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Master’s in Health Science and Technology

Major in “Rehabilitation and Inclusion”

**Structural Brain deviations in Spinal cord injury and neuropathic pain**

**Master Thesis**

Submitted by:

Valentina Haas

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Supervisors:

Prof. Dr. John LK Kramer, Associate Professor

Dr. Sc. ETH Paulina S. Scheuren, Postdoctoral Fellow,

International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

ETH Supervisor:

Prof. Dr. Olivier Lambercy

Adjunct Professor at the Department of Health Sciences and Technology at ETH Zurich, Zurich, Switzerland

# Abstract

Spinal cord injury leads to severe motor, sensory, and autonomic dysfunction, which is often accompanied by neuropathic pain. Neuroimaging studies have demonstrated structural brain alterations after spinal cord injury, but methodological limitations such as small, unmatched control groups make generalizability difficult. This study applied normative modeling to identify individual-level cortical and subcortical deviation in participants with spinal cord injury and assess association with neuropathic pain. We analyzed T1-weighted MRI scans from 34 participants with spinal cord injury (24 with and 10 without neuropathic pain) using Braincharts, a normative modelling framework trained on over 58’000 healthy controls. Cortical thickness and subcortical volume were compared to age- and sex-adjusted trajectories.

Participants with spinal cord injury showed reduced cortical thickness in prefrontal, sensorimotor and temporal regions and increased thickness in occipital and parietal areas. Subcortical volume reductions were observed in the pallidum and amygdala. Deviations from the normative model were more widespread in participants with spinal cord injury and neuropathic pain, with some structural changes correlating with pain intensity and extent. In contrast, certain regions showed a bigger difference in participants with spinal cord injury without neuropathic pain, indicating supraspinal plasticity independent of pain.

This study demonstrates the applicability of normative modeling in spinal cord injury and enables to detect brain deviations, without relying on traditional control groups.

**Keywords:** cortical thickness; braincharts; neuropathic pain, brain normative modeling, spinal cord injury, morphometry, subcortical volume,

Author affiliations:

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# Introduction

Spinal cord injury (SCI) is a traumatic or non-traumatic damage to the spinal cord, which affects over 20 million individuals1. It leads to severe consequences affecting motor, sensory, and autonomic functions at or below level of injury2. The underlying cause is the disruption of ascending and descending neural pathways3. Following SCI, maladaptive plasticity and central nervous system reorganisation, including spinothalamic tract deafferentation, loss of inhibitory pain modulation, increased pain excitability, and neuroinflammatory processes are contributing to the development of neuropathic pain4–6. Approximately 53% of individuals with SCI experience neuropathic pain7. According to the International Association for the Study of Pain (IASP), neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory nervous system”8,9. Most commonly, neuropathic pain manifests at or below the level of injury and is one of the most severe and disabling pain following SCI7,10.

Different neuroimaging studies show that individuals with SCI and neuropathic pain exhibit alterations both brain structure and function. These structural changes include region-specific increases and decrease in grey matter volume (GMV) and white matter integrity in various cortical areas. For instance, individuals with NP following a spinal cord injury exhibit a decrease in GMV in the thalamus and somatosensory cortex, but an increase in GMV in the anterior cingulate cortex and motor cortex. The degree of these changes correlates with pain intensity11,12.

However, existing studies in SCI population are limited by methodological constraints, such as a small sample size and unmatched control groups. For example, Jutzler et al (2016)12 acknowledged that their SCI and control groups were not matched for gender, and in the meta-analysis by Wang et al. (2019)13 several included studies exhibited age differences between groups. Solstrand Dahlberg et al (2018)14 quantitative meta-analysis and review of brain changes after SCI. In the paper it was highlighted that future SCI research would benefit from comparisons to normative datasets, as used in large-scale neuroimaging studies in psychiatry and dementia. Specifically, they advocated for harmonized data collection and comparison to normative datasets to improve generalizability and reproducibility.

To address these limitation, the present study is the first to apply a normative modeling framework to a SCI cohort using the Braincharts platform15. This approach enables to assess individualized age- and sex-adjusted structural brain differences. Normative modeling is based on the understanding that brain structure evolves systematically through the human lifespan, from early to late adulthood. Braincharts model was trained on MRI data from 58’836 participants across 82 scanning sites, covering an age range from 2 to 100 years, providing reference trajectories for cortical and subcortical features. This offers a powerful alternative to group-based comparison and supports a more precise and generalizable characterization of brain deviations in SCI.

The aim of this study is to assess the deviations in SCI in cortical and subcortical features based on the normative model.

The primary aim of this study is to identify cortical and subcortical structural deviations in individuals with SCI using a normative modeling approach. By comparing individual brain morphometry to age- and sex-adjusted normative trajectories, the aim is to characterize patterns of brain alterations beyond conventional group comparison. Additionally, a subgroup analysis will assess whether the presence of neuropathic pain following SCI is associated with disentangling pain-related changes from those primarily driven by the injury itself. Finally, correlations between brain deviations and pain ratings are further explored, to identify the association between structural alterations and pain.

# Methods

## Study design

We performed a secondary analysis of structural MRI data from participants with SCI and healthy controls (HC). The data were originally collected as part of three earlier studies conducted at the Spinal Cord Injury Center, Balgrist University Hospital, University of Zurich, Switzerland (Huynh et al. (2021)16, Huynh et al. (2022)17, and Huynh et al. (2023)18).

All procedures were in accordance with the Declaration of Helsinki and were approved by the local ethics committee “Kantonale Ethikkommission Zürich, KEK” (EK-04/2006, PB\_2016–02,051, clinicaltrial.gov number: NCT02138344). Written informed consent was obtained from all participants.

## Study population

The final sample in this study included 98 participants. The SCI with neuropathic pain (SCI-NP) group comprised 24 participants (20 males, 4 females; mean age = 56.79 ± 9.46 years), SCI without neuropathic pain (SCI-nNP) group 10 participants (8 males, 2 females; mean age 57.00 ± 10.69 years), and the HC group 58 participants (42 males, 16 females; mean age 44.69 ± 13.57 years).

Inclusion criteria for participants with SCI were: age ≥18 years, thoracic (Th1-Th12) or high lumbar (L1) SCI, American Spinal Injury Association (ASIA) Impairment Scale classification A–D 19. For HC the inclusion criteria included age ≥18 years, no history of neurological or psychological conditions and no previous history of chronic pain or pain during participation. Full inclusion and exclusion criteria are described in the original publications16–18.

## Pain phenotyping

Before MRI scanning, participants completed standardized pain drawing indicating the location and intensity of pain on anterior and posterior body charts. Neuropathic pain was identified based on the current diagnostic criteria of the International Association for the Study of Pain (IASP), requiring a spinal cord lesion and a neuroanatomically plausible distribution of pain in relation to the lesion level9. Additionally, characteristic sensory symptoms such as burning, electric or stabbing sensations were used to support the diagnosis, and musculoskeletal pain was ruled out through clinical judgment16,18,20.

Pain intensity was rated for each marked area using an 11-point numerical rating scale (NRS) ranging from 0 (“no pain”) and 10 (“the worst pain”). A standardized dermatome template was overlaid on the drawings to distinguish between at-level and below-level neuropathic pain, defined respectively as pain within or more than three dermatomes below the neurological lesion level16,18.

To quantify the spatial extent of neuropathic pain, pain drawing was digitized and affected areas were converted into pixel-based measurements. Pain extent was then calculated as the percentage of total body surface calculated obtained by dividing the number of neuropathic pain-marked pixels by the total pixel count of the body template21. For each participant, neuropathic pain intensity values were averaged across all marked neuropathic pain regions and the highest rating reported was defined as the maximum intensity.

## MRI acquisition and feature extraction

### MRI data acquisition

High-resolution 3D T1-weighted structural MR images were acquired on a 3 Tesla Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands) using a 32-channel head coil. All imaging was conducted at a single site (XXX) using identical acquisition protocols across all three original studies (voxel size = 1×1×1 mm3, repetition time (TR) = 8.1 ms, and echo time (TE) = 3.7 ms)16–18.

### MRI preprocessing and feature extraction

T1-weighted images were processed using FreeSurfer version 7.4.1, following the standard recon-all pipeline (<https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all>)22. This included skull stripping, white matter segmentation, surface reconstruction, cortical parcellation, and subcortical segmentation.

Morphometric features were extracted using FreeSurfer’s aparcstats2table (Destrieux parcellation, aparc.a2009s23) and asegstats2table (standard aseg segmentation24). In total, 179 structural brain features were obtained per participant: 144 cortical thickness measures (72 per hemisphere) and 35 subcortical volumes.

### Quality assurance

Quality control was performed using the ENIGMA Quality Assurance (QA) pipeline (protocol availabe <https://enigma.ini.usc.edu>), consisting of25:

1. Extraction of subcortical volumes
2. Extraction of cortical thickness and surface area metrics
3. Visualization of subcortical segmentations with HTML reporting
4. Internal cortical parcellation inspection with report generation
5. External cortical surface inspection and reporting

Visual inspection of all segmentations was carried out following the ENIGMA Cortical Quality Control Protocol version 2.0 (protocol available <https://enigma.ini.usc.edu/protocols/imaging-protocols/>)25. All segmentations passed QC criteria and were retained for analysis.

The full preprocessing and quality control workflow is openly documented and available at <https://github.com/ortizo-117/SCI_Map>, ensuring transparency and reproducibility.

## Normative modeling using Braincharts

### Model framework

To assess individualized and age- and sex-adjusted structural brain differences, we applied a normative modeling framework provided by Braincharts15.This model is trained on MRI data from over 58’000 participants across the lifespan and provides age- and sex-adjusted reference trajectories for cortical and subcortical features. For each participant, we extracted residuals representing the deviation between observed brain feature and normative predictions. These individualized residuals enabled the detection of structural alterations relative to expected normative values, independent of group-level comparison.

### Reference data

The Braincharts model was trained on MRI data from 58’836 participants across 82 scanning sites, covering an age range from 2 to 100 years 15. This reference dataset includes both healthy controls and population-based cohorts, enabling robust modeling of age-related variability in brain structure. Data were harmonized across sites and scanners to reduce technical variability and enhancing reliability. By comparing each SCI participant to this large-scale reference model, we were able to quantify participants deviations from normative brain structure.

To improve compatibility between our dataset and the Braincharts reference model, we performed an adaptation step using our own **healthy control participants** (n = 58). As recommended by the Braincharts pipeline, this group was specified as the adaptation dataset to adjust for potential scanner- and site-related biases during model application.

### Model architecture & implementation

Braincharts uses generalized additive models for location, scale, and shape (GAMLSS)26 to model brain trajectories. This regression framework estimates not only the mean of each brain feature, but also the variance and distributional shape as a function of age and sex. Braincharts trained separate models for 144 cortical thickness (72 per hemisphere) and 35 subcortical volumes, based on FreeSurfer-derived metrics. These pre-trained models were then applied to our SCI sample using the publicly available Phyton pipeline (https://github.com/predictive-clinical-neuroscience/braincharts/blob/master/scripts/apply\_normative\_models\_ct.ipynb)15.

For each participant, the model returned adjusted values for cortical and subcortical features based on the normative reference dataset, incorporating corrections for potential scanner- and site-related biases. We then calculated residuals as the difference between the observed values and these predicted means. The residuals were used as the basis for all subsequent statistical analyses.

### Model Output

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KI-generierte Inhalte können fehlerhaft sein.The final output comprised 179 residual values per SCI participant, including 144 cortical thickness and 35 subcortical volume features. Negative residuals indicate that a brain feature is smaller than expected for that participant’s age and sex. Positive residuals reflect larger than expected structure. These continuous residual scores were used for all subsequent statistical analyses.

### *Figure 1: Overview of study pipeline*

*(A) Study Cohorts included individuals with spinal cord injury with neuropathic pain (SCI-NP), spinal cord injury without neuropathic pain (SCI-nNP) and healthy subjects. (B) T1-weighted MRI scans were acquired on a 3 Tesla Philips Ingenia scanner. (C) MRI data were processed using FreeSurfer v7.4.1 to extract cortical thickness and subcortical volume features. (D) Normative modelling was performed using the Braincharts framework, which applies generalized additive model for location, scale and shape (GAMLSS) to derive age- and sex-adjusted trajectories. The healthy controls group was used for model adaption. (E) Residuals represent individual-level deviations from the normative reference, as illustrated in the example.*

## Statistical analysis

All statistical analyses were performed in Python (version 3.8.5), based on residuals representing individual deviations from the age- and sex-adjusted normative model.

### SCI deviations from normative model

To assess whether brain features in participants with SCI differed from the normative reference, we tested whether the residuals significantly differed from zero. The distribution of residuals across all 179 features was evaluated using the Shapiro-Wilk test and visual inspection of Q-Q plots. Although 23 features showed evidence of non-normality, one-sample t-test were applied consistently to all features to ensure methodological comparability. Effect sizes were calculated as Cohen’s d and p-values were corrected for multiple comparisons using false discovery rate (FDR) correction. These analyses were conducted across the entire SCI group, including both SCI-NP and SCI-nNP participants.

### Subgroup comparison

To explore whether the deviations form normative brain features in the overall SCI group were driven by participants with or without neuropathic pain, we conducted post hoc subgroup analyses. Specifically, for brain features that showed significant deviations in the full SCI sample, we repeated one-sample t-tests separately in the SCI-NP and SCI-nNP subgroups against the normative model (median 0). In addition, we performed between-group comparison using independent-samples t-tests to assess whether structural deviations differed between the two subgroups. All analyses were considered exploratory. Effect sizes were reported as Cohen’s d. As these analyses were restricted to features that had already passed FDR corrections in the full sample, no additional correction for multiple comparison was applied.

### Correlations with pain variables

Finally, in the SCI-NP subgroup, we assessed whether the magnitude of structural deviations was associated with clinical pain characteristics. Analyses were restricted to brain features that showed significant deviations from the normative model in the SCI cohort. Spearman correlation analyses were performed between brain features residuals and the three pain variables: (1) maximum pain intensity, (2) average pain intensity and (3) spatial extent of pain.

# Results

## Participant characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | **SCI Total**  **(n=34)** | **SCI-NP**  **(n = 24)** | **SCI-nNP**  **(n = 10)** |
| **Demographics** | | | |
| Age | 56.85 ± 9.67 years | 56.79 ± 9.46 years | 57.00 ± 10.69 years |
| Sex (M/F) | 28/4 | 20/4 | 8/2 |
| Time since injury | 16.53 ± 9.15 | 16.96 ± 9.81 | 15.5 ± 7.72 |
| Neurological level of injury\*, n (%) |  | | |
| Th1 | 1 (2.9 %) | 1 (4.2 %) | - |
| Th2 | 1 (2.9 %) | 1 (4.2 %) | - |
| Th3 | 3 (8.8 %) | 3 (12.5 %) | - |
| Th4 | 3 (8.8 %) | - | 3 (30 %) |
| Th5 | 3 (8.8 %) | 2 (8.3 %) | 1 (10 %) |
| Th6 | 1 (2.9 %) | - | 1 (10 %) |
| Th7 | - | - | - |
| Th8 | 3 (8.8 %) | 2 (8.3 %) | 1 (10 %) |
| Th9 | - | - | - |
| Th10 | 5 (14.7 %) | 4 (16.7 %) | 1 (10 %) |
| Th11 | 7 (20.6 %) | 5 (20.8 %) | 2 (20 %) |
| Th12 | 4 (11.8 %) | 3 (12.5 %) | 1 (10 %) |
| L1 | 2 (5.9 %) | 2 (8.3 %) | - |
| AIS, n (%) |  | | |
| A | 17 (50 %) | 11 (45.8 %) | 6 (60 %) |
| B | 2 (5.9 %) | 2 (8.3 %) | - |
| C | 5 (14.7 %) | 4 (16.6 %) | 1 (10 %) |
| D | 10 (29.4 %) | 7 (29.2 %) | 3 (30 %) |

**Table 1: Demographics and clinical characteristics**

*Demographic and clinical characteristics of the total SCI cohort (SCI Total), SCI-NP and SCI-nNP. Values are presented as mean ± standard deviations for continuous variable and as counts (percentage) for categorical variables.*

*Abbreviations: AIS = ASIA Impairment Scale, L = lumbar, Th = thoracic.*

*\*NLI information was missing for one participant in the SCI-NP group*

The final sample consisted of 34 participants with SCI, of which 24 SCI-NP and 10 SCI-nNP. Demographic and clinical characteristics are summarized in Table 1. The maximum pain intensity in the SCI-NP group was 4.72 ± 1.99 and average pain intensity was reported as 3.78 ± 1.46. The spatial extent pain was reported as 18.4 ± 14.34. There was one missing value in the maximum and average pain category and four in the spatial extent pain.

The 58 HC participants were not included in the statistical analyses, as they were used exclusively to adapt the normative Braincharts model to account for site- and scanner-specific biases.

## Structural brain deviations in SCI relative to the normative model

### Cortical thickness deviations

After FDR correction (*p < 0.05)*, participants with SCI demonstrated significant structural deviations from normative model in 15 cortical regions (Figure 2A/C, see also Table S1). The most pronounced reductions in cortical thickness were observed in anterior frontal regions, particularly the right transverse frontopolar gyrus and sulcus (d= - 0.942, *p < 0.001*) and the right inferior frontal gyrus, opercular part (d = - 0.676, *p = 0.007*). Additional reductions in cortical thickness were detected in the right superior fontal sulus (d = - 0.57, *p = 0.025*), as well as in the anterior (d = - 0.585, *p = 0.022*) and anterior horizontal segments (d = - 0.525, *p = 0.041*) of the left lateral fissure. Further reductions were observed in temporal regions, including the right inferior temporal gyrus (d = - 0.586, *p = 0.022*) and right temporal pole (d = - 0.5, *p = 0.05*).

In contrast, participants with SCI demonstrated increased cortical thickness relative to the normative model was observed in several posterior and parietal regions. The strongest positive deviations were found in the right superior and transverse occipital sulcus (d = 0.962, *p < 0.001*), right medial occipito-temporal and lingual sulcus (d = 0.91, *p <0.001*), and right middle occipital and lunate sulcus (d = 0.777, *p = 0.002*). Increased cortical thickness was also observed in the right intraparietal and transverse parietal sulcus (d = 0.754, *p = 0.002*), compared the normative model.

### Subcortical volume deviations

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KI-generierte Inhalte können fehlerhaft sein.Among the subcortical volumes, eight features showed significant deviations from the normative model after FDR correction (Figure 2B/C; see Table S1). The largest negative deviations were observed in total gray matter volume (d = - 0.832, *p* = 0.001), indicating substantial structural reduction in the SCI group. Additional reductions were found in the right cerebellar cortex (d = -0.71, *p* = 0.005), left pallidum (d = - 0.68, *p* = 0.007), subcortical gray volume (d = -0.632, *p* = 0.013), and left amygdala (d = -0.59, *p* = 0.022). In contrast enlarged volumes were detected in the 3rd ventricle (d = 0.57, *p* = 0.025), right inferior lateral ventricle (d = 0.52, *p* = 0.042), and right vessel structure (d = 0.52, *p* = 0.042).

**Figure 2 Structural brain deviations in spinal cord injury (SCI) compared to the normative model**

(A): Surface-based projection of signficant cortical thickness deviations in participants with SCI comparted to age- and sex-adjusted normative model. Colors indicate Cohen’s d effect sizes are shown for increased (red) and decreased (blue) cortiical thickness in SCI compared to the normative model.

*(B): Subcortical volume deviatin displayed across acial, sagittal and frontal views. Red regions indicate significantly increased volumes and blue indicate decreased volumes in SCI compared to the normative model.\**

*(C): Ranked list of cortical and subcotrial brain features that showed significant deviations from normative model after FDR correction (p<0.05). Red indicating increased and blue indictaing reduced thickness or volume.*

*\* Subcortical gray volume, total gray volume and 3rd ventricle volume are not visualized*

## Structural brain deviations in SCI-NP and SCI-nNP subgroups

### SCI-NP: Deviations from normative structure

In the SCI-NP subgroup, 22 of 23 features showed significant deviations (*p* < 0.05) (Figure 3, for full details see Tabel S2).

#### Cortical thickness

In the SCI-NP subgroup, reductions in cortical thickness were observed in several anterior features, including the right transverse frontopolar gyrus and sulcus (d = - 0.929, *p* < 0.001), right inferior frontal gyrus - opercular part (d = - 0.592, *p* = 0.008), right superior frontal sulcus (d = - 0.427, *p* = 0.017) and left paracentral gyrus and sulcus (d = - 0.684, *p* = 0.003). Decreased temporal cortical thickness was noted in the right inferior temporal gyrus (d = - 0.615, *p* = 0.006) and right transverse temporal sulcus (d = - 0.537, *p* = 0.015) compared to the normative model.

In contrast, increased cortical thickness was found in posterior and parietal features, most notably the right superior and transverse occipital sulcus (d = 0.891, *p* < 0.001), right medial occipito-temporal and lingual sulcus (d = 0.844, *p* < 0.001), right middle occipital and lunate sulcus (d = 0.706, *p* = 0.002), and right intraparietal and transverse parietal sulcus (d = 0.678 *p* = 0.003).

#### Subcortical volumes

In the SCI-NP subgroup, volume reductions were detected in total gray matter (d = - 0.931, *p* < 0.001), the left pallidum (d = - 0.807, *p* < 0.001), the left amygdala (d = - 0.786, *p* < 0.001), the right cerebellar cortex (d = - 0.757, *p* = 0.001) and subcortical gray matter (d = - 0.737, *p* = 0.001) compared to the normative model.

Conversely, enlarged volumes were observed in right vessel structure (d = 0.726, *p* = 0.002), the third ventricle (d = 0.606, *p* = 0.007) and right inferior lateral ventricle (d = 0.446, *p* = 0.039).

### SCI-nNP: Deviations from normative structure

In the SCI-nNP group, 9 out of 23 features showed significant deviations (Figure 3, for full details see Tabel S3).

#### Cortical thickness

Significant reduced cortical thickness was observed in the right transverse frontopolar gyrus and sulcus (d = - 0.941, *p* = 0.016), the right inferior frontal gyrus – opercular part (d = - 0.864, *p* = 0.023) and the right superior frontal sulcus (d = - 0.810, *p* = 0.031). Additional deviations included reduced thickness in the left lateral fissure – anterior horizontal segment (d = - 0.767, *p* = 0.038) and in the right temporal pole (d = - 0.719, *p* = 0.049). In contrast, increased cortical thickness was found in posterior regions, including the right superior and transverse occipital sulcus (d = 1.135, *p* = 0.006), right medial occipito-temporal and lingual sulcus (d = 1.061, *p* = 0.008), right middle occipital and lunate sulcus (d = 0.966, *p* = 0.014), and right intraparietal and transverse parietal sulcus (d = 0.964, *p* = 0.014).

#### Subcortical volumes

None of the subcortical volume measures showed significant deviations from the normative model in the SCI-nNP group (Table S3).

### No differences between SCI-NP and SCI-nNP groups

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KI-generierte Inhalte können fehlerhaft sein.No statistically significant difference in residual values were found between the SCI-NP and SCI-nNP subgroups for any of the 23 tested brain features (Table S4).

**Figure 3: Structural brain deviations in spinal cord injury (SCI) participants with (SCI-NP) and without (SCI-nNP) neuropathic pain**

*Residual values derived from normative modeling are shown for all brain features that were significantly altered in the full SCI group. Each panel displays the residual distributions for the total SCI cohort (left) and both subgroups SCI-NP and SCI-nNP (right). The colors reflect the Cohen’s d form the deviation from normative model (0) with each group. Red indicating increased and blue a decreased cortical thickness or subcortical volume.*

## Structural brain deviations are associated with pain characteristics

To explore the relationship between structural brain deviations and clinical symptoms, we examined correlations between residual values and pain ratings within the SCI-NP subgroup. Analyses were restricted to brain features that showed significant deviations from the normative model in the SCI cohort. Associations were tested using Spearman correlation coefficients (ρ).

Positive correlations with maximum pain were observed in four cortical features (Figure 4 (A), Table S4). These were found in the right medial occipito-temporal and lingual sulcus (ρ = 0.414, *p* = 0.049), right middle occipital and lunate sulcus (ρ = 0.42, *p* = 0.046), right intraparietal and transverse parietal sulcus (ρ = 0.414, *p* = 0.049) and the left paracentral gyrus and sulcus (ρ = 0.531, *p* = 0.009).

Only one region, the left paracentral gyrus and sulcus (ρ = 0.419, *p* = 0.047), showed a positive correlation with average pain intensity (Figure 4 (B), Table S5).

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KI-generierte Inhalte können fehlerhaft sein.A negative correlation was found between spatial pain extent and thickness of the right superior frontal sulcus (ρ = - 0.466, *p* = 0.038) (Figure 4 (C), Table S6).

**Figure 4: Correlations between structural brain deviations and pain ratings in participants with spinal cord injury (SCI) and neuropathic pain (SCI-NP)**

*Scatterplots show significant Spearman correlations (ρ) between residuals and clinical pain ratings in the SCI-NP group. (A) Maximum pain intensity correlated positively with residuals cortical thickness in four regions. (B) Average pain intensity showed a significant positive correlation with residuals in the left paracentral gyrus and sulcus. (C) Spatial extent of pain was negatively correlated with residual thickness in the right superior frontal sulcus.   
Shaded areas represent 95% Confidence intervals of the regression line.*

# Discussion

## Summary of key findings

This is the first study to apply normative modeling based on Braincharts framework15 to investigate structural brain deviation in participants with SCI without relying on a separate control group. This methodological innovation enabled us to go beyond conventional control group comparisons. Such an approach is particularly advantageous in SCI population, where small and heterogenous samples make tradition case-control designs prone to bias and reduced reproducibility.

We observed reductions in cortical thickness, primarily in the prefrontal, sensorimotor and temporal cortices, alongside increases in the occipital and parietal regions. Reduced subcortical volume was evident in gray matter, including the pallidum and amygdala, accompanied by ventricular enlargement. Subgroup analysis revealed more consistent deviations within the SCI-NP group. In the SCI-NP group, specific structural deviations correlated with pain intensity and extent.

## Structural brain deviations in SCI relative to the normative model

The most prominent cortical reduction was observed in prefrontal regions, including the right transverse frontopolar gyrus and sulcus, right superior frontal sulcus and right inferior frontal gyrus. These regions are part of executive and salience-related networks involved in attentional control, goal-directed behavior and affective regulation27,28. While previous studies using voxel-based morphometry (VBM) have reported prefrontal gray matter reductions after SCI, our findings extend these by identifying parallel reduced cortical thickness in the same brain regions29,30. These alterations are interpreted as secondary effects of deafferentation and reduced behavioral engagement29,30.

Reduced cortical thickness was also observed in the left paracentral gyrus and sulcus as well as the subcentral gyrus and sulcus, border zones of the primary motor (M1) and somatosensory cortex (S1)25. The observed reduced cortical thickness in the paracentral gyrus is consistent with prior VMB and meta-analytic findings showing atrophy in lower limb sensorimotor representations following SCI13,32–34. These patterns likely reflect chronic deafferentation, reduced activity-dependent plasticity and transneuronal degeneration due to disrupted ascending and descending sensorimotor pathways14,32,33.

Reduced cortical thickness was observed in the right inferior temporal gyrus, temporal pole and transverse temporal sulcus. These areas are involved in visual objection recognition, semantic and social-emotional processing and auditory perception34–38. Although these subregions are not consistently reported in SCI studies, Karunakaran et al. (2019)30 found a positive association between gray matter volume in the middle temporal gyrus and injury duration, suggesting long-term plasticity. Similarly, Chen et al. (2023)39 reported gray matter reductions in middle and inferior temporal gyri, though effect were less robust and not clearly lateralized. These findings may reflect compensatory changes or altered sensory integration in response to chronic deafferentation and reduced multisensory input30,39.

Increased posterior cortical thickness was observed in occipital and parietal sulci. While occipital sulci are primarily associated with processing visual scene and object features, the intraparietal sulcus plays a key role in spatial attention and multisensory body representation40,41. Together, their increased thickness may reflect a posterior shift in processing load, supporting visual and spatial compensation in response to reduced somatosensory input42.

Reduced subcortical volume was found in the left pallidum and amygdala, alongside reductions in total and subcortical GMV. Prior VBM studies and meta-analyses, confirm subcortical and total GMV loss, including the left pallidum13,43. While direct evidence for amygdala atrophy after SCI remain limited, studies have reported atrophy in functionally related areas such as the insula and orbitofrontal cortex44. The left pallidum regulates motor control and cognitive-motivational process while the amygdala plays a crucial role in emotional and affective regulation45,46. The reduced volume in the pallidum may reflect reduced engagement of motor and motivational circuits following spinal deafferentation29. Similar, amygdala atrophy may be linked to diminished affective drive and social-emotional interaction after injury, as suggested in related limbic areas47. These region-specific changes may be part of a broader pattern of maladaptive plasticity following chronic deafferentation or persistent nociceptive input, consistent with mechanism described in other pain conditions48.

## Structural brain deviations in SCI-NP and SCI-nNP subgroups

To disentangle the contribution of neuropathic pain to brain structure alterations following SCI, we compared residuals deviation SCI-NP subgroup and SCI-nNP subgroup. Significant deviations were observed in 22 features in the SCI-NP group and in 9 features in the SCI-nNP group. While SCI-NP group showed a broader pattern of alterations, effect sizes in overlapping features were intriguingly larger in the SCI-nNP group.

### Common injury-related brain deviations across SCI subgroups

Despite differences in the number and distribution of affected features, both subgroups showed deviation in overlapping brain features, particularly in the prefrontal, occipital and parietal cortices. Notably, the largest effect sizes were found in the prefrontal and occipital regions, suggesting that these areas are particularly sensitive to supraspinal reorganization following SCI. This convergence implies that most prominent structural alterations are more likely driven by the injury itself, through maladaptive and compensatory plasticity following deafferentation, disrupted sensorimotor input and altered brain connectivity, rather than by the presence of pain29,32,49.

### Broader structural changes in SCI-NP

The SCI-NP subgroup exhibits a notably broader pattern of deviations. Alterations in subcortical features, including the left pallidum and left amygdala, were exclusive to this group and suggest pain related disruption of affective, motivational and pain modulatory circuits45–47.

This extended pattern aligns with prior studies reporting enhanced supraspinal plasticity in individuals with neuropathic pain after SCI. For instance, Jutzler et. Al (2016)12 reported greater gray matter reductions in prefrontal and limbic areas in SCI patients with neuropathic pain. Similar evidence form other studies highlights pain-specific alterations in supraspinal nociceptive pathways and network reorganization, supporting the view that chronic pain modifies brain structure beyond injury-related changes16,50.

#### Structural deviations correlate with pain intensity and extent

Within the SCI-NP group, some cortical features not only deviated but also showed correlated with the pain ratings. Increased cortical thickness in right posterior parietal, occipito-temporal and left central features, positively correlated with pain intensity. This aligns with findings by Gustin et al. (2010)51, who reported increased mean diffusivity in the right posterior parietal cortex (PPC) in SCI patients with neuropathic pain. Our finding extent this by demonstrating increased cortical thickness in the same region. Although the PPC is not classically part of the pain matrix, it may contribute to pain processing via attentional modulation and the integrations of noxious and non-noxious signals51–54. The observed right-lateralized further support the idea that the right PPC contributes to maintain heightened alertness in response to persistent pain51.

Interestingly, increased thickness in occipital areas, including the lingual and middle occipital sulci, also correlated with pain intensity. Although these regions are not typically highlighted in neuropathic pain studies, similar findings have been reported in phantom limb pain, where structural increases in visual areas were interpreted as compensatory responses to sensory deafferentation55. Such occipital plasticity may reflect heightened reliance on visual input or spatial processing in the absence of somatosensory feedback, potentially modulation pain perception indirectly55–57.

Our observation of cortical reduction in the right superior frontal sulcus, correlating with pain extent, aligns with evidence from neuropathic and chronic pain populations. The right superior frontal feature, as part of the dorsolateral prefrontal cortex, is implicated in top-down pain modulations and shows volume reductions proportional to pain severity48,58. Contrary, Huynh et al. (2021)16 found increased gray matter volume in the left superior frontal gyrus in association with pain extent in part of the same cohort. These divergent patterns may emphasise region- and method-specific disparities, such as measurement modality and laterality (GMV vs. cortical thickness; left vs. right), highlighting the complexity of supraspinal pain-related plasticity.

### Localized structural changes in SCI-nNP

Although deviations were less widespread, the SCI-nNP subgroup still showed significant deviations in the prefrontal and occipital cortices. These are likely related to spinal deafferentation, reduced sensorimotor feedback, and behavioural disuse, which have been associated with cortical atrophy and altered connectivity even in the absence of pain32,47,59. Notably, effect sizes in overlapping regions were occasionally amplified in the SCI-nNP group, indicating that specific structural adaptations may occur independently of pain and could be indicative of distinct non-nociceptive mechanisms, such as motivational decline, altered body representation, or reduced environmental interaction12,32. These findings emphasise that SCI alone induces significant supraspinal plasticity, which may contribute to non-motor symptoms such as cognitive or affective alterations49.

## Implications & future directions

This study demonstrates for the first time the application of a normative model to a population with SCI and thus shows a new, individualized approach to assessing structural brain changes without relying exclusively on comparison with small control groups. By using normative models, we were able to evaluate age- and sex-adjusted deviations at the individual level, which represents an important step toward precise neuroimaging. This framework not only circumvents the need for perfectly matched control groups but also facilitates comparability between studies and locations by linking the results to a large, harmonized reference dataset.

A key finding was that the greatest structural deviations were found in the prefrontal and occipital cortex, both in the overall group and in the separate subgroups, with and without neuropathic pain. This suggests that these changes are caused by the SCI itself rather than by the pain status. The findings indicate that supraspinal structural reorganization is primarily a consequence of deafferentation and altered sensorimotor feedback after SCI and cannot be explained solely by chronic pain processing.

Future longitudinal studies are crucial to capture the temporal course of these changes after SCI and to understand their causal significance for the development of pain or other neuropsychological symptoms. In addition, meta-analyses could help to test the robustness of the patterns identified here and to systematically investigate other influencing factors.

## Limitation

When interpreting the results, it is important to consider the limitation of this study. First, the SCI-nNP had a relatively small sample size, which may limit statistical power and generalisability. Secondly, the cross-sectional design does not permit causal inference regarding the relationship between brain structure, SCI and neuropathic pain. Longitudinal studies would be required to evaluate the timing and potential progression of these changes. Third, this is the first study to apply Braincharts15 normative framework to a SCI population.

While this approach enables individualized comparison to a huge trained normative model rather than just comparing to a small control group, further assessment of this framework would be required. An additional methodological consideration is that Braincharts normative model were trained on FreeSurfer version 6.0 outputs, whereas our data were processed using FreeSurfer version 7.4.1. Although prior work suggest that version differences have minimal impact on most cortical and subcortical features, subtle discrepancies cannot be fully excluded.

Nonetheless, normative modelling represents a promising tool for precision neuroimaging and may complement traditional case-control designs.

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# References

1. Safdarian M, Trinka E, Rahimi-Movaghar V, et al. Global, regional, and national burden of spinal cord injury, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2023;22(11):1026-1047. doi:10.1016/S1474-4422(23)00287-9

2. Ahuja CS, Nori S, Tetreault L, et al. Traumatic Spinal Cord Injury—Repair and Regeneration. *Neurosurgery*. 2017;80(3S):S9. doi:10.1093/neuros/nyw080

3. Anjum A, Yazid MD, Fauzi Daud M, et al. Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. *Int J Mol Sci*. 2020;21(20):7533. doi:10.3390/ijms21207533

4. Li J, Kang W, Wang X, Pan F. Progress in treatment of pathological neuropathic pain after spinal cord injury. *Front Neurol*. 2024;15. doi:10.3389/fneur.2024.1430288

5. Defrin R, Gruener H, Gaidukov E, et al. From acute to long-term alterations in pain processing and modulation after spinal cord injury: mechanisms related to chronification of central neuropathic pain. *PAIN*. 2022;163(1):e94. doi:10.1097/j.pain.0000000000002315

6. Gruener H, Zeilig G, Gaidukov E, et al. Biomarkers for predicting central neuropathic pain occurrence and severity after spinal cord injury: results of a long-term longitudinal study. *PAIN*. 2020;161(3):545. doi:10.1097/j.pain.0000000000001740

7. Burke D, Fullen BM, Stokes D, Lennon O. Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. *Eur J Pain Lond Engl*. 2017;21(1):29-44. doi:10.1002/ejp.905

8. Terminology | International Association for the Study of Pain. International Association for the Study of Pain (IASP). Accessed June 30, 2025. https://www.iasp-pain.org/resources/terminology/

9. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *PAIN*. 2016;157(8):1599. doi:10.1097/j.pain.0000000000000492

10. Siddall PJ. Management of neuropathic pain following spinal cord injury: now and in the future. *Spinal Cord*. 2009;47(5):352-359. doi:10.1038/sc.2008.136

11. Livny A, Golan Y, Itzhaki N, et al. Higher Regional Gray Matter Volume and White Matter Integrity in Individuals With Central Neuropathic Pain After Spinal Cord Injury. *J Neurotrauma*. 2024;41(7-8):836-843. doi:10.1089/neu.2023.0146

12. Jutzeler CR, Huber E, Callaghan MF, et al. Association of pain and CNS structural changes after spinal cord injury. *Sci Rep*. 2016;6(1):18534. doi:10.1038/srep18534

13. Wang W, Tang S, Li C, et al. Specific Brain Morphometric Changes in Spinal Cord Injury: A Voxel-Based Meta-Analysis of White and Gray Matter Volume. *J Neurotrauma*. 2019;36(15):2348-2357. doi:10.1089/neu.2018.6205

14. Solstrand Dahlberg L, Becerra L, Borsook D, Linnman C. Brain changes after spinal cord injury, a quantitative meta-analysis and review. *Neurosci Biobehav Rev*. 2018;90:272-293. doi:10.1016/j.neubiorev.2018.04.018

15. Rutherford S, Fraza C, Dinga R, et al. Charting brain growth and aging at high spatial precision. Baker CI, Taschler B, Esteban O, Constable T, eds. *eLife*. 2022;11:e72904. doi:10.7554/eLife.72904

16. Huynh V, Lütolf R, Rosner J, et al. Supraspinal nociceptive networks in neuropathic pain after spinal cord injury. *Hum Brain Mapp*. 2021;42(12):3733-3749. doi:10.1002/hbm.25401

17. Huynh V, Lütolf R, Rosner J, et al. Descending pain modulatory efficiency in healthy subjects is related to structure and resting connectivity of brain regions. *NeuroImage*. 2022;247:118742. doi:10.1016/j.neuroimage.2021.118742

18. Huynh V, Lütolf R, Rosner J, et al. Intrinsic brain connectivity alterations despite intact pain inhibition in subjects with neuropathic pain after spinal cord injury: a pilot study. *Sci Rep*. 2023;13(1):11943. doi:10.1038/s41598-023-37783-w

19. Rupp R, Biering-Sørensen F, Burns SP, et al. International Standards for Neurological Classification of Spinal Cord Injury. *Top Spinal Cord Inj Rehabil*. 2021;27(2):1-22. doi:10.46292/sci2702-1

20. Bryce TN, Budh CN, Cardenas DD, et al. Pain After Spinal Cord Injury: An Evidence-based Review for Clinical Practice and Research. *J Spinal Cord Med*. 2007;30(5):421-440. doi:10.1080/10790268.2007.11753405

21. Rosner J, Lütolf R, Hostettler P, et al. Assessment of neuropathic pain after spinal cord injury using quantitative pain drawings. *Spinal Cord*. 2021;59(5):529-537. doi:10.1038/s41393-021-00616-6

22. Fischl B. FreeSurfer. *NeuroImage*. 2012;62(2):774-781. doi:10.1016/j.neuroimage.2012.01.021

23. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*. 2010;53(1):1-15. doi:10.1016/j.neuroimage.2010.06.010

24. Fischl B, Salat DH, Busa E, et al. Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain. *Neuron*. 2002;33(3):341-355. doi:10.1016/S0896-6273(02)00569-X

25. Thompson PM, Stein JL, Medland SE, et al. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav*. 2014;8(2):153-182. doi:10.1007/s11682-013-9269-5

26. Stasinopoulos DM, Rigby RA. Generalized Additive Models for Location Scale and Shape (GAMLSS) in *R*. *J Stat Softw*. 2007;23(7). doi:10.18637/jss.v023.i07

27. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci*. 2007;27(9):2349-2356. doi:10.1523/JNEUROSCI.5587-06.2007

28. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506. doi:10.1016/j.tics.2011.08.003

29. Chen Q, Zheng W, Chen X, et al. Brain Gray Matter Atrophy after Spinal Cord Injury: A Voxel-Based Morphometry Study. *Front Hum Neurosci*. 2017;11:211. doi:10.3389/fnhum.2017.00211

30. Karunakaran KD, He J, Zhao J, et al. Differences in Cortical Gray Matter Atrophy of Paraplegia and Tetraplegia after Complete Spinal Cord Injury. *J Neurotrauma*. 2019;36(12):2045-2051. doi:10.1089/neu.2018.6040

31. White L. Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. *Cereb Cortex*. 1997;7(1):18-30. doi:10.1093/cercor/7.1.18

32. Freund P, Weiskopf N, Ward NS, et al. Disability, atrophy and cortical reorganization following spinal cord injury. *Brain*. 2011;134(6):1610-1622. doi:10.1093/brain/awr093

33. Nardone R, Höller Y, Brigo F, et al. Functional brain reorganization after spinal cord injury: Systematic review of animal and human studies. *Brain Res*. 2013;1504:58-73. doi:10.1016/j.brainres.2012.12.034

34. Trébuchon A, Alario FX, Liégeois-Chauvel C. Functional Topography of Auditory Areas Derived From the Combination of Electrophysiological Recordings and Cortical Electrical Stimulation. *Front Hum Neurosci*. 2021;15. doi:10.3389/fnhum.2021.702773

35. Jackson RL, Bajada CJ, Rice GE, Cloutman LL, Lambon Ralph MA. An emergent functional parcellation of the temporal cortex. *NeuroImage*. 2018;170:385-399. doi:10.1016/j.neuroimage.2017.04.024

36. Mesulam MM. Temporopolar regions of the human brain. *Brain*. 2022;146(1):20-41. doi:10.1093/brain/awac339

37. Herlin B, Navarro V, Dupont S. The temporal pole: From anatomy to function—A literature appraisal. *J Chem Neuroanat*. 2021;113:101925. doi:10.1016/j.jchemneu.2021.101925

38. Olson IR, Plotzker A, Ezzyat Y. The Enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*. 2007;130(7):1718-1731. doi:10.1093/brain/awm052

39. Chen X, Wang L, Zheng W, et al. The gray matter atrophy and related network changes occur in the higher cognitive region rather than the primary sensorimotor cortex after spinal cord injury. *PeerJ*. 2023;11:e16172. doi:10.7717/peerj.16172

40. Grill-Spector K, Malach R. THE HUMAN VISUAL CORTEX. *Annu Rev Neurosci*. 2004;27(1):649-677. doi:10.1146/annurev.neuro.27.070203.144220

41. Richter M, Amunts K, Mohlberg H, et al. Cytoarchitectonic segregation of human posterior intraparietal and adjacent parieto-occipital sulcus and its relation to visuomotor and cognitive functions. *Cereb Cortex*. 2019;29(3):1305-1327. doi:10.1093/cercor/bhy245

42. Bavelier D, Neville HJ. Cross-modal plasticity: where and how? *Nat Rev Neurosci*. 2002;3(6):443-452. doi:10.1038/nrn848

43. Yu H, Chen D, Jiang H, et al. Brain morphology changes after spinal cord injury: A voxel-based meta-analysis. *Front Neurol*. 2022;13. doi:10.3389/fneur.2022.999375

44. Wang W, Tang S, Li C, et al. Specific Brain Morphometric Changes in Spinal Cord Injury: A Voxel-Based Meta-Analysis of White and Gray Matter Volume. *J Neurotrauma*. 2019;36(15):2348-2357. doi:10.1089/neu.2018.6205

45. Nishimura Y, Onoe H, Onoe K, Morichika Y, Tsukada H, Isa T. Neural Substrates for the Motivational Regulation of Motor Recovery after Spinal-Cord Injury. *PLOS ONE*. 2011;6(9):e24854. doi:10.1371/journal.pone.0024854

46. Gallagher M, Chiba AA. The amygdala and emotion. *Curr Opin Neurobiol*. 1996;6(2):221-227. doi:10.1016/S0959-4388(96)80076-6

47. Freund P, Friston K, Thompson AJ, et al. Embodied neurology: an integrative framework for neurological disorders. *Brain*. 2016;139(6):1855-1861. doi:10.1093/brain/aww076

48. Apkarian AV, Sosa Y, Sonty S, et al. Chronic Back Pain Is Associated with Decreased Prefrontal and Thalamic Gray Matter Density. *J Neurosci*. 2004;24(46):10410-10415. doi:10.1523/JNEUROSCI.2541-04.2004

49. Mole TB, MacIver K, Sluming V, Ridgway GR, Nurmikko TJ. Specific brain morphometric changes in spinal cord injury with and without neuropathic pain. *NeuroImage Clin*. 2014;5:28-35. doi:10.1016/j.nicl.2014.05.014

50. Kyathanahally SP, Azzarito M, Rosner J, et al. Microstructural plasticity in nociceptive pathways after spinal cord injury. *J Neurol Neurosurg Psychiatry*. 2021;92(8):863-871. doi:10.1136/jnnp-2020-325580

51. Gustin SM, Wrigley PJ, Siddall PJ, Henderson LA. Brain Anatomy Changes Associated with Persistent Neuropathic Pain Following Spinal Cord Injury. *Cereb Cortex*. 2010;20(6):1409-1419. doi:10.1093/cercor/bhp205

52. Price DD. Central neural mechanisms that interrelate sensory and affective dimensions of pain. *Mol Interv*. 2002;2(6):392-403, 339. doi:10.1124/mi.2.6.392

53. Tracey I, Mantyh PW. The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*. 2007;55(3):377-391. doi:10.1016/j.neuron.2007.07.012

54. Dong WK, Chudler EH, Sugiyama K, Roberts VJ, Hayashi T. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J Neurophysiol*. 1994;72(2):542-564. doi:10.1152/jn.1994.72.2.542

55. Preißler S, Feiler J, Dietrich C, Hofmann GO, Miltner WHR, Weiss T. Gray Matter Changes Following Limb Amputation with High and Low Intensities of Phantom Limb Pain. *Cereb Cortex*. 2013;23(5):1038-1048. doi:10.1093/cercor/bhs063

56. Gustin SM, Wrigley PJ, Gandevia SC, Middleton JW, Henderson LA, Siddall PJ. Movement imagery increases pain in people with neuropathic pain following complete thoracic spinal cord injury. *PAIN*. 2008;137(2):237. doi:10.1016/j.pain.2007.08.032

57. Moseley LG. Using visual illusion to reduce at-level neuropathic pain in paraplegia. *PAIN*. 2007;130(3):294. doi:10.1016/j.pain.2007.01.007

58. May A. Chronic pain may change the structure of the brain. *PAIN*. 2008;137(1):7. doi:10.1016/j.pain.2008.02.034

59. Freund P, Curt A, Friston K, Thompson A. Tracking Changes following Spinal Cord Injury. *The Neuroscientist*. 2013;19(2):116-128. doi:10.1177/1073858412449192

60. Wrigley PJ, Gustin SM, Macey PM, et al. Anatomical Changes in Human Motor Cortex and Motor Pathways following Complete Thoracic Spinal Cord Injury. *Cereb Cortex*. 2009;19(1):224-232. doi:10.1093/cercor/bhn072

61. Jurkiewicz MT, Mikulis DJ, McIlroy WE, Fehlings MG, Verrier MC. Sensorimotor Cortical Plasticity During Recovery Following Spinal Cord Injury: A Longitudinal fMRI Study. *Neurorehabil Neural Repair*. 2007;21(6):527-538. doi:10.1177/1545968307301872

62. Manning B, Mayer D. The central nucleus of the amygdala contributes to the production of morphine antinociception in the rat tail-flick test. *J Neurosci*. 1995;15(12):8199-8213. doi:10.1523/JNEUROSCI.15-12-08199.1995

63. Tershner SA, Helmstetter FJ. Antinociception produced by mu opioid receptor activation in the amygdala is partly dependent on activation of mu opioid and neurotensin receptors in the ventral periaqueductal gray. *Brain Res*. 2000;865(1):17-26. doi:10.1016/S0006-8993(00)02179-X

# Appendix/ Supplementary

## S1: SCI deviations from normative model

The table reports residual deviations from normative model for all 179 structural brain features (based on original atlas labels). One-sample t-tests were used to assess whether each feature significantly deviated from zero in the overall SCI cohort. For each feature, the test statistic (t-value), uncorrected p-value, Cohen’s d effect size and corrected p-value are provided.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Brain features** | **T - Value** | **p-value** | **Cohen’s d** | **p-value (FDR)** |
| rh\_G&S\_transv\_frontopol\_thickness | -5.4931 | 0 | -0.942 | 0 |
| rh\_S\_oc\_sup&transversal\_thickness | 5.6095 | 0 | 0.962 | 0 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 5.3033 | 0.00001 | 0.91 | 0.000597 |
| TotalGrayVol (Vol) | -4.8532 | 0.00003 | -0.832 | 0.001343 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 4.5292 | 0.00007 | 0.777 | 0.002506 |
| rh\_S\_intrapariet&P\_trans\_thickness | 4.399 | 0.00011 | 0.754 | 0.003282 |
| Right-Cerebellum-Cortex (Vol) | -4.123 | 0.00024 | -0.707 | 0.006137 |
| lh\_G&S\_paracentral\_thickness | -4.0616 | 0.00028 | -0.697 | 0.006265 |
| Left-Pallidum (Vol) | -3.9433 | 0.0004 | -0.676 | 0.00716 |
| rh\_G\_front\_inf-Opercular\_thickness | -3.9407 | 0.0004 | -0.676 | 0.00716 |
| SubCortGrayVol (Vol) | -3.6859 | 0.00081 | -0.632 | 0.013181 |
| rh\_G\_temporal\_inf\_thickness | -3.4157 | 0.0017 | -0.586 | 0.022247 |
| Left-Amygdala (Vol) | -3.4154 | 0.00171 | -0.586 | 0.022247 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | -3.4083 | 0.00174 | -0.585 | 0.022247 |
| rh\_S\_front\_sup\_thickness | -3.3208 | 0.0022 | -0.57 | 0.024613 |
| 3rd-Ventricle (Vol) | 3.327 | 0.00216 | 0.571 | 0.024613 |
| lh\_G&S\_subcentral\_thickness | -3.1622 | 0.00335 | -0.542 | 0.035274 |
| rh\_S\_interm\_prim-Jensen\_thickness | -3.0808 | 0.00414 | -0.528 | 0.040793 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | -3.0638 | 0.00433 | -0.525 | 0.040793 |
| Right-vessel (Vol) | 3.0146 | 0.00492 | 0.517 | 0.041937 |
| Right-Inf-Lat-Vent (Vol) | 3.0243 | 0.0048 | 0.519 | 0.041937 |
| rh\_Pole\_temporal\_thickness | -2.9129 | 0.00638 | -0.5 | 0.049887 |
| rh\_S\_temporal\_transverse\_thickness | -2.9111 | 0.00641 | -0.499 | 0.049887 |
| rh\_S\_front\_inf\_thickness | -2.8141 | 0.00818 | -0.483 | 0.05864 |
| rh\_G\_cingul-Post-ventral\_thickness | 2.8137 | 0.00819 | 0.483 | 0.05864 |
| lh\_S\_front\_inf\_thickness | -2.7851 | 0.0088 | -0.478 | 0.060585 |
| SupraTentorialVolNotVent (Vol) | -2.7155 | 0.01045 | -0.466 | 0.064502 |
| Right-Lateral-Ventricle (Vol) | 2.7292 | 0.0101 | 0.468 | 0.064502 |
| lh\_G\_subcallosal\_thickness | 2.7351 | 0.00996 | 0.469 | 0.064502 |
| rh\_G&S\_cingul-Ant\_thickness | -2.6769 | 0.01148 | -0.459 | 0.065671 |
| Right-Pallidum (Vol) | -2.6707 | 0.01166 | -0.458 | 0.065671 |
| rh\_G&S\_subcentral\_thickness | -2.6677 | 0.01174 | -0.458 | 0.065671 |
| lh\_Lat\_Fis-post\_thickness | -2.58 | 0.01452 | -0.442 | 0.074951 |
| Right-Hippocampus (Vol) | -2.5787 | 0.01457 | -0.442 | 0.074951 |
| rh\_S\_front\_middle\_thickness | -2.5469 | 0.01572 | -0.437 | 0.074951 |
| rh\_Lat\_Fis-ant-Vertical\_thickness | -2.542 | 0.0159 | -0.436 | 0.074951 |
| lh\_G&S\_transv\_frontopol\_thickness | -2.5413 | 0.01593 | -0.436 | 0.074951 |
| rh\_G\_insular\_short\_thickness | -2.541 | 0.01594 | -0.436 | 0.074951 |
| rh\_G\_temp\_sup-G\_T\_transv\_thickness | -2.5309 | 0.01633 | -0.434 | 0.074951 |
| lh\_S\_circular\_insula\_ant\_thickness | -2.4956 | 0.01775 | -0.428 | 0.079431 |
| lh\_S\_front\_sup\_thickness | -2.4657 | 0.01905 | -0.423 | 0.08317 |
| SupraTentorialVol (Vol) | -2.4464 | 0.01993 | -0.42 | 0.08494 |
| 4th-Ventricle (Vol) | 2.3431 | 0.0253 | 0.402 | 0.105319 |
| lh\_S\_temporal\_transverse\_thickness | -2.2744 | 0.02957 | -0.39 | 0.120296 |
| lh\_Pole\_temporal\_thickness | -2.2564 | 0.03079 | -0.387 | 0.122476 |
| rh\_S\_cingul-Marginalis\_thickness | -2.2354 | 0.03228 | -0.383 | 0.125611 |
| lh\_G\_precuneus\_thickness | -2.1393 | 0.0399 | -0.367 | 0.150136 |
| rh\_G\_oc-temp\_med-Lingual\_thickness | -2.1352 | 0.04026 | -0.366 | 0.150136 |
| rh\_G\_front\_sup\_thickness | -2.1193 | 0.04167 | -0.363 | 0.152223 |
| rh\_G&S\_paracentral\_thickness | -2.1084 | 0.04267 | -0.362 | 0.152759 |
| rh\_G&S\_cingul-Mid-Ant\_thickness | -2.0841 | 0.04497 | -0.357 | 0.15752 |
| lh\_S\_precentral-inf-part\_thickness | -2.076 | 0.04576 | -0.356 | 0.15752 |
| lh\_S\_circular\_insula\_sup\_thickness | -2.0327 | 0.05019 | -0.349 | 0.16951 |
| rh\_S\_occipital\_ant\_thickness | -1.989 | 0.05504 | -0.341 | 0.182447 |
| Left-Cerebellum-Cortex (Vol) | -1.9715 | 0.0571 | -0.338 | 0.182548 |
| lh\_S\_temporal\_sup\_thickness | -1.9714 | 0.05711 | -0.338 | 0.182548 |
| Left-vessel (Vol) | 1.9449 | 0.06035 | 0.334 | 0.18952 |
| rh\_G\_orbital\_thickness | -1.9363 | 0.06144 | -0.332 | 0.189617 |
| lh\_S\_cingul-Marginalis\_thickness | -1.8698 | 0.0704 | -0.321 | 0.206584 |
| rh\_G\_cuneus\_thickness | 1.8709 | 0.07025 | 0.321 | 0.206584 |
| lh\_S\_suborbital\_thickness | 1.8819 | 0.06869 | 0.323 | 0.206584 |
| lh\_S\_orbital-H\_Shaped\_thickness | -1.8544 | 0.07263 | -0.318 | 0.206702 |
| lh\_S\_central\_thickness | -1.8536 | 0.07275 | -0.318 | 0.206702 |
| lh\_G\_insular\_short\_thickness | -1.7842 | 0.08358 | -0.306 | 0.233763 |
| lh\_S\_pericallosal\_thickness | -1.753 | 0.0889 | -0.301 | 0.244817 |
| lh\_S\_front\_middle\_thickness | -1.7161 | 0.09551 | -0.294 | 0.257707 |
| rh\_S\_orbital\_lateral\_thickness | -1.711 | 0.09646 | -0.293 | 0.257707 |
| Brain-Stem (Vol) | -1.6987 | 0.09878 | -0.291 | 0.260024 |
| lh\_G\_orbital\_thickness | -1.6868 | 0.10108 | -0.289 | 0.262222 |
| lh\_S\_parieto\_occipital\_thickness | -1.6531 | 0.1078 | -0.284 | 0.268948 |
| lh\_MeanThickness\_thickness | -1.6512 | 0.10818 | -0.283 | 0.268948 |
| rh\_S\_precentral-sup-part\_thickness | 1.665 | 0.10538 | 0.286 | 0.268948 |
| Right-Putamen (Vol) | -1.6312 | 0.11236 | -0.28 | 0.275513 |
| Left-Putamen (Vol) | -1.6061 | 0.11777 | -0.275 | 0.284876 |
| lh\_S\_calcarine\_thickness | -1.5599 | 0.12832 | -0.268 | 0.30397 |
| rh\_S\_circular\_insula\_sup\_thickness | -1.5568 | 0.12906 | -0.267 | 0.30397 |
| rh\_MeanThickness\_thickness | -1.5286 | 0.13591 | -0.262 | 0.309104 |
| lh\_G\_front\_inf-Opercular\_thickness | -1.5276 | 0.13614 | -0.262 | 0.309104 |
| lh\_G\_temp\_sup-G\_T\_transv\_thickness | -1.5265 | 0.13642 | -0.262 | 0.309104 |
| Right-Amygdala (Vol) | -1.4756 | 0.14954 | -0.253 | 0.33157 |
| rh\_S\_temporal\_sup\_thickness | -1.4737 | 0.15004 | -0.253 | 0.33157 |
| rh\_G\_oc-temp\_lat-fusifor\_thickness | -1.4483 | 0.15698 | -0.248 | 0.342676 |
| lh\_S\_orbital\_med-olfact\_thickness | 1.3958 | 0.17208 | 0.239 | 0.371112 |
| rh\_G&S\_frontomargin\_thickness | -1.3864 | 0.17492 | -0.238 | 0.372746 |
| rh\_G\_subcallosal\_thickness | 1.3678 | 0.18063 | 0.235 | 0.380386 |
| rh\_G\_precentral\_thickness | 1.3395 | 0.18955 | 0.23 | 0.394528 |
| lh\_G\_temp\_sup-Plan\_polar\_thickness | -1.3268 | 0.19369 | -0.228 | 0.398512 |
| rh\_Lat\_Fis-post\_thickness | -1.3087 | 0.19969 | -0.224 | 0.406188 |
| lh\_S\_orbital\_lateral\_thickness | -1.2668 | 0.21408 | -0.217 | 0.430565 |
| Left-Inf-Lat-Vent (Vol) | 1.2548 | 0.21837 | 0.215 | 0.434314 |
| lh\_G\_temp\_sup-Lateral\_thickness | -1.2096 | 0.23502 | -0.207 | 0.456065 |
| Left-VentralDC (Vol) | -1.2047 | 0.2369 | -0.207 | 0.456065 |
| rh\_G&S\_cingul-Mid-Post\_thickness | -1.2045 | 0.23695 | -0.207 | 0.456065 |
| rh\_S\_orbital-H\_Shaped\_thickness | -1.1933 | 0.24125 | -0.205 | 0.459402 |
| lh\_S\_occipital\_ant\_thickness | 1.1585 | 0.25497 | 0.199 | 0.480417 |
| lh\_G\_pariet\_inf-Angular\_thickness | -1.1343 | 0.26484 | -0.195 | 0.493816 |
| rh\_S\_subparietal\_thickness | -1.1276 | 0.26763 | -0.193 | 0.493874 |
| lh\_G\_front\_middle\_thickness | -1.109 | 0.27545 | -0.19 | 0.498271 |
| lh\_G&S\_frontomargin\_thickness | -1.1087 | 0.27558 | -0.19 | 0.498271 |
| Right-Accumbens-area (Vol) | -1.0914 | 0.28302 | -0.187 | 0.502388 |
| Left-Hippocampus (Vol) | -1.0857 | 0.28546 | -0.186 | 0.502388 |
| lh\_G&S\_cingul-Mid-Post\_thickness | -1.0813 | 0.28742 | -0.185 | 0.502388 |
| lh\_G\_temp\_sup-Plan\_tempo\_thickness | -1.0765 | 0.28952 | -0.185 | 0.502388 |
| Left-Cerebellum-White-Matter (Vol) | -1.0711 | 0.29189 | -0.184 | 0.502388 |
| lh\_G\_oc-temp\_lat-fusifor\_thickness | -1.0266 | 0.31207 | -0.176 | 0.532005 |
| lh\_G\_oc-temp\_med-Parahip\_thickness | 1.0156 | 0.31722 | 0.174 | 0.533721 |
| lh\_Pole\_occipital\_thickness | 1.0117 | 0.31904 | 0.174 | 0.533721 |
| rh\_G\_temp\_sup-Lateral\_thickness | -0.9927 | 0.3281 | -0.17 | 0.543795 |
| lh\_G&S\_cingul-Mid-Ant\_thickness | -0.9549 | 0.34656 | -0.164 | 0.560335 |
| rh\_G\_temp\_sup-Plan\_tempo\_thickness | 0.9531 | 0.34747 | 0.163 | 0.560335 |
| Left-Lateral-Ventricle (Vol) | 0.9538 | 0.34713 | 0.164 | 0.560335 |
| CSF (Vol) | 0.9256 | 0.36137 | 0.159 | 0.577547 |
| lh\_S\_temporal\_inf\_thickness | -0.8874 | 0.38129 | -0.152 | 0.60399 |
| lh\_S\_postcentral\_thickness | -0.8763 | 0.38719 | -0.15 | 0.604257 |
| rh\_G\_temp\_sup-Plan\_polar\_thickness | -0.8744 | 0.38821 | -0.15 | 0.604257 |
| lh\_G\_front\_inf-Orbital\_thickness | -0.8588 | 0.39662 | -0.147 | 0.606795 |
| rh\_G\_occipital\_middle\_thickness | 0.8594 | 0.3963 | 0.147 | 0.606795 |
| rh\_G\_postcentral\_thickness | -0.8411 | 0.40634 | -0.144 | 0.610361 |
| lh\_S\_interm\_prim-Jensen\_thickness | -0.8288 | 0.41315 | -0.142 | 0.610361 |
| Right-VentralDC (Vol) | -0.8223 | 0.41682 | -0.141 | 0.610361 |
| lh\_G\_rectus\_thickness | -0.8177 | 0.41941 | -0.14 | 0.610361 |
| Right-Cerebellum-White-Matter (Vol) | 0.8289 | 0.4131 | 0.142 | 0.610361 |
| lh\_G&S\_occipital\_inf\_thickness | 0.8322 | 0.41129 | 0.143 | 0.610361 |
| lh\_G\_postcentral\_thickness | -0.8091 | 0.42424 | -0.139 | 0.612411 |
| lh\_S\_collat\_transv\_ant\_thickness | 0.7969 | 0.43122 | 0.137 | 0.617507 |
| lh\_G\_front\_inf-Triangul\_thickness | -0.7881 | 0.43625 | -0.135 | 0.618184 |
| rh\_G\_oc-temp\_med-Parahip\_thickness | 0.7841 | 0.4386 | 0.134 | 0.618184 |
| rh\_S\_postcentral\_thickness | -0.7678 | 0.44807 | -0.132 | 0.622545 |
| rh\_S\_circular\_insula\_inf\_thickness | -0.7668 | 0.44865 | -0.132 | 0.622545 |
| lh\_G\_front\_sup\_thickness | -0.754 | 0.45623 | -0.129 | 0.628194 |
| lh\_S\_subparietal\_thickness | -0.7393 | 0.46494 | -0.127 | 0.6353 |
| rh\_S\_pericallosal\_thickness | 0.7325 | 0.46902 | 0.126 | 0.63602 |
| Left-choroid-plexus (Vol) | 0.7209 | 0.47605 | 0.124 | 0.640699 |
| Left-Accumbens-area (Vol) | -0.7033 | 0.4868 | -0.121 | 0.642952 |
| rh\_S\_temporal\_inf\_thickness | -0.7005 | 0.4885 | -0.12 | 0.642952 |
| rh\_Pole\_occipital\_thickness | 0.7014 | 0.48797 | 0.12 | 0.642952 |
| rh\_S\_central\_thickness | -0.6623 | 0.51241 | -0.114 | 0.669499 |
| lh\_G\_temporal\_middle\_thickness | -0.644 | 0.524 | -0.11 | 0.679681 |
| lh\_G\_cuneus\_thickness | 0.636 | 0.52915 | 0.109 | 0.681423 |
| rh\_G&S\_occipital\_inf\_thickness | 0.6189 | 0.54025 | 0.106 | 0.690748 |
| lh\_G\_parietal\_sup\_thickness | 0.606 | 0.54868 | 0.104 | 0.696551 |
| rh\_S\_calcarine\_thickness | -0.596 | 0.55522 | -0.102 | 0.69989 |
| lh\_G\_occipital\_sup\_thickness | -0.5545 | 0.58294 | -0.095 | 0.727685 |
| lh\_S\_oc-temp\_lat\_thickness | -0.5509 | 0.5854 | -0.094 | 0.727685 |
| rh\_G\_occipital\_sup\_thickness | 0.534 | 0.59692 | 0.092 | 0.736887 |
| rh\_S\_circular\_insula\_ant\_thickness | -0.479 | 0.63511 | -0.082 | 0.775651 |
| lh\_G\_oc-temp\_med-Lingual\_thickness | -0.471 | 0.64076 | -0.081 | 0.775651 |
| rh\_S\_collat\_transv\_ant\_thickness | -0.4702 | 0.64132 | -0.081 | 0.775651 |
| EstimatedTotalIntraCranialVol (Vol) | -0.4072 | 0.68652 | -0.07 | 0.824746 |
| rh\_G\_pariet\_inf-Supramar\_thickness | 0.3637 | 0.71838 | 0.062 | 0.857267 |
| Left-Caudate (Vol) | -0.3413 | 0.73502 | -0.059 | 0.871315 |
| rh\_G\_front\_middle\_thickness | -0.321 | 0.75024 | -0.055 | 0.877732 |
| rh\_G\_cingul-Post-dorsal\_thickness | 0.3271 | 0.74564 | 0.056 | 0.877732 |
| lh\_G\_cingul-Post-ventral\_thickness | 0.3137 | 0.75569 | 0.054 | 0.878367 |
| lh\_G&S\_cingul-Ant\_thickness | -0.2906 | 0.77315 | -0.05 | 0.892864 |
| rh\_S\_orbital\_med-olfact\_thickness | -0.269 | 0.7896 | -0.046 | 0.900245 |
| lh\_S\_circular\_insula\_inf\_thickness | 0.2707 | 0.78831 | 0.046 | 0.900245 |
| lh\_G\_occipital\_middle\_thickness | 0.2447 | 0.80819 | 0.042 | 0.915608 |
| rh\_S\_collat\_transv\_post\_thickness | 0.236 | 0.81487 | 0.04 | 0.917369 |
| lh\_G\_precentral\_thickness | -0.2103 | 0.83469 | -0.036 | 0.925133 |
| lh\_G\_temporal\_inf\_thickness | -0.2003 | 0.84244 | -0.034 | 0.925133 |
| rh\_S\_oc-temp\_lat\_thickness | 0.205 | 0.83881 | 0.035 | 0.925133 |
| rh\_S\_parieto\_occipital\_thickness | 0.2086 | 0.83602 | 0.036 | 0.925133 |
| lh\_S\_collat\_transv\_post\_thickness | 0.1932 | 0.84797 | 0.033 | 0.925528 |
| Right-choroid-plexus (Vol) | 0.1853 | 0.85409 | 0.032 | 0.926558 |
| lh\_S\_precentral-sup-part\_thickness | -0.1653 | 0.86973 | -0.028 | 0.933319 |
| lh\_G\_cingul-Post-dorsal\_thickness | 0.164 | 0.87075 | 0.028 | 0.933319 |
| rh\_G\_parietal\_sup\_thickness | -0.1479 | 0.88336 | -0.025 | 0.941051 |
| Right-Caudate (Vol) | -0.1307 | 0.8968 | -0.022 | 0.941051 |
| lh\_G\_pariet\_inf-Supramar\_thickness | -0.1263 | 0.90024 | -0.022 | 0.941051 |
| rh\_G\_front\_inf-Triangul\_thickness | -0.1212 | 0.90425 | -0.021 | 0.941051 |
| rh\_G\_precuneus\_thickness | 0.1342 | 0.89406 | 0.023 | 0.941051 |
| rh\_Lat\_Fis-ant-Horizont\_thickness | -0.1034 | 0.91831 | -0.018 | 0.950017 |
| rh\_S\_suborbital\_thickness | -0.0968 | 0.92348 | -0.017 | 0.950017 |
| rh\_G\_front\_inf-Orbital\_thickness | -0.0821 | 0.93505 | -0.014 | 0.956423 |
| rh\_S\_precentral-inf-part\_thickness | -0.0459 | 0.96366 | -0.008 | 0.980086 |
| rh\_G\_temporal\_middle\_thickness | -0.0186 | 0.98526 | -0.003 | 0.99134 |
| rh\_G\_pariet\_inf-Angular\_thickness | 0.0139 | 0.98899 | 0.002 | 0.99134 |
| rh\_G\_rectus\_thickness | 0.0109 | 0.99134 | 0.002 | 0.99134 |

## Subgroup comparison

### S2: SCI-NP: Deviation from normative structure

One-sample t-tests were performed within the SCI-NP subgroup to assess whether residuals for each brain feature significantly deviated from normative model. The table includes brain features name, test statistics, uncorrected p-values and Cohen’s d effect sizes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Brain features** | **T- value** | **p-value** | **Cohen’s d** |
| TotalGrayVol (Vol) | -4.563 | 0.000138 | -0.931 |
| rh\_G&S\_transv\_frontopol\_thickness | -4.552 | 0.000142 | -0.929 |
| rh\_S\_oc\_sup&transversal\_thickness | 4.363 | 0.000228 | 0.891 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 4.133 | 0.000404 | 0.844 |
| Left-Pallidum (Vol) | -3.954 | 0.000631 | -0.807 |
| Left-Amygdala (Vol) | -3.851 | 0.000814 | -0.786 |
| Right-Cerebellum-Cortex (Vol) | -3.706 | 0.001163 | -0.757 |
| SubCortGrayVol (Vol) | -3.612 | 0.001466 | -0.737 |
| Right-vessel (Vol) | 3.554 | 0.001688 | 0.726 |
| rh\_S\_interm\_prim-Jensen\_thickness | -3.479 | 0.002027 | -0.71 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 3.458 | 0.002135 | 0.706 |
| lh\_G&S\_paracentral\_thickness | -3.35 | 0.002774 | -0.684 |
| rh\_S\_intrapariet&P\_trans\_thickness | 3.321 | 0.002977 | 0.678 |
| rh\_G\_temporal\_inf\_thickness | -3.013 | 0.0062 | -0.615 |
| 3rd-Ventricle (Vol) | 2.968 | 0.006885 | 0.606 |
| lh\_G&S\_subcentral\_thickness | -2.938 | 0.007393 | -0.6 |
| rh\_G\_front\_inf-Opercular\_thickness | -2.9 | 0.008078 | -0.592 |
| rh\_S\_temporal\_transverse\_thickness | -2.631 | 0.014941 | -0.537 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | -2.585 | 0.01656 | -0.528 |
| rh\_S\_front\_sup\_thickness | -2.313 | 0.030027 | -0.472 |
| Right-Inf-Lat-Vent (Vol) | 2.186 | 0.039244 | 0.446 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | -2.143 | 0.042906 | -0.437 |
| rh\_Pole\_temporal\_thickness | -1.917 | 0.067688 | -0.391 |

### S3: SCI-nNP: Deviation from normative structure

One-sample t-tests were performed within the SCI-nNP subgroup to assess whether residuals for each brain feature significantly deviated from normative model. The table includes brain features name, test statistics, uncorrected p-values and Cohen’s d effect sizes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Brain features** | **T- value** | **p-value** | **Effect Size** |
| rh\_S\_oc\_sup&transversal\_thickness | 3.588 | 0.005858 | 1.135 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 3.355 | 0.008453 | 1.061 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 3.055 | 0.013676 | 0.966 |
| rh\_S\_intrapariet&P\_trans\_thickness | 3.049 | 0.013815 | 0.964 |
| rh\_G&S\_transv\_frontopol\_thickness | -2.975 | 0.015587 | -0.941 |
| rh\_G\_front\_inf-Opercular\_thickness | -2.732 | 0.023155 | -0.864 |
| rh\_S\_front\_sup\_thickness | -2.563 | 0.030551 | -0.81 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | -2.424 | 0.038337 | -0.767 |
| rh\_Pole\_temporal\_thickness | -2.274 | 0.049058 | -0.719 |
| Right-Inf-Lat-Vent (Vol) | 2.236 | 0.052197 | 0.707 |
| lh\_G&S\_paracentral\_thickness | -2.215 | 0.053972 | -0.701 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | -2.18 | 0.057181 | -0.689 |
| TotalGrayVol (Vol) | -1.912 | 0.088129 | -0.605 |
| Right-Cerebellum-Cortex (Vol) | -1.902 | 0.089672 | -0.601 |
| rh\_G\_temporal\_inf\_thickness | -1.592 | 0.145838 | -0.503 |
| 3rd-Ventricle (Vol) | 1.576 | 0.149401 | 0.498 |
| lh\_G&S\_subcentral\_thickness | -1.421 | 0.188969 | -0.449 |
| Left-Pallidum (Vol) | -1.267 | 0.236941 | -0.401 |
| rh\_S\_temporal\_transverse\_thickness | -1.218 | 0.254297 | -0.385 |
| Right-vessel (Vol) | 1.151 | 0.279344 | 0.364 |
| SubCortGrayVol (Vol) | -1.131 | 0.287403 | -0.358 |
| Left-Amygdala (Vol) | -0.908 | 0.387654 | -0.287 |
| rh\_S\_interm\_prim-Jensen\_thickness | -0.866 | 0.40891 | -0.274 |

### S4: Between-group comparison

Independent t-test were performed between SCI-NP and SCI-nNP. The table includes brain features name, test statistics, uncorrected p-values and Cohen’s d effect sizes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Brain features** | **T-value** | **p-value** | **Cohen’s d** |
| rh\_Pole\_temporal\_thickness | 1.564 | 0.127725 | 0.589 |
| SubCortGrayVol (Vol) | -1.274 | 0.211777 | -0.48 |
| Left-Pallidum (Vol) | -0.856 | 0.398195 | -0.322 |
| Left-Amygdala (Vol) | -0.78 | 0.441176 | -0.294 |
| rh\_S\_front\_sup\_thickness | 0.766 | 0.449009 | 0.288 |
| rh\_G\_front\_inf-Opercular\_thickness | 0.667 | 0.509387 | 0.251 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | 0.618 | 0.540826 | 0.233 |
| rh\_S\_interm\_prim-Jensen\_thickness | -0.583 | 0.56388 | -0.219 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | 0.569 | 0.573122 | 0.214 |
| TotalGrayVol (Vol) | -0.562 | 0.578087 | -0.211 |
| rh\_G&S\_transv\_frontopol\_thickness | 0.526 | 0.60271 | 0.198 |
| lh\_G&S\_paracentral\_thickness | 0.45 | 0.65554 | 0.169 |
| rh\_S\_temporal\_transverse\_thickness | -0.443 | 0.660587 | -0.167 |
| Right-Inf-Lat-Vent (Vol) | -0.43 | 0.670056 | -0.162 |
| rh\_S\_intrapariet&P\_trans\_thickness | -0.253 | 0.801736 | -0.095 |
| Right-vessel (Vol) | -0.208 | 0.836449 | -0.078 |
| 3rd-Ventricle (Vol) | -0.202 | 0.840998 | -0.076 |
| rh\_S\_oc\_middle&Lunatus\_thickness | -0.185 | 0.854039 | -0.07 |
| lh\_G&S\_subcentral\_thickness | 0.177 | 0.860798 | 0.067 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | -0.145 | 0.885545 | -0.055 |
| Right-Cerebellum-Cortex (Vol) | 0.131 | 0.896463 | 0.049 |
| rh\_S\_oc\_sup&transversal\_thickness | -0.126 | 0.900156 | -0.048 |
| rh\_G\_temporal\_inf\_thickness | -0.016 | 0.987109 | -0.006 |

## Structural brain deviations are associated with pain characteristics

Spearman correlations in the SCI-NP subgroup were performed between brain features and the three pain variables: (1) maximum pain intensity, (2) average pain intensity and (3) spatial extent of pain.

#### S4: Maximum pain intensity

|  |  |  |
| --- | --- | --- |
| **Brain features** | **Spearman ρ** | **p-value** |
| lh\_G&S\_paracentral\_thickness | 0.531 | 0.0091 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 0.42 | 0.0458 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 0.414 | 0.0493 |
| rh\_S\_intrapariet&P\_trans\_thickness | 0.414 | 0.0493 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | 0.412 | 0.051 |
| rh\_S\_oc\_sup&transversal\_thickness | 0.369 | 0.0829 |
| rh\_S\_interm\_prim-Jensen\_thickness | 0.336 | 0.1175 |
| lh\_G&S\_subcentral\_thickness | 0.205 | 0.3485 |
| Right-vessel (Vol) | -0.197 | 0.3681 |
| Right-Cerebellum-Cortex (Vol) | -0.166 | 0.4483 |
| rh\_S\_temporal\_transverse\_thickness | -0.149 | 0.4982 |
| rh\_S\_front\_sup\_thickness | -0.121 | 0.5833 |
| TotalGrayVol (Vol) | -0.12 | 0.5849 |
| Left-Amygdala (Vol) | -0.11 | 0.6168 |
| rh\_G\_temporal\_inf\_thickness | -0.106 | 0.6313 |
| Right-Inf-Lat-Vent (Vol) | -0.101 | 0.646 |
| 3rd-Ventricle (Vol) | -0.07 | 0.7506 |
| SubCortGrayVol (Vol) | -0.064 | 0.7714 |
| rh\_Pole\_temporal\_thickness | 0.06 | 0.7853 |
| Left-Pallidum (Vol) | -0.052 | 0.8134 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | -0.026 | 0.9061 |
| rh\_G&S\_transv\_frontopol\_thickness | -0.025 | 0.9097 |
| rh\_G\_front\_inf-Opercular\_thickness | -0.01 | 0.9638 |

#### S5: Average pain intensity

|  |  |  |
| --- | --- | --- |
| **Brain features** | **Spearman ρ** | **p-value** |
| lh\_G&S\_paracentral\_thickness | 0.419 | 0.0469 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 0.387 | 0.0681 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 0.382 | 0.072 |
| rh\_S\_intrapariet&P\_trans\_thickness | 0.381 | 0.0732 |
| rh\_S\_oc\_sup&transversal\_thickness | 0.352 | 0.0996 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | 0.328 | 0.126 |
| rh\_S\_interm\_prim-Jensen\_thickness | 0.318 | 0.1398 |
| lh\_G&S\_subcentral\_thickness | 0.194 | 0.3753 |
| Left-Amygdala (Vol) | -0.16 | 0.4651 |
| rh\_G\_temporal\_inf\_thickness | -0.152 | 0.4891 |
| Right-vessel (Vol) | -0.14 | 0.5241 |
| TotalGrayVol (Vol) | -0.123 | 0.5755 |
| Right-Cerebellum-Cortex (Vol) | -0.1 | 0.6485 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | 0.097 | 0.6599 |
| Right-Inf-Lat-Vent (Vol) | -0.09 | 0.6845 |
| SubCortGrayVol (Vol) | -0.087 | 0.6945 |
| rh\_S\_front\_sup\_thickness | -0.074 | 0.7365 |
| rh\_G&S\_transv\_frontopol\_thickness | 0.017 | 0.9402 |
| 3rd-Ventricle (Vol) | 0.016 | 0.9429 |
| rh\_G\_front\_inf-Opercular\_thickness | -0.015 | 0.9446 |
| rh\_Pole\_temporal\_thickness | 0.015 | 0.9464 |
| Left-Pallidum (Vol) | 0.01 | 0.9625 |
| rh\_S\_temporal\_transverse\_thickness | -0.01 | 0.9643 |

#### S6: Spatial extent pain

|  |  |  |
| --- | --- | --- |
| **Brain features** | **Spearman ρ** | **p-value** |
| rh\_S\_front\_sup\_thickness | -0.466 | 0.0383 |
| Right-vessel (Vol) | 0.355 | 0.1247 |
| rh\_S\_oc\_middle&Lunatus\_thickness | 0.333 | 0.1519 |
| rh\_S\_oc-temp\_med&Lingual\_thickness | 0.312 | 0.1812 |
| rh\_S\_intrapariet&P\_trans\_thickness | 0.312 | 0.1812 |
| rh\_S\_oc\_sup&transversal\_thickness | 0.305 | 0.1903 |
| lh\_G&S\_paracentral\_thickness | -0.296 | 0.2047 |
| TotalGrayVol (Vol) | 0.208 | 0.38 |
| Right-Cerebellum-Cortex (Vol) | 0.198 | 0.4015 |
| lh\_G&S\_subcentral\_thickness | 0.185 | 0.435 |
| rh\_S\_interm\_prim-Jensen\_thickness | 0.164 | 0.4899 |
| rh\_Pole\_temporal\_thickness | 0.158 | 0.5061 |
| rh\_G&S\_transv\_frontopol\_thickness | -0.156 | 0.5101 |
| Left-Amygdala (Vol) | 0.15 | 0.5269 |
| lh\_Lat\_Fis-ant-Vertical\_thickness | 0.131 | 0.5825 |
| Left-Pallidum (Vol) | -0.123 | 0.6045 |
| rh\_G\_temporal\_inf\_thickness | 0.108 | 0.6496 |
| lh\_Lat\_Fis-ant-Horizont\_thickness | 0.077 | 0.7479 |
| SubCortGrayVol (Vol) | -0.075 | 0.7527 |
| rh\_G\_front\_inf-Opercular\_thickness | -0.06 | 0.8011 |
| rh\_S\_temporal\_transverse\_thickness | -0.057 | 0.8109 |
| Right-Inf-Lat-Vent (Vol) | -0.041 | 0.865 |
| 3rd-Ventricle (Vol) | 0.008 | 0.9749 |

# Supplementary