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Neuropathic Pain and Functional Reorganization in the Primary Sensorimotor Cortex After Spinal Cord Injury

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Abstract: **Refractory to most types of treatment, neuropathic pain (NP) is a major problem for people living with spinal cord injury (SCI). The underlying mechanisms among problems related to treatment are poorly understood. The aim of the present study was to investigate the association between cortical reorganization and NP after SCI. Twenty-four individuals with sensorimotor complete and incomplete paraplegia and tetraplegia (12 with NP, 13 pain free) and 31 healthy individuals were examined. Functional magnetic resonance imaging was used to assess activation in primary somatosensory and motor cortices in response to motor (ie, active and passive wrist extension) and sensory (ie, heat and brushing) tasks applied on the dorsum of the hand. In individuals with SCI, there were no group-level differences in task-related activation (ie, movement or sensory) compared with the healthy controls. However, based on the Euclidean distance measure, individuals with SCI demonstrated a lateral shift of peak activity in primary sensory and motor cortices ($P < .05$). Among those with NP, chronic pain intensity inversely correlated with the magnitude of the shift in the primary motor cortex during active wrist extension. The findings reveal that NP in motor and sensory tasks at or above the level of the lesion is not associated with increased plasticity. In line with previous studies, changes in somatotopy and activation after SCI are rather limited and the influence of NP on plasticity remains controversial.**

Perspective: ***Using functional magnetic resonance imaging, we have provided novel evidence that reorganization (i.e., topographical shifts in peak activity) in the primary motor cortex after spinal cord injury is limited to individuals without neuropathic pain.***

Key words: *Magnetic resonance imaging, plasticity, primary somatosensory cortex, primary motor cortex, tetraplegia, paraplegia, Euclidean distance.*

Neuropathic pain (NP) represents a major secondary complication for people living with spinal cord injury (SCI), negatively affecting quality of life and functional independence.[56,57] Among the difficulties related to the development of more effective interventions, the mechanisms of NP are poorly understood. One prevailing theory is that NP from below the level of neurological injury arises from maladaptive changes in the supraspinal anatomy and physiology.[9,24,44,65,66] Central to this theory is that the intensity of NP symptoms positively correlates with the extent of cortical reorganization, such that greater reorganization is observed in individuals with more severe NP.[15,65] In individuals with phantom limb pain, evidence of maladaptive plasticity has been largely demonstrated in primary sensorimotor areas after executed (contralateral to missing limb) or imagined (missing limb) movement.[35,36,39,53] Supporting maladaptive plasticity, Wrigley et al[65] recently demonstrated that greater reorganization in the primary somatosensory cortex in response to brushing was associated with more severe NP in individuals with SCI.

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Previous studies on SCI have also considered reorganization in the primary motor cortex,[11,27] although not in the context of NP (ie, the relationship between the extent of reorganization and the severity of pain symptoms). A common readout of cortical reorganization has been to measure changes in the center of gravity (CoG)[10,22] or the Euclidean distance (ED) between peak activity associated with a motor task or afferent stimulation (eg, brushing, finger tapping, etc), relative to a known (and fixed) anatomic landmark.[3,23,65]

The primary aim of the present study was to address the relationship between the intensity of NP and cortical reorganization after SCI in brain areas processing sensorimotor information. In line with phantom limb studies, we hypothesized that SCI would induce sensory and motor reorganization, the degree of which would be associated with the intensity of NP symptoms. Using functional magnetic resonance imaging (fMRI), individuals with SCI were examined during sensory stimulation (ie, brushing and heat) and movement tasks (ie, active and passive wrist extension). Based on the presence and intensity of the individuals' reported NP symptoms, the analysis focused on addressing group-level differences in activity, as well as changes in the location of peak activity (ie, ED) in primary sensory and motor areas.

Methods

Participants

A total of 26 individuals with chronic traumatic SCI (mean age (SD) = 46.3 (11.9) years, 3 women, 23 men), including individuals with tetraplegia (n = 11) and paraplegia (n = 15), were recruited. Only individuals who could perceive brushing and heat stimulation applied on the C6 dermatome, as well as independently perform active wrist extension were included in the study. Two individuals with SCI (1 with tetraplegia and 1 with paraplegia) were excluded because of technical measurement errors. In addition, 31 neurologically healthy individuals (mean age (SD) = 31.9 (9.9) years; 14 women, 17 men) were enrolled in the study. Participants' demographic and clinical details are summarized in Table 1. All participants provided written informed consent and all procedures described below were in accordance with the Declaration of Helsinki and approved by the local ethics board (ref. number: EK-04/2006).

Clinical Assessments

Before functional magnetic resonance imaging (fMRI), all participants were interviewed to determine handedness and the existence of pain using the German versions of the Edinburgh inventory (14 item version[46]) and the European Multicenter Study about SCI pain questionnaire (V4.2, http://www.emsci.org/), respectively. The pain questionnaire examines various aspects of pain (eg, duration, maximal, and average pain intensity) as well as pain-associated psychosocial factors. Accordingly, pain can be grouped into nociceptive (eg, musculoskeletal or visceral) or NP (eg, at or below the lesion). To be classified as below-NP, symptoms (eg, burning, cold, tingling) reported had to be located 3 or more segments below the neurological level of the lesion. In individuals with SCI, the neurological level of injury was assessed using the International Standards for Neurological Classification of Spinal Cord Injury published by the American Spinal Injury Association.[4,42,43] Briefly, sensory, motor, and neurological levels of injury were identified allowing characterization of sensory/motor functioning as well as determination of the completeness of injury by means of the International Standards for Neurological Classification of Spinal Cord Injury Impairment Scale (AIS).

Image Acquisition

MRI data were collected on a Philips 3-T Achieva system (Philips Medical Systems, Best, the Netherlands) using an

Table 1. Demographic and Clinical Details of the Sample

	Groups			
Parameter	Healthy Controls	Tetraplegic SCI	Paraplegic SCI	Significant Pairwise Comparisons (P < .05*)
Gender, men:women	17:14	10:0	12:2	Controls-tetraplegic SCI (<.001); controls-paraplegic SCI (<.001)
Age, y	31.9 ± 9.9	41.5 ± 12.2	45.2 ± 9.94	Controls-tetraplegic SCI (<.001); controls-paraplegic SCI (.002)
Handedness, right:left†	30:2	9:1	14: 0	ns
AIS motor score	100 ± 0	64.2 ± 30.1	57.9 ± 18.5	Controls-tetraplegic SCI (<.001); controls-paraplegic SCI (<.001)
AIS sensory score	224 ± 0	159.4 ± 47.5	143.1 ± 39.4	Controls-tetraplegic SCI (<.001); controls-paraplegic SCI (<.001)
Duration of SCI, y		11.0 ± 7.3	16.5 ± 9.4	ns
Injury severity, complete: incomplete		2:8	9:5	ns
NP, yes:no		4:6	8:6	ns
Duration of pain, y‡		7.1 ± 1.9	16.1 ± 8.2	ns
Mean pain intensity‡		4.1 ± 1.9	4.3 ± 2.3	ns
Maximum pain intensity‡		4.9 ± 2.9	6.3 ± 3.0	ns

Abbreviation: ns, not significant.
NOTE. Results are displayed as the mean ± standard deviation.
*Bonferroni corrected.
†German version of the Edinburgh inventory questionnaire.
‡European Multicenter Study about SCI pain questionnaire with incorporated visual analog scale ranging from 0 (no pain) to 10 (worst pain imaginable).