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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). Among problems related to treatment, underlying mechanisms are poorly understood. The aim of the present study was to investigate the association between cortical reorganization and NP after SCI. 24 individuals with sensorimotor complete and incomplete para- and tetraplegia (12 suffering from NP, 13 pain-free) and 31 healthy subjects were examined. Functional magnetic resonance imaging was used to assess activation in primary somatosensory and motor cortices in response to motor (i.e., active and passive wrist extension) and sensory (i.e., 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 (i.e., movement or sensory) compared to healthy control subjects. However, based on the Euclidean Distance measure, individuals with SCI demonstrated a lateral shift of peak activity in primary sensory and motor cortices ($p<0.05$). Among those with NP, chronic pain intensity inversely correlated with magnitude of the shift in the primary motor cortex during active wrist extension. The findings reveal that neuropathic pain in motor and sensory tasks at/above the level of lesion is not associated with increased plasticity. In line with previous studies changes in somatotopy and activation following SCI are rather limited while the influence of neuropathic pain on plasticity remains controversial.

1. Introduction

Neuropathic pain (NP) represents a major secondary complication for people currently living with SCI, negatively impacting quality of life and functional independence [56; 57]. Among difficulties related to the development of more effective interventions, mechanisms of NP are poorly understood. One prevailing theory is that NP from below the level of neurological injury arises from maladaptive changes in 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 following executed (contralateral to missing limb) or imagined (missing limb) movement [35; 36; 39; 53]. Supporting 'maladaptive plasticity', Wrigley and colleagues recently demonstrated that greater reorganization in the primary somatosensory cortex in response to brushing was associated with more severe neuropathic pain in individuals with SCI [65]. Previous studies in SCI have also considered reorganization in the *primary motor cortex* [11; 27], although not in the context of NP (i.e., relationship between the extent of reorganization and the severity of pain symptoms). A common readout of cortical reorganization has been to measure changes in center of gravity (CoG) [10; 22] or Euclidean distance between peak activity associated with a motor task or afferent stimulation (e.g., brushing, finger-tapping, etc.), relative to a known (and fixed) anatomical 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 (i.e., brushing and heat), and movement tasks (i.e., active and passive wrist extension). Based on the presence and intensity of individuals reported NP symptoms, the analysis focused on addressing group-level differences in activity, as well as changes in the location of peak activity (i.e., Euclidean distance) in primary sensory and motor areas.

2. Material and Methods

2.1. Subjects

A total of 26 individuals with a chronic traumatic SCI (mean (SD) 46.3 (11.9) years; sex: 3 female, 23 male) including individuals with tetra- (N=11) and paraplegia (N=15) were recruited. Only individuals that 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 individual with tetraplegia and 1 with paraplegia) were excluded due technical measurement errors. Additionally, 31 neurologically healthy individuals (mean (SD) 31.9 (9.9) years; sex: 14 female, 17 male) 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).

Table 1. Demographic and clinical details of the sample

Parameter	Groups			Significant pairwise comparisons (p<0.05‡)
	Healthy controls	Tetraplegic SCI	Paraplegic SCI	
Gender [male : female]	9:12	10 : 0	12 : 2	Controls-tetraplegic SCI (<0.001); Controls – paraplegic SCI (<0.001)
Age [yrs]	31.9 ± 9.9	41.5 ± 12.2	45.2 ± 9.94	Controls-tetraplegic SCI (<0.001); Controls – paraplegic SCI (=0.002)
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 (<0.001); Controls – paraplegic SCI (<0.001)
AIS sensory score	224 ± 0	159.4 ± 47.5	143.1 ± 39.4	Controls-tetraplegic SCI (<0.001); Controls – paraplegic SCI (<0.001)
Duration of SCI [yrs]		11.0 ± 7.3	16.5 ± 9.4	ns
Injury severity [complete : incomplete]		2 : 8	9 : 5	ns
Neuropathic pain (yes : no)		4 : 6	8 : 6	ns
Duration of pain [yrs]*		7.1 ± 1.9	16.1 ± 8.2	ns
Mean pain intensity*		4.1 ± 1.9	4.3 ± 2.3	ns
Max pain intensity*		4.9 ± 2.9	6.3 ± 3.0	ns

Results are displayed as mean ± standard deviation.
‡: Bonferroni corrected
†: German version of the Edinburgh inventory questionnaire
*: EMSCI pain questionnaire with incorporated visual analogue scale ranging from 0 (no pain) to 10 (worst pain imaginable). y= yes, n= no

SCI: Spinal cord injury

2.2. Clinical assessments

Prior to the 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 (EMSCI) pain questionnaire (V4.2, http://www.emsci.org/), respectively. The pain questionnaire examines various aspects of pain (e.g., duration, maximal and average pain intensity) as well as pain associated psychosocial factors. Accordingly, pain can be grouped into nociceptive (e.g., musculoskeletal or visceral) or neuropathic pain (e.g., at or below the lesion). To be classified as below-neuropathic pain, symptoms (e.g., burning, cold, tingling) reported had to be located three or more segments below the neurological level of 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 (ASIA) [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 ISNCSCI Impairment Scale (AIS).

2.3. Image acquisition

MRI data was collected on a Philips 3 T Achieva system (Philips Medical Systems, Best, the Netherlands) using an eight-channel Philips Sense head coil. Functional time series were acquired with a sensitivity-encoded (reduction factor 2), single-shot echo-planar sequence (SENSE-sshEPI) [54] with a measured resolution of 2.75 x 2.75 x 4 mm. The 29 axial slices without interslice gaps covered the entire cerebrum. Slices were aligned to the anterior commissure–posterior commissure line. Other scan parameters were as follows: echo time =35 ms; flip angle= 90°; repetition

time= 3000s; field of view =220 x 135 x 220mm; reconstruction matrix of scan resolution 72x72 voxels with 3 x 3 x 3 mm, and scan time of 16:12min. The first three scans were acquired to reach steady-state magnetization and then discarded. In total, 320 volumes were acquired.

A 3D-GRE T1-weighted (T1w) sequence was used to acquire a whole-brain, structural scan optimized for simultaneous assessment of the brain and spinal cord [17]. The imaging parameters were: isotropic 1 mm^3 resolution, field of view 256 x 256 x 180, repetition time = 6.88 ms, echo time = 3.1 ms, flip angle 8°, fat saturation, scan resolution 256x256 voxels, and a scan time of 6:31min. Prior to analysis the MRI data were screened for movement artefacts.

2.4. Functional MRI paradigm

The functional task comprised active 20s blocks of uni-lateral (i.e., right hand) active and passive wrist extension, heat stimulation, and brushing. Six repetitions of each task blocks were performed alternating with 20s rest blocks (starting with a rest block). The active blocks were presented in pseudo-randomized order (Figure 1).

All participants were scanned lying in a supine position and viewed visual stimuli projected screen via a mirror system mounted above the magnetic resonance head-coil. The right arm was secured to the MR bed only allowing the subject to execute the wrist extension following a physiological range of motion (i.e., range through which the wrist can be moved pain-free). In order to standardize sensory input, participants hold a handle in the hand during the entire time of scanning session (Figure 1). In addition, the strap attached to the handle was used to perform the passive wrist extension without touching the participant. During the passive wrist extension, the examiner extended the participants right hand-wrist along the physiological individual range of motion and then

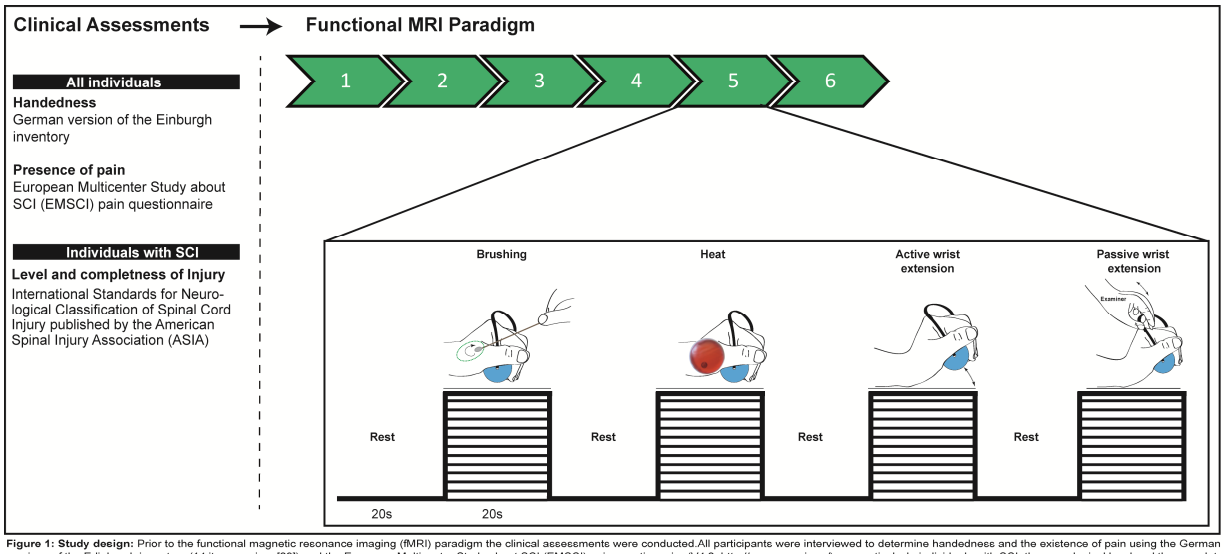

Figure 1: Study design: Prior to the functional magnetic resonance imaging (fMRI) paradigm the clinical assessments were conducted.All participants were interviewed to determine handedness and the existence of pain using the German versions of the Edinburgh inventory (14 item version, [29]) and the European Multicenter Study about SCI (EMSCI) pain questionnaire (V4.2, http://www.emsci.org/), respectively. In individuals with SCI, the neurological level and the completness of the injury was also determined using the International Standards for Neurological Classification of Spinal Cord Injury published by the American Spinal Injury Association. Cortical activation was assessed in response to sensory and motor task. The functional paradigm was composed of active 20s blocks of uni-lateral (i.e., right hand) brushing, heat stimulation, active and passive wrist extension. Six repetitions of each task blocks were performed alternating with 20s rest blocks (starting with a rest block). The active blocks were presented in pseudo-randomized order. Heat stimulation and brushing were applied to the C6 dermatome. Active and passive wrist extensions were conducted 10 times/ block. In order to reduce the sensory input, a handle was used to execute the passive wrist extension. In order to correct for the sensory input of the handle, participants were holding it during the entire experiment.

brought it back to its original starting position using the strap [38; 60; 63]. For the active wrist extension task, participants were asked to actively extend their right wrist along the physiological range of motion and bring it back to the original starting position [27]. For both motor tasks, the hand was initially positioned in resting pronation, and was extended upward against gravity with a cadence of 10 movements/ block (i.e., 2Hz). Each subject practiced this cadence prior to entering the scanner. Heat stimulation comprised of placing heat packs (average temp: 52.3℃; Trevolution, Zurich, Switzerland) onto the right C6 dermatome for 20s [14; 30]. A new heat pack was used for each 20s block. Brushing involved consistently brushing the right C6 dermatome with cotton swabs [51; 55; 65]. Brushing was performed at the base of the thumb. Importantly, the area of brushing did not overlap with the area of heating. For both sensory tasks, participants were instructed to lie quietly and minimize the eye-movement.

2.5. Validation of the temperature of the heat packs

Fourteen reusable heat packs contain a supersaturated solution of sodium acetate (3H2O CH3COONa) in water were tested. The heat pack is activated by

triggering the crystallization of the sodium acetate by bending a small flat disc of notched ferrous metal embedded in the liquid. To account for the effect of the room temperature on the temperature of the heat pack, the validation study was conducted in at similar room temperature (i.e., 21℃) as in the MRI Scanner . Heat packs were tested twice, on two separate days by the same examiner (CRJ). The temperatures of the heat packs were assessed using the YSI 4600 Series Precision Thermometers (YSI Incorporated). The temperature was considered stable when the peak reading did not change for two minutes. This procedure was repeated twice and the averaged was calculated. Additionally, we determined the time it takes from initiating the crystallization until the stable temperature was reached.

2.6. MRI Data Analysis

Functional volumes were preprocessed and analyzed in Matlab 2010b using Statistical Parametric Mapping 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The images were initially realigned to the first scan and unwarped to control for movement- and susceptibility-induced image distortions [1]. Movement parameter were calculated to be later included in the statistical model. Following coregistration of the anatomical and functional images, spatial normalization of the functional images was executed. Using a unified segmentation approach, individual brains were normalized to the Montreal Neurological Institute standard space (MNI space). Lastly, spatial smoothing was conducted by applying an isotropic 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel to reduce image noise.

A voxel-wise general mixed model was used for the first-level analysis (i.e., within a subject) in order to calculate contrast images for each task separately (i.e., heat,

brushing, active and passive wrist extension). Vectors of motion estimates were included as 'nuisance variables' (covariates of no interest) to account for the variance due to motion in the GLMs [26]. Significant increases in BOLD signal were identified using a repeated box car model convolved with a canonical form of the hemodynamic response function [19]. The second-level analysis (i.e., group analysis) was performed to identify task-specific pattern of activation for each group (i.e., healthy controls, individuals with paraplegia, and individuals with tetraplegia). Significant differences between the control and SCI groups, between SCI without pain and SCI with pain groups during each task were also determined. Age, sex, level of lesion, and total intracranial volume (TIV) were included in the model as nuisance variables. All results reported were corrected for multiple-comparisons using the family-wise error (FWE).

For group comparisons, whole-brain analyses as well as region of interest (ROI) analyses were computed. The whole brain analysis was conducted for a comprehensive overview. Additionally, the ROI approach was performed to explore *regional* differences in task-related brain activation between all the groups. Thus, the ROIs were included as a mask in order to restrict the voxel-by-voxel statistical analysis (including FWE-correction) to pre-specified brain areas [52]. These ROIs incorporated primary (S1) and secondary (S2) somatosensory cortices, primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), thalamus, anterior cingulate cortex (ACC), and cerebellum and were generated using the WFU Pickatlas [33; 41]. The rational for the selected ROIs stemmed from all areas mainly being involved in the encoding and processing of either motor output (M1, PMC, SMA, and cerebellum) or sensory input (S1, S2, thalamus, ACC) [12; 50].

2.7. Euclidean Distance

The point at which the central sulcus meets the longitudinal fissure at the dorsal aspect of the brain was set as anatomical marker [65]. The Euclidean distance (ED) between the anatomical marker and the maximally activated voxel in task-specific ROIs (i.e., S1 for heat/brushing, M1 for active/passive wrist extension) was computed for the anterior–posterior, medial–lateral and superior–inferior coordinates. The ED between two points in a plane is calculated with the Pythagorean theorem and provides an absolute value independently of direction [18].

2.8. Statistics

All statistical procedures were performed using IBM`s Statistical Package for the SocialSciences (SPSS) version 19.0 (Armonk, New York, U.S.). Non-parametric tests (Mann-Whitney-U and Kruksal-Wallis) were applied to determine significant differences in ED, peak activation, and cluster size between healthy controls, individuals with SCI and an intact C6 dermatome, as well as individuals with SCI and an impaired C6 dermatome. Pain-specific changes of ED, peak activation, and cluster size were explored by comparing the control group with the neuropathic pain SCI group as well as the pain-free SCI group. $P < 0.05$ was considered significant. All multiple comparisons were Bonferroni corrected. Spearman correlation was applied to assess the relationship of EDs and pain parameters (e.g., intensity, duration). Level of lesion and injury severity (i.e., AIS score) were included as covariates.

Contrast estimates of all ROIs from the SCI patients were extracted in order to perform Spearman correlations to identify associations between task-specific cortical activation and clinical characteristics (i.e., SCA, AIS motor and sensory scores, disease duration, level of lesion, pinprick and light touch scores, as well as pain intensity and duration).

3. Results

3.1. Injury and pain characteristics, subject demographics

Of the 28 individuals with SCI, 11 had AIS complete (2 tetraplegic, 9 paraplegic) and 17 incomplete (12 tetraplegic, 5 paraplegic) injuries. In total, 13 patients (8 with paraplegia, 5 with tetraplegia) reported neuropathic pain (NP) (Table 2). The mean and maximal pain intensities were 4.5 ± 3.1 and 5.2 ± 3.8, respectively, and the duration of ongoing pain ranged from 4 to 33 years (mean 17.5 +/-12.3 years).

Table 2. Clinical data for the spinal cord injured individuals

ID	Age [yrs]	Gender	Etiology of the injury	Time since Injury [yrs]	Level of Lesion‡	AIS*	Motor score (0-100)	Sensory score (0-224)+	Neuropathic pain
Individuals with paraplegic SCI									
P01	50	m	Vehicle accident	7	Th4/Th5	A	50	90	Below-level
P02	50	m	Vehicle accident	9	Th4	B	50	200	no
P03	35	m	Gunshot	12	Th4	B	50	144	Below-level
P04	48	m	Vehicle accident	16	Th6/7	A	50	112	Below-level
P05	44	m	Vehicle accident	26	Th7	B	50	168	Below-level
P06	44	m	Gun shot	17	Th6	A	50	96	no
P07	29	m	Sports accident	14	Th11	A	50	128	Below-level
P08	38	m	Vehicle accident	16	Th8	A	50	104	no
P09	29	f	Sports accident	5	L3	D	100	217	Below-level
P10	65	m	Vehicle accident	33	Th12	A	50	158	Below-level
P11	60	m	Vehicle accident	2	Th12	D	100	185	no
P12	50	m	Vehicle accident	4	Th11	A	60	148	no
P13	43	m	Vehicle accident	24	Th6	A	50	110	no
P14	48	f	Hit by tree	19	L1	A	50	144	Below- / at-level
Individuals with tetraplegic SCI									
T01	25	m	Sports accident	2	C6/ C7	D	71	134	no
T02	39	m	Vehicle accident	20	C6	C	38	126	no
T03	53	m	Gun shot	10	C8	B	30	165	no
T04	57	m	Vehicle accident	6	C6/ C7	D	96	202	Below-level
T05	40	m	Vehicle accident	19	C6	B	24	78	no
T06	50	m	Vehicle accident	27	C6/ C7	A	30	83	no
T07	35	m	Sports accident	5	C6/ C7	D	93	176	no
T08	40	m	Vehicle accident	10	C7	D	96	160	Below-level
T09	24	m	Vehicle accident	7	C6/ C7	A	40	185	no
T10	65	m	Vehicle accident	9	C6	D	88	220	Below-level
	40	m	Vehicle accident	6	C7	D	100	224	Below-level

‡: The level of lesion refers to the neurological level

*ASIA impairment scale: A, no sensory or motor function is preserved; B, sensory function is preserved below the level of the injury, but there is no motor function; C, motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade of < 3; D, motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade of > 3.

+Sensory Score: Sum of segmental light touch and pinprick classifications

3.2. Validation of the temperature of heat packs

From a total of 14 heat packs evaluated two were excluded because the average temperature did significantly differ from the other heat packs as the temperatures did not reach 50℃ (i.e., 49.2 and 48.6℃) and the time to reach the stable temperature was longer than 20s. The temperatures of the remaining 12 heat packs averaged at 52.3℃ ± 0.4℃ (range 51.8 - 53.1℃). The measured average t emperature is in line with the vendor's specification (Trevolution by MIGROS, Switzerland, http://www.sportxx.ch/de/trevolution-shop). The time between initiating the crystallization and reaching the stable temperature ranged from 10 to 13s.

3.3. Patterns of brain activation in response to brushing, heat stimulation, active and passive wrist extension

There were no task-related activation differences between SCI and healthy controls (Figure 2). Active and passive wrist extension evoked significant increases in signal intensity in contralateral primary motor cortex, primary and secondary sensory cortex, premotor cortex, and cerebellum. Heat and brushing stimulation resulted in significant signal intensity increases in left (heat and brushing) and right secondary sensory cortex (heat only), and left primary somatosensory cortex (brushing only) (Table 3).

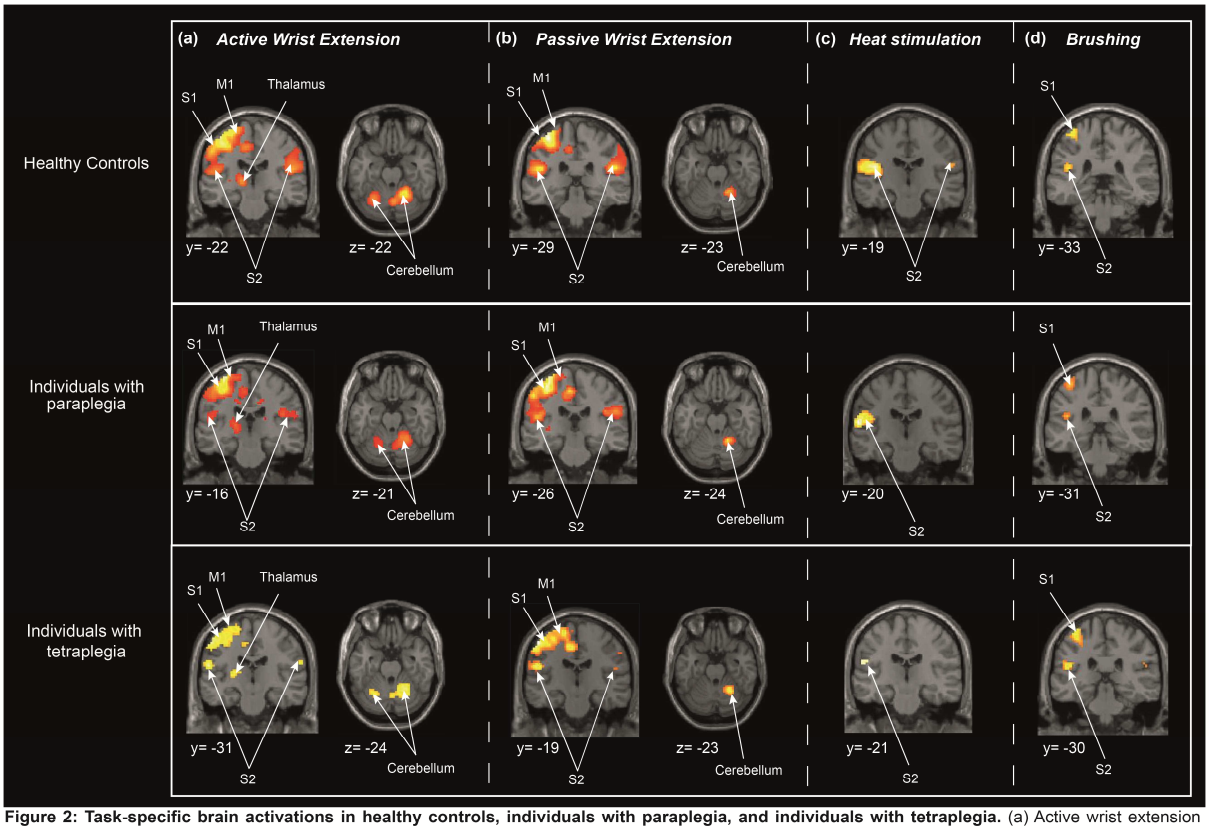

Figure 2: Task-specific brain activations in healthy controls, individuals with paraplegia, and individuals with tetraplegia. (a) Active wrist extension evoked BOLD signal increase in M1, S1, and thalamus (unilateral), as well as S2 and cerebellum (bilateral). (b) Similar areas were significantly activated during passive wrist extension with the exception of unilateral signal increase in cerebellum. (c) Heat and (d) brushing stimulation resulted in significant signal intensity increases in left (heat and brushing) and right secondary sensory cortex (heat only), and left primary somatosensory cortex (brushing only).

S1: Primary sensory cortex; S2: Secondary sensory cortex; M1: Primary motor cortex

Table 3: Cortical and subcortical areas activated in response to active and passive wrist extension, heat stimulation, and brushing. Areas, cluster size, Z- and T-values, and MNI coordinates are listed for healthy controls and individuals with SCI.

Groups	Area	P-value (FWE-corrected)	Z-Value	T-Value	Cluster size	Coordinates in MNI (mm)		
						x	y	z
Active wrist extension								
Controls	M1 (l)	<0.001	>8	19.29	151	-36	-31	61
	S1 (l)	<0.001	>8	20.00	158	-36	-34	61
	S2 (l)	<0.001	6.67	10.26	123	-48	-28	19
	PMC (l)	<0.001	>8	17.12	902	-33	-28	67
	Cerebellum (l)	<0.001	6.5	9.76	150	-27	-58	-26
	Cerebellum (r)	<0.001	7.66	13.71	342	18	-52	-23
Individuals with SCI	M1 (l)	<0.001	6.75	11.08	117	-36	-31	67
	S1 (l)	<0.001	6.49	10.23	96	-36	-34	55
	S2 (l)	<0.001	5.74	8.16	48	-48	-31	22
	PMC (l)	<0.001	6.63	10.69	568	-36	-28	67
	Cerebellum (l)	<0.001	4.99	6.48	35	-24	-61	-23
	Cerebellum (r)	<0.001	6.20	9.37	267	27	-49	-26
Passive wrist extension								
Controls	M1 (l)	<0.001	>8	20.93	129	-36	-31	61
	S1 (l)	<0.001	>8	20.30	136	-36	-34	61
	S2 (l)	<0.001	7.81	14.40	131	-51	-28	19
	PMC (l)	<0.001	>8	18.55	885	-36	-28	67
	Cerebellum (r)	<0.001	7.20	11.97	161	18	-52	-20
Individuals with SCI	M1 (l)	<0.001	7.50	14.05	119	-36	-31	67
	S1 (l)	<0.001	7.28	13.09	112	-36	-34	61
	S2 (l)	<0.001	6.91	11.67	97	-45	-28	19
	PMC (l)	<0.001	7.63	14.64	794	-33	-28	67
	Cerebellum (r)	<0.001	6.72	10.99	116	24	-52	-23
Heat stimulation								
Controls	S1 (l)	0.005	4.13	5.84	12	-33	-31	61
	S2 (l)	<0.001	7.25	12.15	212	-42	-19	19
	S2 (r)	<0.001	5.0	6.31	7	57	-19	22
Individuals with SCI	S1 (l)	0.013	4.12	5.1	8	-34	-30	60
	S2 (l)	<0.001	4.79	8.21	97	-60	-16	13
	S2 (r)	<0.001	4.1	6.2	4	54	-19	23
Brushing								
Controls	S1 (l)	<0.001	5.57	7.45	7	-57	-16	37
	S2 (l)	<0.001	6.97	11.19	119	-48	-25	19
Individuals with SCI	S1 (l)	<0.001	6.17	9.30	16	-39	-34	58
	S2 (l)	<0.001	6.31	9.70	95	-54	-19	22

FWE: Family-wise error; S1: primary somatosensory cortex; S2: secondary somatosensory cortex; M1: primary motor cortex; PMC: premotor cortex; l: left; r: right; MNI: Montreal Neurological Institute; SCI: spinal cord injury

3.4. Shifts in primary somatosensory and primary motor cortices topography

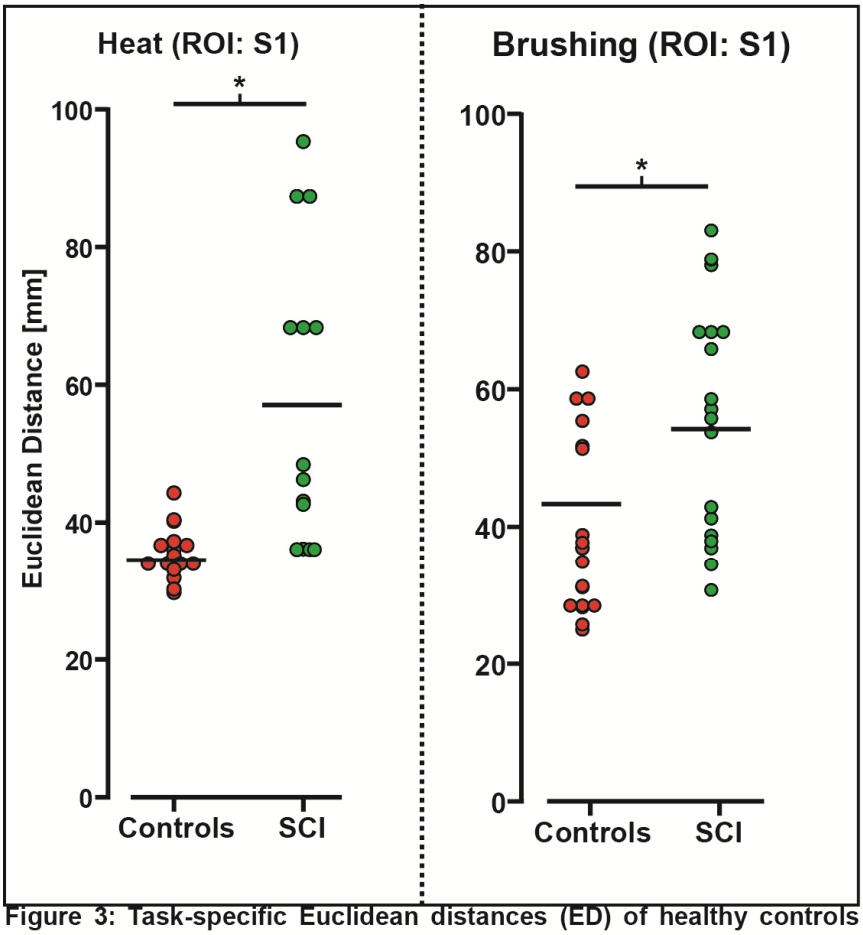

Figure 3: Task-specific Euclidean distances (ED) of healthy controls and individuals with SCI. Significant differences in EDs for heat, brushing were found in individuals with spinal cord injury (SCI) when compared to the control group. Selected region of interest (ROI) was for both tasks the primary sensory cortex.

S1: Primary sensory cortex

Although the pattern of the task-specific brain activation was similar across the group, there were significant differences in the location of peak activation. In individuals with SCI compared to control subjects, the analysis yielded significant differences in ED for heat and brushing (Figure 3), as well as for active movement (Figure 4a). In control subjects, the mean (±SD) X, Y, Z co-ordinates for active wrist extension: -33 ± 2.8, -28.8 ± 2.8, 60.7 ± 5.7; passive wrist extension: -33.8 ± 2.5, -27.9 ± 10.5, 63.9 ± 5.0; heat stimulation: -33.7 ± 3.1, -30.5 ± 6.4, 61.0 ± 4.0; brushing: -39.2 ± 9.6, -31.3 ± 8.5, 58.9 ± 10.0. These coordinates yielded mean ED of 35.7 ± 3.3 mm, 36.3 ± 7.0 mm, 35.9 ± 3.6 mm, and 42.5 ± 12.6 mm for active wrist extension, passive wrist extension, heat stimulation, and brushing, respectively. In individuals with SCI, the mean (±SD) X, Y, Z

co-ordinates for active wrist extension were -38.9 ± 4.7, -24.0 ± 4.3, 58.5 ± 4.7; passive wrist extension: -35.0 ± 2.7, -27.9 ± 2.8, 60.5 ± 5.8; heat stimulation: -46.6 ± 11.4, -17.7 ± 18.4, 44.1 ± 16.2; and brushing: -46.9 ± 11.4, -21.5 ± 8.4, 43.7 ± 10.3 (respectively). The mean ED between the anatomical marker and the MNI co-ordinates for active wrist extension were 42.2 ± 5.8 mm; passive wrist extension 37.5 ± 3.11 mm; heat stimulation 56.1 ± 22.2 mm, brushing 55.9 ± 16.8 mm (Table 4). Pain-related changes in ED were found for primary motor cortex during the active wrist extension task (Figure 4b). While pain-free individuals with SCI exhibit an increase in ED compared to healthy controls, the ED of individuals with SCI reporting neuropathic pain did not differ from healthy control values. In pain-free individuals with SCI, the mean (±SD) X, Y, Z co-ordinates were active wrist extension: -35.7 ± 4.2, -26.0 ± 3.4, 59.3 ± 3.7, and the mean ED

Table 4. Euclidean Distances and coordinates.

Groups	Euclidean distance (mm)	Coordinates in MNI (mm)			Significant pairwise comparisons (p<0.05‡)
		x	y	z	
Active wrist extension					
Controls	35.7 ± 3.3	-33 ± 2.8	-28.8 ± 2.8	60.7 ± 5.7	Controls – Individuals with SCI (p<0.05)
Individuals with SCI	42.2 ± 5.8	-38.9 ± 4.7	-24.0 ± 4.3	58.5 ± 4.7	
Passive wrist extension					
Controls	36.3 ± 7.0	-33.8 ± 2.5	-27.9 ± 10.5	63.9 ± 5.0	n.s.
Individuals with SCI	37.5 ± 3.11	-35.0 ± 2.7	-27.9 ± 2.8	60.5 ± 5.8	
Heat stimulation					
Controls	35.9 ± 3.6	-33.7 ± 3.1	-30.5 ± 6.4	61.0 ± 4.0	Controls – Individuals with SCI (p<0.05)
Individuals with SCI	56.1 ± 22.2	-46.6 ± 11.4	-17.7 ±18.4	44.1 ± 16.2	
Brushing					
Controls	42.5 ± 12.6	-39.2 ± 9.6	-31.3 ± 8.5	58.9 ±10.0	Controls – Individuals with SCI (p<0.05)
Individuals with SCI	55.9 ± 16.8	-46.9 ± 11.4	-21.5 ± 8.4	43.7 ± 10.3	

Results are displayed as mean ± standard deviation.
‡: Bonferroni corrected
MNI=Montreal Neurological Institute
n.s. = not significant

between the anatomical marker and the MNI co-ordinates were active wrist extension

37.7 ± 2.8 mm. In individuals with SCI suffering from NP, the mean (±SD) X, Y, Z co-ordinates were active wrist extension: -35.1 ± 4.5, -26.1 ± 4.6, 57.8 ± 5.4; and the mean ED between the anatomical marker and the MNI co-ordinates were active wrist extension 40.5 ± 3.8 mm. Based on the classification with NP, EDs for brushing, heat stimulation, and passive movement were not significantly different.

3.5. Correlation with pain intensity and other variables

The correlation between topographical shifts in primary motor cortex during active wrist extension and the intensity of chronic NP is illustrated in Figure 4c. The magnitude of cortical reorganization of primary motor cortex during active wrist extension negatively correlated with the intensity of ongoing neuropathic pain, such that shifts in peak activation were less pronounced in individuals with more severe NP compared to individuals with less severe NP. A sensitivity analysis indicated that the level and severity of injury had no impact on the correlation. No significant correlations were found between the ongoing pain and the task-specific brain activation during passive movement, heat stimulation, and brushing.

4. Discussion

Applying fMRI, the current study assessed reorganization in brain areas involved in processing sensorimotor information after SCI. Furthermore, the study aimed at determining if neuropathic pain constitutes a contributing factor for the observed plasticity. In line with investigations in phantom limb pain, we were primarily interested to examine primary motor cortex (M1) reorganization in response to movement, executed above the level of injury (i.e., intact spinal segments) [35; 40]. In response to SCI, topographical shifts in peak activity were observed following sensory stimulation (brushing and heat in primary somatosensory), as well as active movement (primary motor cortex). Interestingly, peak activation topography in response to wrist extension was significantly shifted to a greater extent in pain-free individuals compared to healthy controls and individuals with NP. A correlation analysis in individuals with NP revealed a significant negative relationship, such that larger topographical shifts in primary motor cortex were associated with less reported chronic neuropathic pain (i.e., individuals with higher NP intensities were more similar to healthy controls). In addition to demonstrating reorganization after SCI, these novel findings indicate that NP may preserve functional cortical topography.

4.1. Preserved functional organization associated with neuropathic pain

In agreement with previous studies, deafferentation due to SCI was shown to induce changes in the topographical organization of primary sensory and motor cortices [20; 21; 24; 27; 28; 62]. In contrast to Wrigley et al. [65], our findings suggest that cortical reorganization is dependent on individuals *not* reporting the presence of NP. This observation is further supported by a negative correlation between NP intensity and topographical shifts in primary motor cortex, indicating that individuals with more severe

NP are more similar to healthy controls than pain-free individuals (Figure 4c). The negative correlation we observed in primary motor cortex contrasts the maladaptive plasticity model, which fundamentally states that greater cortical reorganization is associated with more severe pain symptoms [15; 16; 51; 58; 65].

Makin and colleagues recently demonstrated the need to revisit the relationship between pain and cortical organization, demonstrating intact functional and structural representations of the hand in amputees with phantom limb pain [40]. Pain was postulated to replace peripheral afferent input resulting from amputation, contributing to "maintained cortical representation" of the missing hand. Similar to amputation, cortical organization of the hand in primary motor area after SCI may be preserved by painful sensory input arising from areas of the body deafferented by damage in the spinal cord. Such an interpretation inherently suggests that preserved functional organization in primary motor cortex is a consequence of neuropathic pain. Conversely, cortical reorganization could also be preventing the development of neuropathic pain after SCI – a form of adaptive plasticity. In such a case, reorganization in primary motor cortex is protective and the failure to reorganize is maladaptive.

Interestingly, we did not observe an effect of injury severity (i.e., completeness, lesion level, as well as AIS motor and sensory scores) on cortical reorganization. On one hand, this finding conflicts with the idea that residual sensation below the level of injury (i.e., NP) preserves functional activity in the brain. Several factors could explain why NP but not other forms of sensory sparring maintained cortical organization. First, clinical methods to assess residual sensory and motor sparing below the level of lesion may not be sensitive to detect subtle differences in injury severity. According to the ISNCSCI,

residual sensation (light touch and pinprick) is only examined using a 3-point scale (0-absent, 1-impaired, and 3-normal). Second, the intensity and persistence of below-level NP may represent greater afferent input compared to other residual sensation. In turn, chronic pain places higher demands on cortical structures, both ascending and descending, and thus has a greater impact on function.

4.2. The primary motor cortex and NP

Several studies in individuals with amputations have investigated the relationship between reorganization in primary motor cortex and phantom limb pain [13; 15; 35; 40]. Supporting the concept of maladaptive plasticity, evidence of functional reorganization in primary motor cortex has emerged from imagined and executed movement of the missing hand, and executed movement of the opposing (intact) hand [13; 16; 36; 39]. In healthy subjects, the primary motor cortex has been ascribed a role in processing normal responses to experimental noxious stimuli [29; 59]. Suggesting a role in anti-nociception, projections from the motor cortex to the periaqueductal gray matter have been elucidated in naïve rats [47]. Indicative of a role in chronic pain, targeting the primary motor cortex with neuromodulatory therapies (e.g., repetitive transcranial magnetic stimulation of the primary motor cortex) has proven effective in the relief of some NP symptoms in patient populations [25; 34; 61]. Based on our findings, one potential avenue for therapeutic benefit of neuromodulatory therapies targeting primary motor cortex could be the induction of “adaptive plasticity” in individuals with NP. The responsiveness of peak topography shifting towards “normal deafferentation” organization in primary motor cortex is a potential avenue for future research.

4.3. Task-related activation of distinct brain areas

In line with previous studies, our active and passive motor tasks elicited increased BOLD responses in the primary motor cortex, premotor cortex, primary sensory cortex, supplementary motor area, and cerebellum (active motor task only) [32; 37; 38]. The brushing task resulted in significant signal increases in the primary and secondary cortices [8; 65]. In line with previous studies, the secondary somatosensory cortex was also consistently active in response to noxious thermal stimulation [8; 49]. At a group level, however, activation in other prominent areas (e.g., thalamus, insula, and anterior cingulate) was not observed in response to noxious heat. A number of factors may explain why we did not observe activation in these areas, including methodological differences between studies. For example, in the current study, we applied a thermal stimulus using commercially available heat packs for 20 seconds, which nominally reached ~53^{o}C. In general, our protocol involves longer duration and higher temperature, and a greater number of stimulation blocks (n=6) than comparable studies applying contact heat [2; 6-8; 45]. Due to repeated presentation of stimuli (noxious and non-noxious), activation in some brain areas (e.g., thalamus and ACC) may have been attenuated by habituation [2].

4.4. Limitations

In contrast to previous studies, we found no evidence for shifts primary somatosensory cortex (S1) topography related to the presence and intensity of NP during brushing in individuals with SCI compared to healthy control subjects [65]. Wrigley and colleagues found that the extent of cortical reorganization was associated with NP in response to brushing of the little finger, but not the thumb [65]. The present

study examined only the base of the thumb using different sensory modalities, and thus did not address reorganization in response to stimulation in other areas (e.g., little finger, lip). Also compared with Wrigley, a limitation of our study is the heterogeneity of the SCI sample, which included both individuals with tetra- and paraplegia, as well as all severities of injury [65]. While our statistical analysis took these differences into account, a more powerful study design may be required to examine the interaction between pain and specific injury characteristics. On the other hand, it is important to consider that NP after SCI is not related to level or injury severity [57], thus a heterogeneous sample is potentially more reflective of the clinical condition. Furthermore, we accounted for the variability between individuals with SCI and healthy volunteers by explicitly modeling the linear variance of age, sex, level of lesion, and total intracranial volume (TIV) in all GLM analyses. [5; 48]. Due to the small and heterogenetic sample size, weak effects may not have been detected. However, careful statistical tests ensure that the results are robust and controlled for Type I error – even when based on a small sample size. Lastly, employing an eight-channel head coil constitutes a limiting factor from a technical perspective. In fact, previous studies have demonstrated the advantages of 12- and 32-channel head coils over an eight-channel coil including improved signal-to-noise ratio, enhanced resolution, and shorted scanning times [31; 64].

4.5. Conclusion

Cortical reorganization in sensory and motor systems after SCI was observed as a shift in peak activation topography during sensory stimulation (i.e., brushing and heat) and active wrist extension. In agreement with a recent study in individuals with phantom limb pain [40], shifts in the primary motor cortex topography were negatively correlated

with pain intensity, supporting an emerging theory that NP preserves cortical organization after deafferentation.

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6. Authors Contribution

Catherine Jutzeler contributed substantially to the conception and design of the study, the data acquisition, analysis, and interpretation. Furthermore, she drafted the research article. Eveline Huber contributed substantially to the data acquisition and participated in revising the research article. Patrick Freund contributed substantially to the conception and design of the study, the data analysis, and interpretation. He was involved in revising the research article. Armin Curt made substantial contributions to conception and design and participated in revising the research article critically for important intellectual content. John Kramer contributed substantially to the conception and design of the study, data analysis and interpretation, as well as drafting the research article.

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Highlights (max 85 characters per bullet point)

- Limited large scale cortical reorganization observed after human spinal cord injury
- Neuropathic pain is not associated with increased plasticity in the brain
- Reorganization in the CNS could be an adaptive process preventing development of neuropathic pain