantly different from the A-B *z*-score values ($p<0.001$). As expected, SCI subjects had significant thermal detection deficits compared to the A-B control subjects. There was no statistically significant interaction effect on the ADT *z*-score values, based on the participant's pain status (SCI-NP or SCI-noNP) depending upon the test site location relative to the LOI (at or below the LOI),

$F=0.3$, $p=0.610$ (Fig. 2). There was a statistically significant main effect of test site location relative to the LOI, $F=9.0$, $p=0.006$, with sites tested at the LOI having significantly fewer deficits ($z\text{-score} = -2.0 \pm 0.2$) than sites tested below the LOI (-2.8 ± 0.1 , $p=0.006$). There was not a statistically significant main effect of pain status on ADT *z*-score values, $F=1.3$, $p=0.255$.

STT mediated function: APD. The mean APD *z*-score values were within the A-B control range for all SCI participants, regardless of pain status. However, the mean APD *z*-score values for SCI participants were significantly lower than the APD values for the A-B control subjects ($p<0.001$). There was no statistically significant interaction effect on APD *z*-score values based on the participant's pain status (SCI-NP or SCI-noNP) depending upon the test site location relative to the LOI (at or below the LOI), $F=0.0$, $p=0.963$, (Fig. 2). There was a statistically significant main effect of test site location relative to LOI, $F=8.5$, $p=0.008$, with sites tested at the LOI having significantly less deficits ($z\text{-score} = -0.6 \pm 0.1$) than sites tested below the LOI (-0.9 ± 0.1 , $p=0.008$). There was not a statistically significant main effect of pain status on ADT *z*-score values, $F=0.3$, $p=0.579$.

DCML mediated function:VD. For the SCI-noNP subjects, the mean VD *z*-score values were within the normative range for test sites at the LOI, but outside the normative range below the LOI. For the SCI-NP participants, VD *z*-score values were outside the normative range for both at- and below-level test sites. In addition, VD *z*-score values in SCI participants were significantly different from those in the A-B control subjects ($p<0.001$). As expected, SCI subjects (both SCI-NP and SCI-noNP groups combined) had significant VD deficits compared with the A-B control subjects.

VD was significantly related to the location of the test site relative to the LOI (at or below the LOI) depending upon the participant's pain status (interaction effect: $F=6.6$, $p=0.016$). *Post-hoc* analysis showed that sites tested at the LOI in SCI-NP participants had significantly more vibratory sensory deficits ($z = -3.9 \pm 0.5$) than did the test sites in SCI-noNP participants ($z = -1.9 \pm 0.7$), $p=0.034$, (Fig. 2). However, there were no statistically significant differences in vibratory detection between the SCI-NP and SCI-noNP groups on sites tested below the LOI, $p=0.535$.

DCML mediated function: MD. The mean mechanical detection *z*-score values were within the normative range in the SCI-noNP participants in test sites at the LOI, but outside the A-B control range for test sites located below the LOI. The SCI-NP participants had mean mechanical detection *z*-score values outside the normative range at and below the LOI. As expected, SCI subjects had significant mechanical detection deficits compared with the A-B control subjects ($p<0.001$).

MD was not influenced by the participant's pain status relative to the test site location relative to the LOI (at or below the LOI), interaction effect: $F=1.9$, $p=0.179$. Although not statistically significant, there were relatively greater tactile deficits at the LOI in SCI-NP subjects ($z = -2.7 \pm 0.4$) than in SCI-noNP subjects ($z = -1.9 \pm 0.7$, $p=0.167$), (Fig. 2). There were statistically significant differences in MD *z*-score values between sites located at and below the LOI, main effect: $F=61.3$, $p<0.001$, showing a greater degree of MD deficits in sites below the LOI than in those at the LOI.

Comparison of somatosensory function for the SCI participants in the STT and DCML mediated modalities at the LOI are represented graphically in Figure 2.

TABLE 2. SENSORY MEASURE Z-SCORE VALUES IN THE SCI PARTICIPANTS (N=65)

	SCI-NP (n=47)	Within A-B range? ^a	SCI-noNP (n=18)	Within A-B range? ^a	p
VD					
At	-3.89±0.5	No	-1.95±0.7	Yes	0.034
Below	-3.99±0.4	No	-4.48±0.4	No	0.535
MD					
At	-2.69±0.4	No	-1.92±0.7	Yes	0.167
Below	-5.89±0.4	No	-6.15±0.5	No	0.377
ATD					
At	-1.98±0.3	No	-2.17±0.3	No	0.663
Below	-2.58±0.2	No	-3.02±0.2	No	0.125
APD					
At	-0.50±0.2	Yes	-0.59±0.2	Yes	0.718
Below	-0.87±0.1	Yes	-0.97±0.1	Yes	0.561

^aYes=value falls within the 2 standard deviations of the A-B values (-1.96 to +1.96).

A-B, able-bodied pain-free control subjects; SCI, spinal cord injury; NP, neuropathic pain; VD, vibratory detection; mechanical detection; ATD, average thermal detection; APD, average pain detection.

FIG. 2. Z-score values at the level of injury for the spinal cord injury (SCI) participants ($n=65$). NP, neuropathic pain.

Relationship between neuropathic pain severity and sensory function

Immediately before each sensory testing session, SCI subjects were interviewed regarding the severity of their NP symptoms present within the last 24 h using the NPSI. Pearson product-moment correlations were used to examine the relationship between NP severity, as reflected by the total score on the NPSI, and sensory function in painful sites within the worst NP area, as reflected by the ATD, APD, VD, and MD z-score values in the SCI-NP participants. NPSI sum scores were not significantly related to VD, MD, or APD z-score values. The NPSI sum score was significantly correlated with the ATD z-score values in the worst pain sites located below the LOI ($r=0.50$, $p=0.038$, $n=32$, Fig. 3), but not for pain sites located at the LOI ($r=0.04$, $p=0.912$, $n=12$), signifying that the more severe NP symptoms a person had, the more sensitive that person was to innocuous thermal stimuli below the LOI. NPSI severity was not significantly correlated with the APD z-score values at the LOI ($r=0.45$, $p=0.140$, $n=12$), or below the LOI ($r=0.21$, $p=0.286$, $n=32$). Because of the significant relationship between the NPSI total score and ATD z-score values below the LOI, we further explored this relationship with each subscale of the NPSI. We found that the paroxysmal pain, ($r=0.40$, $p=0.032$), evoked pain ($r=0.41$, $p=0.026$), and paraesthesia/dysesthesia ($r=0.37$, $p=0.049$) NPSI subscales were significantly independently correlated with the ATD

z-score, but none were statistically significant after adjusting for multiple comparisons.

Discussion

To our knowledge, this is the first large study in SCI using the guidelines from the DFNS as a basis for the comparison of sensory function after SCI in persons with and without NP. The heterogeneity of the pain conditions after SCI makes this approach useful by allowing a direct comparison of multiple test sites without the confounding effects of differences in pain distribution and test site location relative to an individual's level of injury.

The present study showed that both the SCI-NP and the SCI-noNP groups had significant STT and DCML-mediated deficits, whereas persons with SCI-NP had significantly more deficits in DCML (vibratory) mediated function at the LOI than did persons in the SCI-noNP group. These findings support our alternate hypothesis that deficits in both DCML and STT-mediated function increase the likelihood of experiencing NP after SCI. This is consistent with several basic research studies indicating that large lesions, encompassing the dorsal spinal pathways and the STT, are necessary for the development of NP signs and behaviors.^{19–21} Our results are also consistent with previous findings in persons with SCI and pain. Specifically, Finnerup and colleagues,¹⁰ observed that mean vibratory detection thresholds tended to be elevated in

FIG. 3. Relationship between Neuropathic Pain Symptom Inventory (NPSI) and thermal sensitivity in the worst pain sites located below the level of injury (LOI) ($n=32$). ATD, average thermal detection.

SCI pain patients (mean = 150 μ m) compared with SCI pain-free patients (mean = 18.8 μ m). However, this result failed to reach statistical significance, possibly because of the small sample size, with 20 in the NP group. In a follow-up study by the same group of investigators,¹¹ in which spinal damage was estimated based on MR images, the authors reported a tendency toward a larger lesion of the dorsolateral gray matter and of the dorsal columns in the SCI pain group compared with the SCI pain-free group ($p=0.068$). However, similar to their previous study, the 2007 study¹¹ did not detect statistically significant differences, presumably because of insufficient power resulting from the small samples size of 10 participants in the pain group.

An intriguing question is whether injury to the DCML pathway contributes to the development of NP. Some evidence suggests that dorsal column injury does not lead to the development of NP, as persons with selective damage to the dorsal columns do not develop pain, but only paraesthesias.³⁶ However, patients with large spinal cord lesions that included the dorsal columns have reported increased sensitivity to noxious stimuli.³⁷ Based on the anatomical organization of the somatosensory system,³⁵ damage to the dorsolateral aspect of the spinal cord potentially involves not only ascending pathways but also the disruption of endogenous descending inhibitory pathways, which may contribute to increased nociceptive activity and pain.³⁸ Recently, descending inhibition from the rostral ventromedial medulla via the dorsolateral funiculus to the dorsal horn of the spinal cord has been proposed as important in the transition from acute to chronic NP.³⁹ Thus, interruption of this endogenous pain modulatory pathway may contribute to the development of SCI-related NP.

The balance between convergent inputs from the STT and DCML may also be important for the development of pain.^{24,25} For example, the non-human primate research literature supports the idea that reduced afferent input to cortical area 3b/1 from the DCML leads to enhanced responses in cortical area 3a, which receives input from unmyelinated nociceptors.^{40–43} The reduction in the reciprocal and predominantly inhibitory intracortical interactions between areas 3a and 3b/1 proposed by Whitsel et al.,⁴³ could be a possible supraspinal mechanism contributing to neuropathic pain after SCI. Large afferent input into cortical area 3b/1 could be increased by treatments such as transcutaneous electrical nerve

stimulation and vibration, thereby producing a subsequent increase in inhibitory activity on the nociceptive-specific cortical area 3a. Future imaging studies in persons with SCI could further examine this potential mechanism.

The present study also showed that, although thermal sensitivity (reflective of STT-mediated function) was significantly decreased in both SCI groups compared with A-B controls, greater severity of NP symptoms *within* the SCI-NP group was associated with greater sensitivity to thermal stimuli (within the normative range) below the LOI. This result concurs with clinical studies in which damage to the STT by itself was not a significant predictor of NP in persons with SCI. For example, Defrin et al.⁹ and Finnerup et al.^{10,11} found substantial thermal detection deficits (i.e., STT-mediated function) in all SCI participants, and no significant differences between pain and pain-free patients. However, the relationship between greater severity of NP symptoms and greater sensitivity to thermal stimuli relative to those with less severe NP concurs with other studies suggesting that residual STT function is a mechanism contributing to severe NP after SCI.¹³ Results from the present study are consistent with our previous result in persons with SCI and NP, in which NPSI scores were significantly related to less severe deficits in STT-mediated modalities.³³ Our findings are also consistent with those from Wasner and colleagues,⁴⁴ in which only persons with SCI and NP (and not those with SCI without NP) had residual STT transmission after sensitization with three chemicals that specifically activate unmyelinated afferents (i.e., histamine, L-menthol, and capsaicin). In another study,⁴⁵ enhanced spontaneous recovery of STT function was found to be associated with the development of NP. This interpretation was based on their findings that the degree of enhanced pinprick sensation (reflective of STT-mediated function) over the first year after SCI was significantly related to the subsequent development and/or maintenance of NP and its intensity. Therefore, our results, together with other clinical studies,^{13,33,44,45} support basic research studies in SCI proposing facilitation, disinhibition, or hyperexcitability of STT neurons as potential underlying mechanisms of NP (for a recent review see Gwak and Hulsebosch⁴⁶).

Limitations

The present study has some methodological limitations. The assumption made about the specificity with which different tracts convey the various modalities is a potential limitation. Vibratory sensation has been questioned as a proper dorsal column-mediated function.^{47,48} Studies have suggested that combined lesions of dorsal and posterolateral columns are necessary to abolish the sense of vibration.^{47,48} In the present study, we were unable to determine whether the observed deficits were the result of lesions including either or both the dorsal and posterolateral columns. Furthermore, we have found that vibration threshold can be difficult to determine correctly after SCI because of the distribution of vibration stimuli beyond the testing site to more rostral areas with preserved sensation, and the presence of spontaneous or evoked sensations that may be difficult to separate from true vibration sense (unpublished observations). However, in our study, the experimenter asked our subjects to confirm that the sensation felt was of a vibratory quality for each trial, and it was located at the site of testing. In future studies, other methods, such as two-point discrimination and graphesthesia, may be used to assess DCML function.

A potential source of bias in our data was the need for a third person to press the button to respond to the stimulus. However, 54% of the study participants with SCI had a cervical LOI, consistent

with population statistics in SCI. Therefore, an approach that was consistent across all subjects, regardless of their ability to press a button, was needed. Several steps were taken to minimize this source of variability. First, the same research assistant controlled the computer and pressed the stop button for all subjects tested, including SCI and healthy controls. This allowed a similar reaction time artifact across all subject groups. Second, the research assistant was blinded to the study hypotheses and had no knowledge of our analysis plan. Therefore, our analysis and findings are not likely affected by the response procedures used in the study. Keeping this procedure consistent across all subjects significantly reduced the variability in the measurements that may otherwise have been attributed to differences in manual dexterity caused by different levels and severities of injury.

In the present study, all the pain detection z -score values were within the A-B control 95% confidence range (i.e., within z -score values of -1.96 and $+1.96$) in both groups of SCI participants. This may be the result of the normal variability in our healthy subject sample that covered the major part of the available measurement range for the nociceptive thresholds, similar to findings from studies by the DFNS.⁴⁹ The fact that STT function was statistically and significantly impaired in those with SCI compared with normative controls, but still within a “normative” range (i.e., within ± 1.96 SD), may be a limitation of applying z -score value standardization methodology to determine “normality” of pain threshold data. In general, caution should be taken when using z -scores to determine sensory “normality.” The two standard deviation cutoff as normal may be appropriate for heterogeneous NP populations, and other values may be better suited for measuring pain-specific sensory function after SCI.

Because individuals with SCI may not perceive any sensation in areas where sensory dysfunction is present, cutoff values (i.e., ceiling/floor effects) are commonly assigned for data analytic purposes. In the present study, the cutoff values used were 0°C as the lower limit and 50°C as the upper limit for thermal and pain detection. This temperature range is considered safe and has been previously used in NP states including by the DFNS group.^{26,27,44,49–51} It is possible that other temperature ranges are more appropriate for use in the SCI population. However, the most appropriate method to treat QST data obtained in test sites where sensation is absent has not been thoroughly investigated in the literature or resolved by published consensus opinion. Lastly, the present findings may only be generalizable to individuals who have experienced a traumatic SCI and have been chronically injured. The abovementioned methodological issues need to be further examined in future studies in persons with SCI.

Conclusion

In conclusion, the present study supports the hypothesis that damage to both the DCML pathway and the STT is associated with NP after SCI. However, only DCML-mediated function was significantly lower in those with NP than in those with no NP. These results, together with the significant relationship between residual thermal function and increased NP severity, suggest that extensive damage including the DCML and the STT in combination with residual STT function is associated with a greater likelihood for the development and maintenance of NP after SCI.

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