


## RESEARCH ARTICLE

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# Supraspinal nociceptive networks in neuropathic pain after spinal cord injury

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## Abstract

Neuropathic pain following spinal cord injury involves plastic changes along the whole neuroaxis. Current neuroimaging studies have identified grey matter volume (GMV) and resting-state functional connectivity changes of pain processing regions related to neuropathic pain intensity in spinal cord injury subjects. However, the relationship between the underlying neural processes and pain extent, a complementary characteristic of neuropathic pain, is unknown. We therefore aimed to reveal the neural markers of widespread neuropathic pain in spinal cord injury subjects and hypothesized that those with greater pain extent will show higher GMV and stronger connectivity within pain related regions. Thus, 29 chronic paraplegic subjects and 25 healthy controls underwent clinical and electrophysiological examinations combined with neuroimaging. Paraplegics were demarcated based on neuropathic pain and were thoroughly matched demographically. Our findings indicate that (a) spinal cord injury subjects with neuropathic pain display stronger connectivity between prefrontal cortices and regions involved with sensory integration and multimodal processing, (b) greater neuropathic pain extent, is associated with stronger connectivity between the posterior insular cortex and thalamic sub-regions which partake in the lateral pain system and (c) greater intensity of neuropathic pain is related to stronger connectivity of regions involved with multimodal integration and the affective-motivational component of pain. Overall, this study provides neuroimaging evidence that the pain phenotype of spinal cord injury subjects is related to the underlying function of their resting brain.

## KEYWORDS

contact heat evoked potentials, neuropathic pain, pain extent, quantitative sensory testing, resting-state functional connectivity, spinal cord injury, voxel-based morphometry

Michèle Hubli and Lars Michels shared last-authorship.

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## 1 | INTRODUCTION

Traumatic spinal cord injury (SCI) causes disruption of efferent and afferent pathways yielding distinct sensorimotor deficits below the level of lesion (Ahuja et al., 2017). Damage to the somatosensory system leads to central neuropathic pain (NP; IASP, 2012) in 53% of subjects with SCI (Burke, Fullen, Stokes, & Lennon, 2017) of which a third report it to be severe (Slotnick, Moo, Segal, & Hart Jr, 2003; Siddall et al., 2003) and whose quality of life is harshly decreased (Burke, Lennon, & Fullen, 2018). The development of NP involves a complex pathophysiology along the whole neuroaxis leading to central sensitization, that is, neuronal and glial changes, neuroinflammation, dysregulated descending inhibitory pathways, upregulated descending facilitation and spinal hyperexcitability, (see reviews: Costigan, Scholz, & Woolf, 2009; Ossipov, Dussor, & Porreca, 2010; Ossipov, Morimura, & Porreca, 2014; Colloca et al., 2017). These pathophysiological changes may contribute to the variable clinical presentation of NP after SCI, that is, at- and/or below-level, evoked pain (hyperalgesia and allodynia) and/or spontaneous NP that could spread beyond the primary injury (Colloca et al., 2017; Slotnick, Moo, Segal, & Hart Jr, 2003; Widerström-Noga, 2017; Woolf & Mannion, 1999). One factor considered to contribute to NP after SCI is an affection of spinothalamic tract integrity, which can be investigated with quantitative sensory testing (QST) and contact-heat evoked potentials (CHEPs). Here, painful stimulation with concurrent recordings of cortical responses serves the purpose of indexing the functional integrity of thermo-nociceptive pathways. In this context, evoked potentials are used to document the damage within thermo-nociceptive pathways, which is only indirectly linked to the presence of spontaneous NP. Previous studies have shown that thermal thresholds were either higher (Gruener, Zeilig, Laufer, Blumen, & Defrin, 2016) or lower (Kumru et al., 2012) in subjects with SCI and NP (SCI-NP) compared to those without NP (SCI-nonNP). A combination of QST and evoked potentials were considered a useful objective tool to investigate somatosensory function in SCI-NP subjects (Landmann, Berger, Stockinger, & Opsommer, 2017) and CHEPs can be utilised as a sensitive marker of spinal cord pathology, that is, myelopathy (Jutzeler et al., 2017) and provides both subjective and objective readouts of spinothalamic tract integrity.

Moreover, prior neuroimaging studies have provided evidence of structural and functional cortical reorganisation that accompany SCI (Athanasίου et al., 2017; Nardone et al., 2013, 2018; Solstrand Dahlberg, Becerra, Borsook, & Linnman, 2018) and pain (including NP; Alomar & Bakhaidar, 2018; Apkarian, Bushnell, Treede, & Zubieta, 2005; Kuner & Flor, 2016; Moisset & Bouhassira, 2007; Morton, Sandhu, & Jones, 2016). Previous resting-state functional connectivity (rsFC) studies have shown disruption of sensorimotor networks and resting-state networks following SCI. This includes decreased synchronicity between within the sensorimotor cortex, that is, inter-hemispheric primary motor cortex (M1) and somatosensory cortex (S1; Hou, Sun, et al., 2014a; Oni-Orisan et al., 2016), and decreased rsFC within the default-mode, salience, dorsal-attention networks

overall in SCI subjects compared to healthy controls (Hawasli et al., 2018) following SCI. In SCI-related NP, SCI-NP subjects showed less grey matter volume (GMV) in S1 (Jutzeler et al., 2016; Mole, MacIver, Sluming, Ridgway, & Nurmikko, 2014) alongside higher GMV in the anterior cingulate cortex (ACC) and M1 (Jutzeler et al., 2016). SCI-NP subjects NP intensity also positively correlated with higher GMV of M1 (Jutzeler et al., 2016) and decreased GMV of S1 (Mole, MacIver, Sluming, Ridgway, & Nurmikko, 2014). A more recent study observed stronger rsFC between the insular sub-regions to cortical regions, that is, temporal cortex and hippocampus, which positively correlated with SCI-NP subject's pain intensity (Li et al., 2020). In other chronic pain conditions, that is, diabetic neuropathy, decreases in rsFC have been observed in the sensorimotor cortices, ACC, alongside stronger rsFC within the precuneus, dorsolateral prefrontal regions, frontal gyri and thalamus (Cauda et al., 2009). In fibromyalgia, bidirectional rsFC changes within insula sub-regions (Ichesco et al., 2014) and stronger rsFC between regions of the descending pain modulatory areas, that is, periaqueductal grey (PAG) and rostroventral medulla has been observed to be correlated with pain facilitation (Harper et al., 2018). Overall, these studies suggest that alterations in brain plasticity could be a contributing factor to the presence of chronic pain and may correlate to individuals' pain characteristics, that is, intensity.

Next to pain intensity, the spatial extent of pain is believed to be a consequence of central sensitization in conditions such as fibromyalgia (Harte, Harris, & Clauw, 2018; Ji, Nackley, Huh, Terrando, & Maixner, 2018; Meeus & Nijs, 2007; Woolf, 2011). In a study of chronic pelvic pain subjects, stronger pain extent was shown to correlate positively with GMV and rsFC of the supplementary motor cortex (SMC), S1/M1 and the salience network (Kutch et al., 2017). This finding indicates that pain extent could be a complementary measure to neuroimaging readouts and may prove useful for personalising treatment in pain conditions by capturing the amount of centralised pain (Kutch et al., 2017). However, the role of pain extent as a marker of NP and its relation to GMV and rsFC changes in SCI-related NP is unknown.

Therefore, this study implements structural and resting-state functional MRI (fMRI) to understand: (a) the neural markers that delineate SCI-NP and SCI-nonNP subjects and the NP characteristics that correlates with these changes and (b) the relationship between the severity of NP extent and intensity and remote brain changes within SCI-NP subjects. By exploring these aspects together, this will provide an insight to the neuroplastic changes in SCI-NP subjects and the accompanying neural correlates of NP extent.

Based on prior studies, we hypothesise that SCI-NP subjects will show predominantly GMV decreases in pain-related regions such as S1, but may also show higher GMV of other cortical regions, that is, ACC and M1. Moreover, we expect SCI-NP subjects to show stronger rsFC between pain processing regions compared to HC and SCI-nonNP subjects. We also hypothesise that within SCI-NP subjects only; those with greater NP extent and intensity will show higher GMV and rsFC of pain processing areas.

## 2 | METHODS

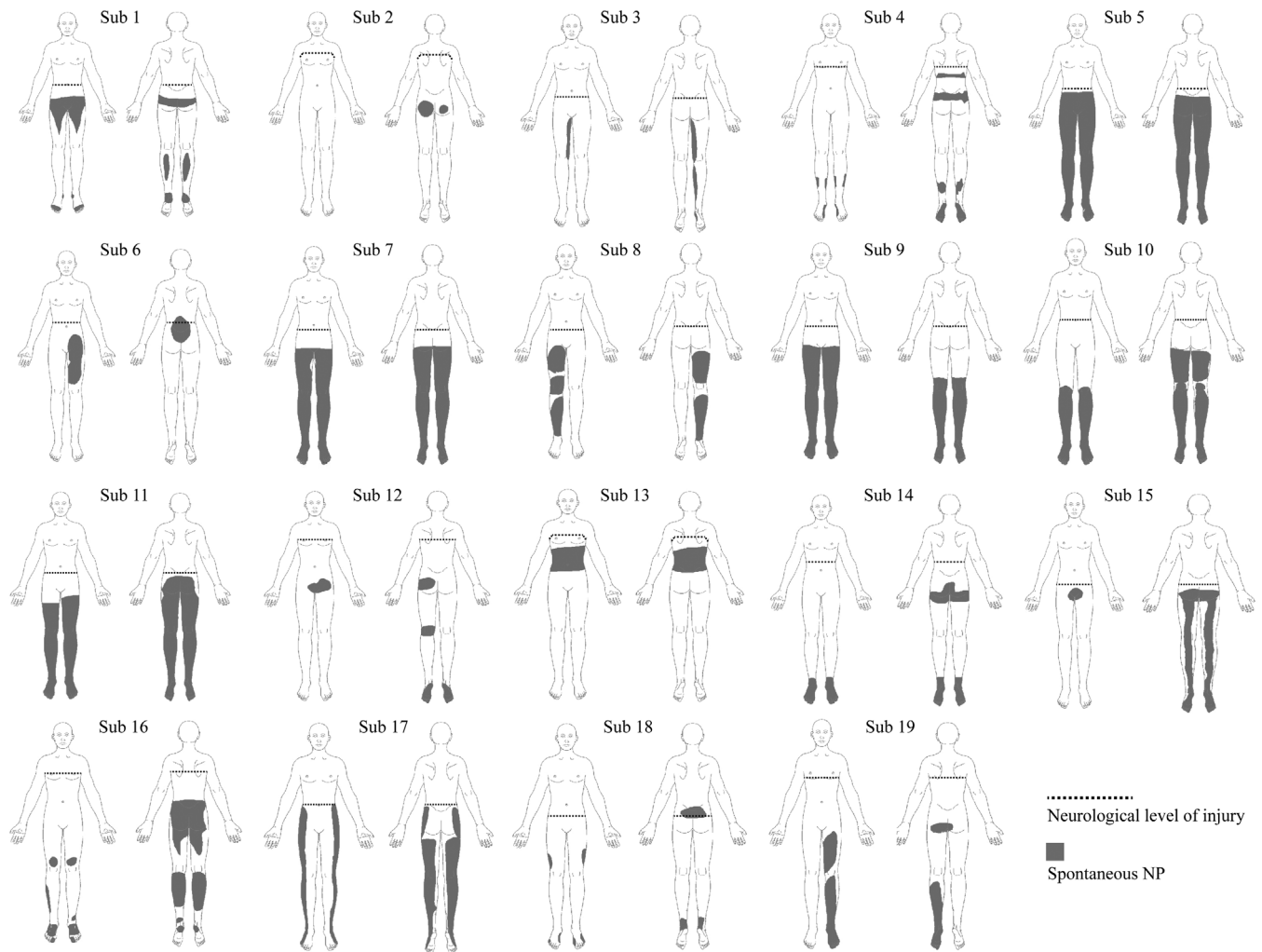
### 2.1 | Subjects

Fifty-four subjects were recruited: 29 SCI subjects (19 SCI-NP, 10 SCI-nonNP) and 25 HC. SCI subjects were contacted and recruited via flyer advertisements and phone calls from the Spinal Cord Injury Center at Balgrist University Hospital and the Swiss Spinal Cord Injury Cohort Study. The inclusion criteria were: (a) Thoracic (T1-T12) SCI and all levels of impairment as measured by the American Spinal Injury Association (ASIA) impairment scale (A-D) (Kirshblum et al., 2014); (b) no contraindications for MRI and (c) no history or presence of other medical conditions (i.e., traumatic brain injury, cancer, diabetes). The diagnosis of NP was made following current recommendations that includes the presence of a neurological lesion or disease (Finnerup et al., 2016). Briefly, typical sensory signs and symptoms had to be present within the painful area, and the pain distribution needed to follow a plausible neuroanatomical distribution with respect to the lesion level. The classification into at- and below level

pain was performed according to the recommendations of the International Association for the Study of Pain taskforce for SCI pain (Bryce et al., 2007). Nineteen out of the 30 SCI subjects experienced persistent, spontaneous NP (Figure 1). The inclusion criteria for HC were: (a) no history of neurological or other medical illness and (b) no current diagnosis of pain and pain-free during participation (one HC was excluded due to experiencing low back pain while scanning). All subjects provided written informed consent prior to the assessments and all procedures described below were in accordance with the Declaration of Helsinki. The study has been approved by the local ethics board “Kantonale Ethikkommission Zürich, KEK” (EK-04/2006, PB\_2016-02051, clinicaltrial.gov number: NCT02138344).

### 2.2 | Pain drawings and quantifying the spatial extent of NP

To assess the intensity and spatial extent of NP, each subject completed a pain drawing prior to MRI scanning. The drawing consisted of



**FIGURE 1** Spinal cord injury (SCI) subjects with chronic spontaneous NP. Diagram illustrating the area of spontaneous neuropathic pain (NP) in SCI-NP subjects. Dark grey regions indicate the body area of spontaneous NP whereas the dashed lines indicate the neurological level of SCI

a body schematic (front and back) where subjects were asked to draw the pain's location and its intensity indicated from a 0 to 10 on a numerical rating scale (NRS; 0 = "no pain" to 10 = "worst pain imaginable"). Pain experienced as a constant shooting, electric, burning, pulling or stabbing pain at- and/or below the neurological level of injury and below was considered NP (Bryce et al., 2007). This corresponds to a neuroanatomically plausible pain distribution for SCI-related NP according to accepted guidelines (Finnerup et al., 2016). Clinical judgement was used to rule out musculoskeletal pain components below the level of lesion. After MRI scanning, subjects were asked if the pain extent or intensity changed during or after the procedure. For further analyses, pain drawings prior to MRI scanning was taken into account as they did not differ extensively during or after scanning.

A standardised scheme presenting the full body dermatomes was laid on the pain drawing in order to delineate at- and below-level NP, which was distinguished as pain within or below three dermatomes of the lesion, respectively. After identifying the NP present in the subject, each affected area was highlighted and quantified into a percentage of extent (%). This was determined by the sum of total pixel count from both front and back of subjects' digitalised pain drawings and divided by the total pixel count of the body schematic. This provided the following readouts (%): overall NP and lateralised NP (left and right overall NP), at- and below-level NP. Quantifying pain extent with these pain drawings has shown excellent inter-session reliability (Rosner et al., 2021). Maximum NP intensity was taken from the area with the highest reported NRS rating.

## 2.3 | Questionnaires

Subjects completed the pain catastrophizing scale (PCS) and Beck's Depression Inventory version II (BDI) on the same day as somatosensory phenotyping.

## 2.4 | Somatosensory phenotyping

QST and CHEPs were implemented to assess thermo-sensation and spinothalamic tract (STT) integrity.

### 2.4.1 | Quantitative sensory testing

Thermal QST was performed at the right L2 dermatome (mid-thigh) for all SCI subjects and 13 HC who were able to participate in the QST session. Cold detection threshold (CDT), cold pain threshold (CPT), warm detection threshold (WDT) and heat pain threshold (HPT) measurements were performed with the PATHWAY Pain & Sensory Evaluation system (Medoc Ltd., Ramat Yishai, Israel) using a 3 cm × 3 cm square thermode attached. Each trial began with a baseline temperature of the thermode at 32°C and decreased (for

CDT/CPT) and increased (for WDT/HPT) at a rate of 1°C per second. To determine each threshold value, subjects were required to press the response unit, as they perceived a change in temperature (WDT/CDT) or at the beginning of pain sensation (CPT/HPT). Average thermal and pain thresholds were calculated after presenting three trials of individual stimuli. Safety temperatures for CPT and HPT were set at 0°C and 50°C, respectively. During the QST procedure, subjects were blinded from the operator screen.

### 2.4.2 | Contact heat evoked potentials

CHEPs were acquired according to the recently published protocol by Rosner et al., 2018 (Rosner et al., 2018) using a contact heat stimulator (Pathway Pain & Sensory Evaluation System. Medoc Ltd., Ramat Yishai, Israel). Cortical potentials to heat stimuli were recorded with 9 mm Ag/AgCl cup electrodes positioned on the vertex (Cz) referenced to the earlobes (A1-A2). The vertex position was chosen for its high reliability to record N2 and P2 potentials (Wydenkeller, Wirz, & Halder, 2008). All electroencephalographic signals were sampled with a sampling rate of 2000 Hz using a preamplifier (×20,000 [amplification rate], bandpass filter 1–300 Hz, ALEA Solutions, Zurich, Switzerland). Within a customised program on LabView (V2.04 CHEP, ALEA Solutions, Zurich, Switzerland), data was acquired with a 100 ms pre-trigger and a 1 s post-trigger. Contact heat stimuli were applied with a thermode using the increased baseline temperature, that is, from 42 to 52°C, (Kramer, Haefeli, Curt, & Steeves, 2012) at the subjects' right L2 dermatome (mid-thigh) whilst they lay in supine position. Repetitive heat stimuli were applied at an inter-stimulus interval of 9–12 s with the aim to acquire 15 artefact-free signals without exceeding 20 trials. Each signal was visually analysed and trials with obvious artefacts, that is, muscle or ocular, were discarded. The remaining signals were averaged and the N2P2 amplitude was visually inspected. CHEPs were considered "intact" if the latency lay within two standard deviations of recently published norm data (Rosner et al., 2018).

## 2.5 | MRI data acquisition

All subjects' images were obtained using a 3.0 T Philips Ingenia system (Philips Medical Systems, Best, the Netherlands) using a 32-channel Philips head coil. 3D T1-weighted (T1w) structural images were acquired with a Turbo Field Echo sequence with the following parameters: repetition time (TR), 8.1 ms; echo time (TE), 3.7 ms; flip angle (FA), 8°; number of slices, 160; slice thickness, 1 mm; field of view (FOV), 240 × 240 × 160 mm; matrix, 240 × 240 and isotropic voxel 1 × 1 × 1 mm and a scan time of 4:53 min. Resting-state functional images were acquired using an echo-planar-imaging sequence with the following parameters: TR, 2000 ms; TE, 14 ms; FA, 78°; number of slices, 40; FOV, 220 × 200 × 40 mm; matrix, 72 × 74; voxel size, 3.0 × 3.0 × 3.0 mm; reconstructed voxel size, 1.72 × 1.72 × 3 mm and a scan time of 6:00 min. Participants were instructed to relax and fixate

on a motionless cross projected on the NordicNeuroLab 32" screen (<https://www.nordicneurolab.com>). To minimise head motion, cushions were placed around subject's head.

## 2.6 | Pre-processing for voxel-based morphometry and rsFC analysis

Both raw structural T1w images and resting-state functional images were pre-processed using Statistical Parametric Mapping (SPM12) software (Statistical parametric mapping; Wellcome Department of Imaging Neuroscience, London, United Kingdom: (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB 2017a (The Mathworks, Inc, Natick, MA). Prior to pre-processing steps, structural and functional images of each subject were realigned to the anterior commissure (Montreal Neurological Institute [MNI] co-ordinates; MNI = 0, 0, 0) using SPM12 display function. Structural scans were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the New Segment tool in SPM12 (Mechelli, Price, Friston, & Ashburner, 2005). The average characteristics of study subjects' GM maps were used to create templates using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) with default values (Mechelli, Price, Friston, & Ashburner, 2005). GM volumetric maps were normalised to MNI space using the DARTEL-generated template and modulation function. For voxel-based morphometry (VBM) analysis, images were smoothed using a kernel size of 6 mm full-width at half maximum. Functional images were pre-processed in the following steps: Realignment (head motion correction), centring, slice-timing correction (ascending), outlier detection and outlier scrubbing (using ARTifact detection Tools) during the denoising step (Power et al., 2014; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), MNI normalisation and smoothing with 6 mm Gaussian FWHM. The pre-processing steps generated  $2 \times 2 \times 2$  mm resolution images for the analyses. Head motion during the resting-state scan was assessed using three translational and rotational dimensions for each scan. Subjects whose mean head motion during the functional scan exceeded +1 mm for translation and/or  $1^\circ$  for rotation were removed from rsFC analyses. During the denoising step, alongside the motion parameters, the white matter and cerebrospinal fluid signals were used as covariates of no interest to decrease the variance unlikely to reflect functional connectivity related to neuronal activity-related functional connectivity. This step has been shown to normalise the distribution of voxel-to-voxel connectivity values effectively (Behzadi, Restom, Liau, & Liu, 2007). In addition, this step generates a histogram of voxel-to-voxel functional connectivity values after regression of the selected temporal confounding factors (Susan & Alfonso, 2012). Therefore, the denoising step removes confound factors, normalises the raw functional connectivity values and increases inter-subject reliability (Susan & Alfonso, 2012). All subjects showed normally distributed data after denoising and were included for further analyses. Distribution of connectivity values before, and after denoising can be found in Data S4.

## 2.7 | Regions of interests for rsFC analyses

We included ROIs to investigate brain alterations due to both SCI and NP, these areas were generated using the WFU Pickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) (Table S1). We also included the sub-regions of the thalamus (i.e., ventroposterior, mediodorsal) and the posterior insula created with the SPM anatomy toolbox (Eickhoff et al., 2005). 6mm<sup>3</sup> spheres of the multiple insular cortex regions were also defined (anterior [AIC], middle [MIC] and posterior [PIC]; Ichresco et al., 2014), alongside the left and right ventrolateral periaqueductal grey (vlPAG) previously reported to be involved in descending pain modulation (Kong, Loggia, et al., 2010; Kong, Tu, Zyloney, & Su, 2010; Sprenger, Bingel, & Büchel, 2011) (Table S1). All ROIs were set to MNI space.

## 2.8 | VBM and rsFC analysis

Whole brain analysis was performed alongside hypothesis-led searches of a priori regions. For both VBM and rsFC analysis one-way analysis of covariance (ANCOVA) were used to investigate significant differences between the cohorts (SCI-NP, SCI-nonNP and HC). Multiple linear regression models were used to investigate the associations of overall NP extent (alongside overall left and right NP extent) and max NP intensity with altered brain regions within the SCI-NP cohort only.

For VBM analysis, voxel-wise corrected threshold for the whole brain was set at an uncorrected value of  $p < .001$  ( $k = 18$ ) to provide a  $p < .05$  cluster-level correction (Slotnick, Moo, Segal, & Hart Jr, 2003). The cluster-extent threshold was obtained with simulations using a custom software written in MATLAB (Slotnick, Moo, Segal, & Hart Jr, 2003). In a single simulation, modelling the entire image matrix ( $240 \times 240$ ), assuming a type 1 error probability of .001, and smoothing the structural data by convolution with a 6 mm FWHM Gaussian kernel, the size of each cluster of voxels was determined. After performing 10,000 simulations, probability of the cluster size was determined and the cluster extent that provided a  $p < .05$  cluster-level correction was 18 voxels, which was used as the threshold. NP intensity and overall NP extent were included as covariates and age, sex and total intracranial volume were added as covariates of no interest. For rsFC analysis, pre-processed resting-state functional data was analysed using the Functional Connectivity Toolbox (CONN 18a; [www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn)) in SPM12. CONN utilises a component-based noise correction method (CompCor) that increases selectivity, sensitivity and allows a higher degree of inter-scan reliability (Behzadi, Restom, Liau, & Liu, 2007). A band-pass filter (0.01–0.1 Hz) was applied removing linear drift artefacts and high-frequency noise. CONN also accounts for outlier data points and movement time courses as nuisance regressors. The six motion parameters, WM and CSF were included as regressors of no interest, thereby reducing noise and signal unlikely to reflect neuronal activity related to functional connectivity. NP intensity and overall NP extent were included as covariates alongside age and sex were added as

covariates of no interest. Significance was set at  $p < .05$  Family Wise Error (FWE)-level correction for multiple comparisons (with  $p < .05$  two-sided false-discovery rate [FDR] correction; Susan & Alfonso, 2012).

To visualise multiple linear regression models, rsFC strength and GMV were extracted and plotted against NP characteristics with partial correlation coefficients ( $r$ ). Fisher-transformed correlation coefficients were extracted for every ROIs analysed and summarised in separate correlation matrixes for each cohort (Data S3). Warmer colours depict stronger correlations between each ROI.

## 2.9 | Statistical analysis

Independent  $t$ -test and Chi-squared tests were performed in SPSS to assess differences in age and sex between the cohorts, respectively. The following clinical variables failed the Kolmogorov–Smirnov normality test and were analysed using nonparametric tests between

each group (Mann–Whitney rank-sum test and Kruskal–Wallis on ranks): time since injury (TSI), PCS, BDI, QST and CHEPs readouts (Table 1). Partial correlation analyses were performed to assess correlations between NP extent, intensity and age within the SCI-NP group controlling for TSI.

## 3 | RESULTS

### 3.1 | Subject demographics, somatosensory and pain phenotype

VBM results are from 53 structural datasets: 29 SCI (19 SCI-NP and 10 SCI-nonNP) and 24 HC, whereas rsFC results are from 49 resting-state functional datasets: 26 SCI (17 SCI-NP and nine SCI-nonNP) and 23 HC. One HC and one SCI-NP subject were excluded from analysis due to technical issues. One SCI-nonNP subject was excluded from rsFC analysis due to technical issues and one SCI-NP subject was

**TABLE 1** Overview of subjects' demographics, pain and somatosensory phenotypes

	HC (n = 24)	SCI-NP (n = 19)	SCI-nonNP (n = 10)	Differences between SCI sub-groups $p$
<b>Demographics</b>				
Age (years)	51.9 ± 12.9	57.2 ± 10.2	57.0 ± 10.7	0.979
Sex (F/M)	4/20	3/16	2/8	0.775
NLI	-	Th1–Th12	Th4–Th12	-
TSI (years)	-	16.3 ± 9.4	17.4 ± 14.5	0.769
AIS (A–D)	-	9A; 4C; 6D	6A; 1C; 3D	0.715
<b>Psychological questionnaires<sup>a</sup></b>				
BDI (0–63)	1.5 ± 1.6***	7.9 ± 5.2	6.2 ± 5.0	0.356
PCS (0–52)	3.4 ± 3.9**	10.9 ± 9.8	11.4 ± 9.8	0.910
<b>Pain phenotype</b>				
Overall NP (%) (n = 19)	-	16.5 ± 14.3	-	-
At-level NP (%) (n = 9)	-	1.6 ± 2.3	-	-
Below-level NP (%) (n = 19)	-	14.9 ± 12.5	-	-
Max NP intensity (0–10 NRS)	-	5.1 ± 2.0	-	-
<b>Thermal QST<sup>a</sup></b>				
CDT (°C)	30.2 ± 1.1***	10.9 ± 13.5	8.95 ± 14.4	0.804
CPT (°C)	8.9 ± 11.3	4.2 ± 8.7	2.25 ± 7.1	0.512
WDT (°C)	35.5 ± 1.8**	46.0 ± 6.2	45.7 ± 7.0	0.946
HPT (°C)	45.8 ± 4.6**	48.5 ± 3.4	49.6 ± 1.4	0.512
<b>CHEPs<sup>a</sup></b>				
Intact CHEPs	100%	58%	48%	-
N2/P2 amplitude (µV)	27.1 ± 11.1	33.4 ± 21.3	19.0 ± 6.1	0.171
N2 latency (ms)	325.4 ± 28.2**	365.2 ± 72.2	428.4 ± 81.6	0.368

Note: Summary of subjects' information. Mean and standard deviations are reported.  $p$  = significance value. Statistical significance set at  $p < .05$  indicated by italics. \* ( $p < .05$ ), \*\* ( $p < .01$ ), \*\*\* ( $p < .001$ ) = significant difference with whole SCI cohort.

Abbreviations: AIS, ASIA Impairment Scale: A, sensorimotor complete, C and D, sensorimotor incomplete; BDI, Beck's Depression Inventory; CDT, cold detection threshold; CHEPs, contact heat evoked potentials; CPT, cold pain threshold; HPT, heat pain threshold; NLI, neurological level of injury; NP, neuropathic pain; NRS, numerical rating scale; PCS, pain catastrophizing scale; QST, quantitative sensory testing; Th, thoracic; TSI, time Since Injury; WDT, warm detection threshold.

<sup>a</sup>Data only collected in 13 HC.

excluded from rsFC analysis due to excess head movement. No other subjects exceeded 1 mm head motion and were deemed suitable for the analysis. The mean composite motion (maximum voxel displacement from the combined translational and rotational displacement) of each group were  $0.24 \pm 0.09$  for HC,  $0.22 \pm 0.07$  for SCI-NP and  $0.4 \pm 0.24$  for SCI-nonNP (Data S1). Inspection of T1w images revealed no gross abnormalities for included subjects and all resting-state fMRI data were normally distributed after denoising.

The whole SCI group had a mean age of  $57.1 \pm 10.2$  and an injury chronicity of  $16.7 \pm 11.2$  years. Fifteen SCI subjects had a sensorimotor complete lesion (ASIA Impairment Scale [AIS] A) and 14 had a motor incomplete lesion (5 AIS C, 9 AIS D). Nine of 15 SCI subjects with a sensorimotor complete lesion had NP (60%), whereas eight of 14 SCI subjects with a motor incomplete lesion had NP (57%). No differences in age or sex were seen between HC and the whole SCI group ( $p = .11$ ,  $p = .76$ , respectively) and SCI sub-groups: SCI-NP ( $p = .15$ ,  $p = .82$ , respectively) and SCI-nonNP ( $p = .28$ ,  $p = .79$ , respectively). SCI subjects scored significantly higher on BDI and PCS questionnaires compared to HC ( $p < .001$  and  $p = .004$ , respectively; Table 1).

Compared to the 13 HC who participated in somatosensory phenotyping, SCI subjects showed an overall impairment of STT integrity CDT ( $p < .001$ ); CPT ( $p = .103$ ); WDT ( $p < .001$ ); HPT ( $p = .008$ ); CHEPs N2P2 amplitude ( $p = .794$ ) and N2 latency ( $p = .004$ ). However, no differences in age, sex, time since injury, BDI, PCS and somatosensory phenotype were observed between the SCI-NP and SCI-nonNP subjects (Table 1).

Within the SCI-NP cohort, age was positively correlated to max NP intensity ( $r = .678$ ,  $p = .002$ ). Overall NP extent was not correlated to max NP intensity ( $r = .303$ ,  $p = .222$ ). Pain phenotypes are summarised in Table 1 and Figure 1. Full details of NP extent that is, overall NP (total and lateralisation), at- and below-level NP percentages can be found in Table S2.

### 3.2 | Brain volumetric and rsFC differences between cohorts

#### 3.2.1 | Brain volumetric differences

Compared to HC, SCI-NP subjects showed small decreases of GMV in the frontal gyrus (Table S3). On the other hand, SCI-nonNP subjects showed increases of GMV in the precuneus, superior parietal lobule (SPL), ACC and orbital frontal gyrus (OFG) and decreased GMV in the right inferior temporal gyrus and left middle-posterior insula (Table S3). No significant volumetric differences were observed between SCI-NP and SCI-nonNP ( $p > .05$  cluster-level correction).

#### 3.2.2 | rsFC alterations

Table 2 summarises rsFC differences between the three cohorts using the ROI analysis (all  $p < .05$  FWE-level corrected).

Compared to HC, SCI-NP subjects showed stronger rsFC between the right ventroposterior thalamus and left medial OFG. SCI-NP subjects also showed stronger rsFC between the right dorsomedial PFC and left angular gyrus compared to SCI-nonNP (Figure 2, Table 2).

SCI-nonNP subjects showed decreased rsFC between the right dorsomedial PFC to right SPL and left angular gyrus compared to HC (Table 2).

### 3.3 | Association of NP extent and intensity with brain volume and rsFC in SCI-NP subjects

Greater NP extent is associated with stronger rsFC and higher GMV of brain regions involved with pain processing in SCI-NP subjects (Table 3, Figures 3a and 4a). SCI-NP subjects with greater NP extent displayed higher GMV was observed of the left SFG/SMA, right SMC and left posterior insula (Table 3, Figure 3a). In addition, SCI-NP subjects with greater overall NP extent on the right side showed stronger rsFC between the left PIC to thalamic sub-regions (Table 3, Figure 4a).

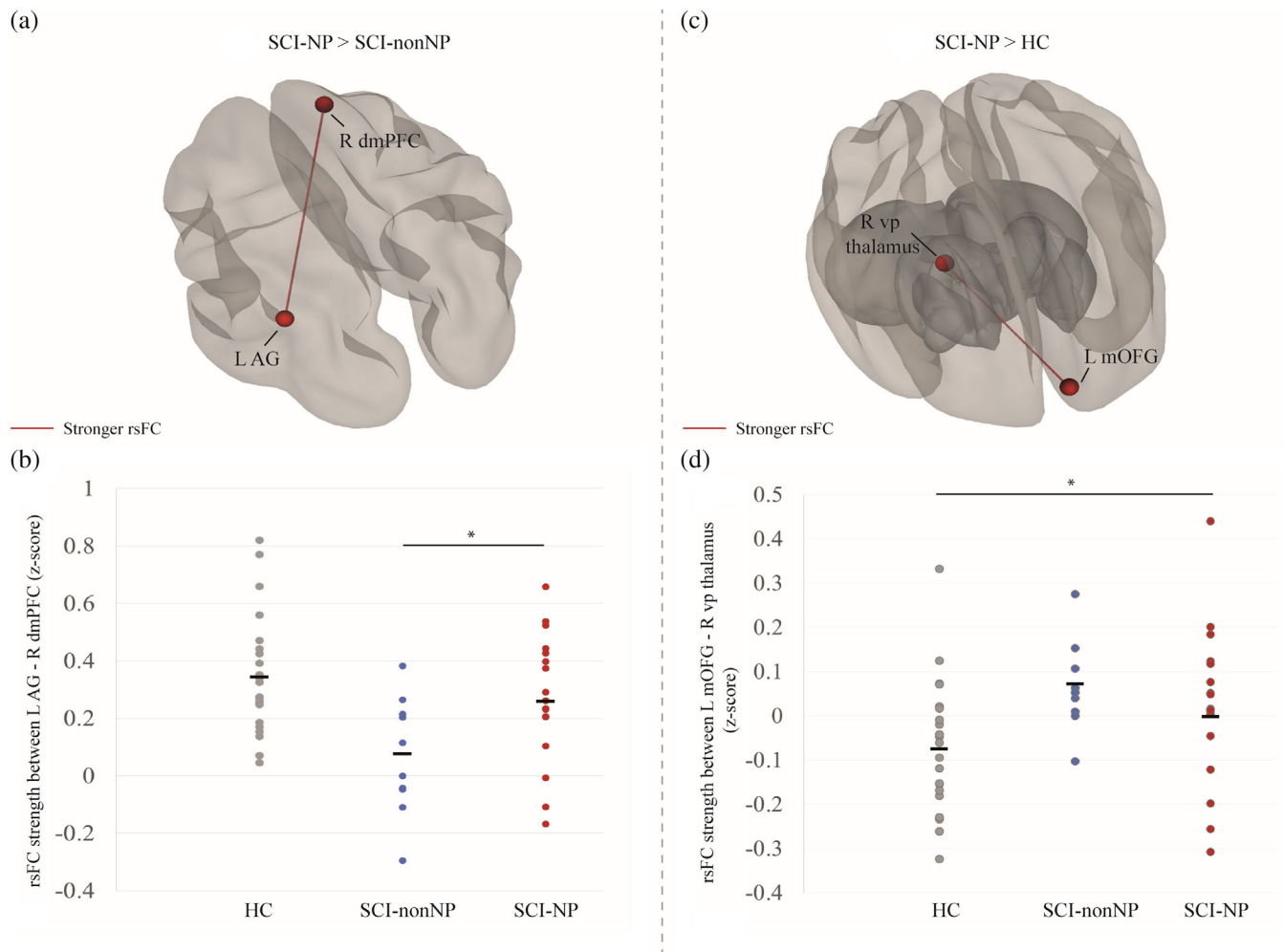
SCI-NP subjects with a greater NP intensity showed stronger rsFC between the right AIC to right amygdala ( $p$ -FDR two-sided =  $.008$ ) and left SPL to left angular gyrus ( $p$ -FDR two-sided =  $.008$ ) (Figure 4e). On the contrary, greater NP intensity was related to lower GMV of the thalamus, ACC, middle frontal gyrus and temporal lobes (Figure 3c, Table 4;  $p < .05$  cluster-level corrected).

**TABLE 2** rsFC differences between groups

Brain region(s) showing rsFC differences ( $p < .05$ FWE-level corrected)	$p$ Value (FDR two-sided)	$t$ Value
<b>SCI-nonNP versus HC</b>		
<i>HC &gt; SCI-nonNP:</i>		
R dmPFC–L AG	.048	3.44
R dmPFC–R SPL	.048	3.34
<i>SCI-nonNP &gt; HC</i>	–	–
<b>SCI-NP versus HC</b>		
<i>SCI-NP &gt; HC:</i>		
R ventroposterior thalamus–L medial OFG	.048	3.60
<i>HC &gt; SCI-NP</i>	–	–
<b>SCI-NP versus SCI-nonNP</b>		
<i>SCI-NP &gt; SCI-nonNP:</i>		
R dmPFC–L AG	.031	3.74
<i>SCI-nonNP &gt; SCI-NP</i>	–	–

Note: Overview of rsFC differences between cohorts. All rsFC results are presented as  $p < .05$  FWE-level corrected (with FDR two-sided correction).

Abbreviations: AG, angular gyrus; dmPFC, dorsomedial prefrontal cortex; L, left; OFG, orbital frontal gyrus; R, right; SCI, spinal cord injury; SCI-nonNP, spinal cord injury without neuropathic pain; SCI-NP, spinal cord injury with neuropathic pain.



**FIGURE 2** Stronger rsFC in SCI subjects with chronic spontaneous NP. Illustrations of rsFC changes in SCI-NP subjects compared to non-NP cohorts ( $p < .05$  FWE-level corrected). (a–b) Stronger rsFC between the left angular gyrus (AG) and right dorsomedial prefrontal cortex (dmPFC) in SCI-NP subjects compared to SCI-nonNP subjects. (c–d) Stronger rsFC between the right ventroposterior (vp) thalamus and left medial orbital frontal gyrus (mOFG) compared to HC. HC, healthy controls; L, left; rsFC, resting-state Functional Connectivity; R, right; SCI-NP, spinal cord injury with neuropathic pain; SCI-nonNP, spinal cord injury without neuropathic pain. Z-scores are Fisher-transformed correlation coefficients. Scatter plots are presented for visualisation

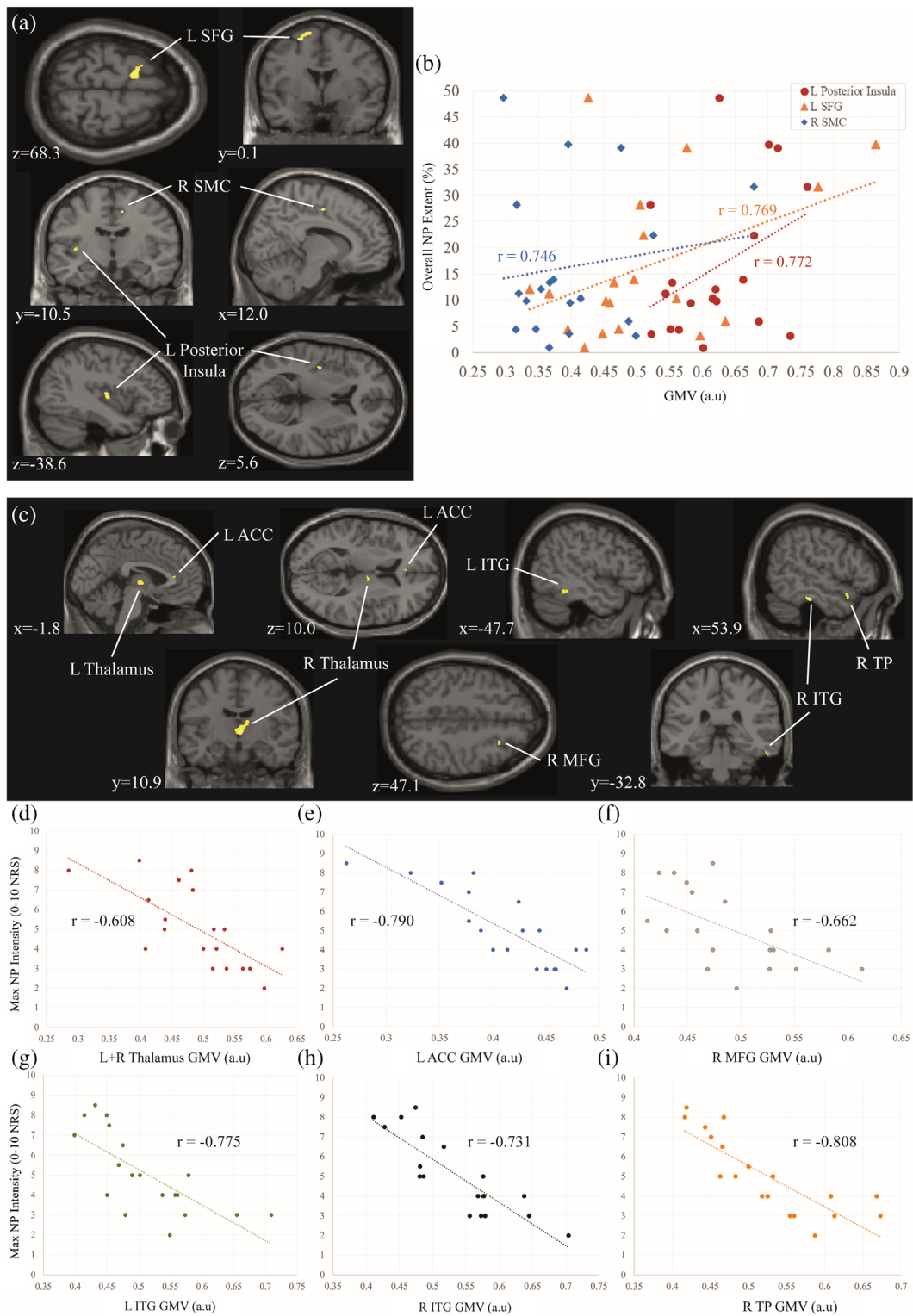
**TABLE 3** Influence of NP extent on GMV and rsFC within SCI-NP subjects

Positive correlations with NP extent	Significant brain regions	MNI co-ordinates of peak clusters (x, y, z)	t Value	Cluster size
<b>GMV</b>				
Overall NP extent	L SFG/SMA	-14, -1, 69	5.29	438
	L posterior insula	-39, -12, 2	4.30	52
	R supplementary motor cortex	11, -10, 49	4.70	39
Positive correlations with NP extent	Significant brain regions	p value (FDR two-sided)	t Value	
<b>rsFC</b>				
Overall NP extent R	L PIC–L thalamus (ventrolateral)	.038	3.83	
	–L thalamus (mediodorsal)	.004	5.72	
	–L thalamus (ventroposterior)	.019	4.41	

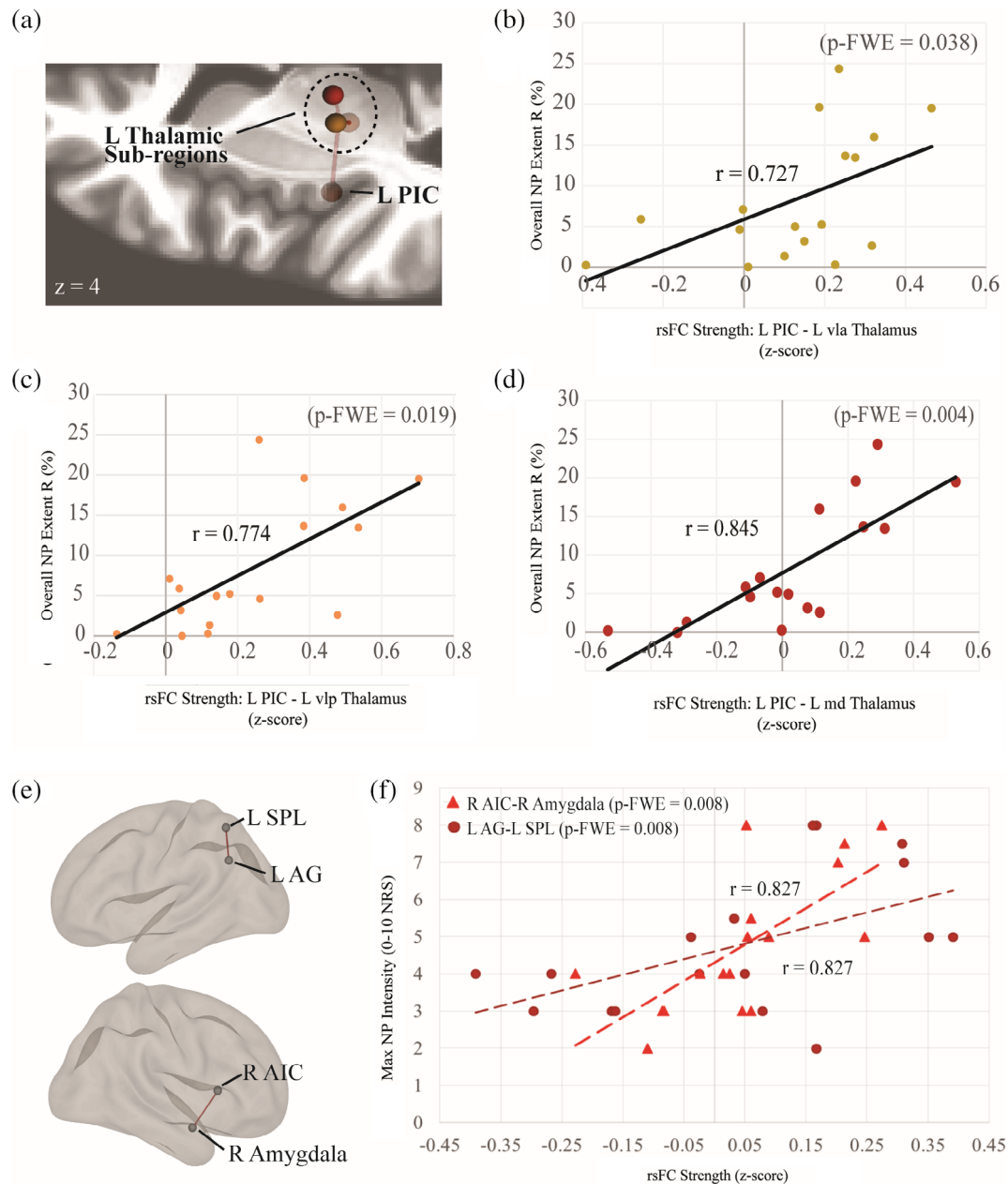
Note: Positive associations of NP extent with GMV and rsFC within SCI-NP subjects. GMV results are presented at  $p < .05$  cluster-level corrected; rsFC results are presented as  $p < .05$  FWE-level corrected (with FDR two-sided correction).

Abbreviations: GMV, grey matter volume; L, left; MNI, Montreal Neurological Institute; NP, neuropathic pain; PIC, posterior insular cortex; R, right; rsFC, resting-state functional connectivity; SCI-NP, spinal cord injury with neuropathic pain; SFG, superior frontal gyrus; SMA, supplementary motor area.





**FIGURE 3** Pain phenotype is associated with GMV alterations of pain-related regions. Illustrations of GMV changes associated with pain phenotype in SCI-NP subjects ( $p < .05$  cluster-level corrected). (a) Positive associations between overall NP extent and GMV of the left superior frontal gyrus (SFG), posterior insula and right supplementary motor cortex (SMC). (c) Negative associations between NP intensity and GMV of the left thalamus, anterior cingulate cortex (ACC), right middle frontal gyrus (MFG), bilateral inferior temporal gyrus (ITG) and right temporal pole (TP). (b, d-i) Scatter plots and partial correlation coefficients are presented for visualisation. GMV, grey matter volume; L, left; NP, neuropathic pain; NRS, numerical rating scale; R, right; SCI-NP, spinal cord injury with neuropathic pain. GMV are in arbitrary units



**FIGURE 4** Pain phenotype is associated with rsFC alterations of lateral and medial pain processing pathways. Illustrations of rsFC changes which are positively associated with the pain phenotype in SCI-NP subjects ( $p < .05$  FWE-level corrected). (a) Positive associations between rsFC strength of the left (L) posterior insular cortex (PIC) to thalamic sub-regions and NP extent on the right side. (e) Positive associations between rsFC of the right (R) anterior insular cortex (AIC) to right amygdala and left superior parietal lobule (SPL) to left angular gyrus (AG) with max NP intensity. (b–d, f) Scatter plots and partial correlation coefficients are presented for visualisation. L, left; md, mediadorsal; NP, neuropathic pain; NRS, numerical rating scale; rsFC, resting-state functional connectivity; R, right; SCI-NP, spinal cord injury with neuropathic pain; vla, ventrolateral anterior; vlp, ventrolateral posterior. Z-scores are Fisher-transformed correlation coefficients

## 4 | DISCUSSION

To our knowledge, this is the first study to observe an association of NP extent upon brain connectivity and structure in chronic SCI. Overall, the findings of this study indicate that SCI-related NP is accompanied by upregulated neural activity of prefrontal cortices and sensory integrative regions, including the medial and lateral pain processing pathways which could be contributing to more intense and widespread NP, respectively.

### 4.1 | NP phenotype in SCI-NP subjects is associated with alterations of pain processing pathways

Our findings support the original claim that the quantification of pain extent could be a useful clinical marker for the degree of centralised pain and offers valuable insight when combined with neuroimaging methods (Kutch et al., 2017). SCI-NP subjects with greater NP extent

**TABLE 4** Negative associations of GMV with max NP intensity

	Significant brain region(s)	MNI co-ordinates of peak clusters (x, y, z)	t Value	Cluster size
Negative associations with max NP intensity	R ITG	55, -30, -25	6.31	92
	L + R thalamus	3, -11, -1	5.38	910
		11, -8, 14	4.40	
	L ACC	-2, 33, 11	4.05	22
	R MFG	28, 18, 48	4.29	20
	R temporal pole	54, 14, -21	4.84	74
	L ITG	-48, -43, -17	4.66	67

Note: Negative associations of grey matter volume (GMV) and neuropathic pain (NP) intensity in SCI-NP subjects with multiple linear regression. Volumetric results were significant at  $p < .05$  cluster-level correction.

Abbreviations: ACC, anterior cingulate cortex; ITG, inferior temporal gyrus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; NP, neuropathic pain; R, right.

showed stronger rsFC of the contralateral posterior insular and thalamic sub-regions (Table 3; Figure 4a), suggesting a relationship between the sensory-discriminative pain pathway (Groh, Krieger, Mease, & Henderson, 2018) and greater NP extent. We also observed structural increases of the posterior insula, SMC and SFG/SMA with greater NP extent (Figure 3a). Although it is unknown what greater GMV reflects at the neuronal level, a study with fibromyalgia subjects suggests an involvement of neuronal plasticity (Pomares et al., 2017). Therefore, we propose that greater NP extent in SCI-NP subjects is associated with increases in volume and connectivity strength within regions of the lateral pain pathway.

Furthermore, greater NP intensity was associated with stronger rsFC of regions involved with affective-motivational (limbic) components of pain, attention and polymodal sensory integration in our SCI-NP cohort (Figure 4e). The amygdala and anterior insular regions are known to have reciprocal connections and is part of the limbic circuitry involved with fear, anxiety and affective-motivational components of pain processing (Ghaziri et al., 2018; Martucci & MacKey, 2018; Moayed, Salomons, & Atlas, 2018; Neugebauer, Li, Bird, & Han, 2004; Thompson & Neugebauer, 2017; Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). Stronger rsFC between the amygdala to the executive network have been observed in chronic low back pain (Jiang et al., 2016) and the anterior insula cortices is altered in a variety of chronic pain conditions, that is, osteoarthritis (Cottam, Iwabuchi, Drabek, Reckziegel, & Auer, 2018), diabetic neuropathy (Cauda et al., 2009) complex regional pain syndrome and fibromyalgia (Ichesco et al., 2014). Although the specific role of the parietal lobe in pain perception is unclear, previous electrophysiological studies in rhesus monkeys have shown nociceptive processing within the SPL but may be processed with other sensorimotor information (Dong et al., 1989; Dong, Hayashi, Roberts, Fusco, & Chudler, 1996). The angular gyrus also functionally integrates multiple inputs and is subpart of the default-mode network (Seghier, 2013) which is altered in a variety of chronic pain conditions (Martucci & MacKey, 2018) including: altered rsFC of brain regions involved with sensorimotor functions (Kutch et al., 2015), reward and motivation processes (Apkarian et al., 2004; Berger et al., 2014). Moreover, NP

intensity was associated with large GMV decreases of the primary sensory relay and smaller GMV decreases in regions involved with cognition and descending pain modulation (Figure 3c). The ACC plays key roles in descending pain modulation (Ossipov, Dussor, & Porreca, 2010; Ossipov, Morimura, & Porreca, 2014), affective-motivational components of pain (Fuchs, Peng, Boyette-Davis, & Uhelski, 2014; Talbot, Madden, Jones, & Moseley, 2019) and its abnormalities are considered important in pain chronification (Bliss, Collingridge, Kaang, & Zhuo, 2016). Furthermore, the right MFG is part of the dorsolateral prefrontal cortex involved in the perceived control of pain (Wiech et al., 2006), individual pain sensitivity (Sevel, Letzen, Staud, & Robinson, 2016) and is a site of structural abnormalities in various chronic pain cohorts (Seminowicz & Moayed, 2017). The temporal lobe is also involved in processing varying amounts of pain, showing altered activity during high and low intensities of painful stimulus (Kong, Loggia, et al., 2010; Kong, Tu, et al., 2010).

The findings in this study indicate that stronger synchronicity of the lateral and medial pain processing pathways, attention/saliency and multi-sensory integrative regions accompany more severe NP in SCI-NP subjects. Interestingly, higher NP intensity is also related to structural atrophy of regions involved with differing roles in pain processing. Since NP extent was not significantly correlated with NP intensity these particular characteristics of NP may be driven by differing underlying mechanisms reflected in different brain regions.

#### 4.2 | SCI-NP is associated with stronger rsFC between regions involved with cognitive control of pain and thalamocortical pathways

SCI-NP subjects in this study displayed stronger rsFC between the prefrontal cortices to the ventroposterior thalamus and angular gyrus indicating an upregulation of networks involved with cognition, sensory and pain processing (Figure 2). Abnormalities of the prefrontal cortex may contribute to pain chronification through via multiple complex connections to the PAG, basal nuclei, thalamic nuclei and amygdala (see review: Ong, Stohler, & Herr, 2019). The ventroposterior thalamus primarily

relays nociceptive signals to the somatosensory cortex, is involved with the sensory-discriminative components of pain, (Groh, Krieger, Mease, & Henderson, 2018; Groh, Mease, & Krieger, 2017) and shows structural and functional abnormalities, for example, decreased  $\gamma$ -aminobutyric acid, in SCI-related NP (Gustin et al., 2010, 2014). More recently, stronger rsFC between insula sub-regions to the hippocampus, temporal and occipital cortices were also observed in SCI-NP subjects compared to HC and SCI-nonNP subjects (Li et al., 2020). Taken together, stronger rsFC within cognitive networks and thalamocortical pathways may accompany and contribute to chronic NP.

Our SCI-NP cohort also showed small decreases of GMV in the frontal regions compared to HC, but no significant differences compared to SCI-nonNP subjects. Previous studies have shown bidirectional changes of GMV within chronic pain conditions (May, 2008; Schmidt-Wilcke, 2015) including NP after SCI (Jutzeler et al., 2016; Mole, MacIver, Sluming, Ridgway, & Nurmikko, 2014). Whilst decreases in GMV of pain processing regions is placed in context with “maladaptive structural plasticity” (Flor et al., 1995; May, 2008), increases could be linked to “preserved structure” potentially associated with persistent nociceptive input to the brain (Makin et al., 2013) and changes in neuronal plasticity, that is, receptor density (Pomares et al., 2017). Although VBM cannot ascertain the underlying neurobiological correlates (Mechelli, Price, Friston, & Ashburner, 2005), decreases of GMV could reflect a loss of inhibitory interneurons (Foerster et al., 2012) and/or neuronal degenerative processes, that is, shrinkage, apoptosis, transneuronal degeneration (Schmidt-Wilcke, 2015). While our findings are inconsistent with previous studies observing structural alterations of pain processing regions in SCI-NP subjects compared to SCI-nonNP subjects (Jutzeler et al., 2016; Mole, MacIver, Sluming, Ridgway, & Nurmikko, 2014), we observed small decreases of GMV in the bilateral frontal gyrus of SCI-NP subjects compared to HC as reported previously (Yoon, Kim, Shin, Lee, & Kim, 2013). Furthermore, insignificant GMV differences (of insular sub-regions) between SCI-NP and SCI-nonNP subjects was observed in a recent study (Li et al., 2020). Taken together, small decreases in GMV of the frontal regions may accompany SCI-NP subjects compared to healthy cohorts whilst GMV changes may not be significant compared to SCI-nonNP subjects. As there are a limited number of studies to date, future studies are required to corroborate the GMV differences between SCI-NP and SCI-nonNP subjects.

Interestingly, no observable differences in somatosensory profiles between SCI-NP and SCI-nonNP subjects were found (Table 1), indicating that STT integrity may not play a role in the presence of NP within this particular cohort. Although studies have observed both impaired, (Gruener, Zeilig, Laufer, Blumen, & Defrin, 2016) and more STT functional integrity (Wasner, Lee, Engel, & McLachlan, 2008) in SCI-NP subjects compared to SCI-nonNP subjects, the relation to brain differences remains unclear. A recent neuroimaging study explored the brain activity of SCI subjects during innocuous brushing below the level of injury (Wrigley, Siddall, & Gustin, 2018). This study showed significant activation of S1 in 48% of sensorimotor complete SCI subjects, indicating preserved (dorsal column) pathways below the level of injury in clinically complete subjects. No correlation was

observed with preserved pathways and the presence of NP (Wrigley, Siddall, & Gustin, 2018).

### 4.3 | Global changes in brain connectivity and structure after SCI without NP

SCI-nonNP subjects displayed decreased rsFC between the dorsomedial prefrontal cortex and the parietal lobe indicating abnormal synchronicity between regions involved with cognitive function and multimodal integration including spatial attention (Table 3). Previous studies that included a variety of SCI subjects have observed both decreases and increases of connectivity in sensory and motor regions/networks (Hou, Sun, et al., 2014, Hou, Yan, et al., 2014, 2016; Min et al., 2015; Oni-Orisan et al., 2016; Pan et al., 2017) and decreases of connectivity within other core networks, that is, default-mode and salience network (Hawasli et al., 2018; Kaushal et al., 2017). Our SCI-nonNP cohort also showed bidirectional volumetric brain changes (Table S3). Decreased GMV of the right inferior temporal gyrus and left middle-posterior insula may indicate atrophy of regions involved with cognitive and sensory impairment whilst higher GMV in the ACC, OFG, SPL, precuneus, and hippocampus may be related to compensatory mechanisms after thoracic SCI. Interestingly, increases of the hippocampus in chronic SCI subjects after a period of training have been observed before (Villiger et al., 2015). Previous studies have identified a broad range of volumetric changes following SCI, that is, no changes or decreases in primary sensorimotor cortices, cerebellum, frontal and temporal areas (Chen et al., 2017, 2018, 2019; Crawley et al., 2004; Freund et al., 2011, 2013; Grabher et al., 2015; Henderson, Gustin, Macey, Wrigley, & Siddall, 2011; Hou, Sun, et al., 2014, Hou, Yan, et al., 2014; Jurkiewicz, Crawley, Verrier, Fehlings, & Mikulis, 2006; Jutzeler et al., 2016; Karunakaran et al., 2018; Lundell et al., 2011; Mole, MacIver, Sluming, Ridgway, & Nurmikko, 2014; Seif et al., 2018; Wrigley et al., 2009). The variety of structural findings in current literature may reflect the variability within SCI cohorts that is, chronicity, injury level, completeness, presence of NP, and the analytic approach, that is, whole brain or ROI (Huynh et al., 2020). We particularly observed divergent volumetric changes when comparing SCI sub-groups to HC—the presence of NP after SCI causes some decreases in GMV and is contrary to GMV increases observed in SCI-nonNP subjects (Table S3).

### 4.4 | Limitations and methodological considerations

There are some limitations to consider in this study. The sample size of the SCI-nonNP group ( $n = 10$ ) was smaller than the SCI-NP group ( $n = 19$ ), which may overlook differences in other brain regions due to statistical power. In addition, the mean head motion of SCI-nonNP were significant compared to HC and SCI-NP (Data S1), although this was corrected for in the analysis and the groups were well-matched in demographics (Table 1). Surprisingly,

we only observed a significant association of overall NP extent on the right side with rsFC changes (Figure 4a), which could be due to the number of subjects included in this study. However, the lateralised effects of NP extent were also observed with volumetric changes of the left posterior insular cortex (Figure 3a; Table 3), which may also suggest underlying supraspinal changes that accompany NP extent. In combination, investigating NP based on body percentage and lateralisation may be sensitive to supraspinal changes, however, our study is limited based on our small cohort with high variation of pain phenotype. Characterising the NP extent in a larger cohort will be necessary for future studies.

Nine out of 19 SCI-NP subjects and three out of 10 SCI-nonNP subjects were on analgesic medication (Table S2). Due to ethical and practical reasons, it was not possible to investigate these subjects off medication for several days/weeks. Indeed, chronic pain sufferers either use or do not use various pain medications which can confound structural and functional changes of the brain. Although a previous study has shown minimal relationship between medication and rsFC in cohorts with chronic pain (Baliki, Mansour, Baria, & Apkarian, 2014), different forms of medication may exert differing effects on rsFC. For example, cannabinoid use increases fronto-striatal rsFC (Bhattacharyya et al., 2015) and ketamine use in healthy subjects decreased rsFC between the prefrontal cortex and default-mode network (Scheidegger et al., 2012). Therefore, the complex interactions of medication use in our cohort is a confounding factor for our results and requires future investigation in larger cohorts of SCI subjects. For the analyses, we implemented a ROI-approach for the rsFC analysis to be consistent with previous studies investigating SCI and chronic pain, whilst using a whole-brain approach for VBM. Although we applied a strict threshold to correct for the rsFC results as done in a recent study (Li et al., 2020), we implemented a cluster-level correction based on uncorrected p-values to investigate GMV changes. Therefore, a careful interpretation of the underlying mechanisms is required and larger cohorts of SCI patients with and without NP are necessary to corroborate our results. In addition, whilst rsFC investigates the correlations of spontaneous activity between remote brain areas (Fox & Greicius, 2010; Fox & Raichle, 2007), the causal relationships between the observed regions cannot be determined. Future studies that implement methods such as effective connectivity, may be able to probe the directionality of communication between pain processing regions.

Nevertheless, we observed novel group differences in rsFC and an effect of NP extent in both VBM and rsFC analyses, alongside some volumetric differences in line with previous literature. In general, MRI readouts may be confounded by factors such as inter-individual differences in brain structure, head movement and cardiac-respiratory noise. Hence, correcting for these parameters, that is, DARTEL registration, motion and CompCor correction allows a higher validity for interpretation.

## 4.5 | Summary

Our findings may have implications for future neuroimaging studies investigating SCI-related NP or other pain conditions. This study

observed stronger connectivity in SCI-NP subjects between prefrontal cortices and regions involved with nociceptive transmission and multi-modal integration compared to SCI-nonNP subjects.

Moreover, we provide corroborating evidence that characterising pain extent offers additional value to the assessment of pain intensity, and allows a broader understanding of the neural plastic changes that accompanies subjects' pain phenotype. NP extent in our particular cohort of SCI-NP subjects demonstrated higher structure and underlying connectivity of regions involved with pain, including the lateral pain system. Furthermore, NP intensity was associated with stronger connectivity between regions involved with the affective-motivational components of pain and multi-modal integration alongside decreased structure of brain areas involved with cognition and descending pain modulation. In sum, the processes of neural plasticity accompany chronic NP following SCI.

Prospective neuroimaging studies that investigate both pain extent and intensity in chronic pain conditions may provide valuable insight to the potentially differing mechanisms reflected in the brain (Kutch et al., 2017). Future longitudinal studies are necessary to understand the onset of NP following SCI and the accompanying pain phenotype with remote brain changes.

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## CONFLICT OF INTERESTS

The authors report no competing interests.

## DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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