Primary somatosensory/motor cortical thickness distinguishes paresthesia-dominant from pain-dominant carpal tunnel syndrome

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Abstract
Paresthesia-dominant and pain-dominant subgroups have been noted in carpal tunnel syndrome (CTS), a peripheral neuropathic disorder characterized by altered primary somatosensory/motor (S1/M1) physiology. We aimed to investigate whether brain morphometry dissociates these subgroups. Subjects with CTS were evaluated with nerve conduction studies, whereas symptom severity ratings were used to allocate subjects into paresthesia-dominant (CTS-paresthesia), pain-dominant (CTS-pain), and pain/paresthesia nondominant (not included in further analysis) subgroups. Structural brain magnetic resonance imaging data were acquired at 3T using a multiecho MPRAGE T1-weighted pulse sequence, and gray matter cortical thickness was calculated across the entire brain using validated, automated methods. CTS-paresthesia subjects demonstrated reduced median sensory nerve conduction velocity \((P = 0.05)\) compared with CTS-pain subjects. In addition, cortical thickness in precentral and postcentral gyri (S1/M1 hand area) contralateral to the more affected hand was significantly reduced in CTS-paresthesia subgroup compared with CTS-pain subgroup. Moreover, in CTS-paresthesia subjects, precentral cortical thickness was negatively correlated with paresthesia severity \((r(34) = -0.40, P = 0.016)\) and positively correlated with median nerve sensory velocity \((r(36) = 0.51, P = 0.001)\), but not with pain severity. Conversely, in CTS-pain subjects, contralesional S1 \((r(9) = 0.62, P = 0.042)\) and M1 \((r(9) = 0.61, P = 0.046)\) cortical thickness were correlated with pain severity, but not median nerve velocity or paresthesia severity. This double dissociation in somatotopically specific S1/M1 areas suggests a neuroanatomical substrate for symptom-based CTS subgroups. Such fine-grained subgrouping of CTS may lead to improved personalized therapeutic approaches, based on superior characterization of the linkage between peripheral and central neuroplasticity.

Keywords: Carpal tunnel syndrome, Neuropathic pain, Paresthesia, Entrapment neuropathy, Primary somatosensory/motor cortex

1. Introduction
Many chronic neuropathic pain disorders are characterized by not just pain, but a diverse set of symptoms including numbness, tingling, etc. The impact of different symptom presentations is not fully understood. Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, with a US prevalence of 3.72%.\(^{52}\) Carpal tunnel syndrome pathophysiology includes compression of the distal median nerve by an elevated pressure in the carpal tunnel,\(^{51}\) leading to altered median nerve conduction and a range of sensory symptoms primarily in the first through fourth digits of the hand. However, multiple studies have reported lacking correlation between general CTS symptomatology and median nerve conduction,\(^{21, 55}\) assessed by electroneurography. This discrepancy may be related to distinct, symptom-dominant CTS subgroups. Electroneurography mainly measures A-beta fiber transmission, which has been linked to paresthesia,\(^{54, 55}\) whereas pain in CTS has instead been linked to A-delta and C-fiber transmission.\(^{52}\) Paresthesia represents the most common CTS symptom\(^{56}\) and may result from ectopic impulse activity generated by ischemic nerve damage.\(^{54, 56}\) In addition, previous studies have used factor analysis to separate paresthesia-dominant symptom patterns from pain-dominant symptom patterns, with the former more closely correlated to nerve conduction.\(^{56}\)

Another reason for a lack of correlation between electroneurography and symptom report may be due to variable central nervous system plasticity. Recent studies have demonstrated altered functional\(^{10, 29, 37}\) and structural\(^{30}\) properties for CTS in primary somatosensory (S1) cortices of the brain. We found that

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reduced gray matter volume within the S1 hand area contralateral to the more affected hand was associated with median nerve sensory velocity. Other studies have also demonstrated reduced gray matter volume in patients with chronic pain and reduced cortical thickness in cases of more severe peripheral deafferentation, such as peripheral nerve transection. However, the association between such structural brain changes and specific symptomatology or peripheral nerve function in patients with chronic neuropathic pain is not well understood.

Different symptom presentations may differentially impact brain physiology, which may improve our understanding of specific pathophysiology and help determine appropriate therapeutic options for symptom-based patient subgroups. We evaluated brain cortical thickness in CTS with dominant pain, compared with dominant paresthesia. We hypothesized that compared to CTS with dominant pain, CTS with dominant paresthesia will demonstrate decreased cortical thickness in the S1 cortical representation for the hand/wrist and that thickness will be associated with distinct (pain vs paresthesia) symptom severity for these specific CTS subgroups.

2. Methods

2.1. Subject enrollment and demographics

We enrolled 59 women with CTS (48.9 ± 9.6 years, mean ± SD) with a history of pain and/or paresthesia symptoms for greater than 3 months in median nerve-innervated regions of the hand/fingers. In addition, 24 female age-matched healthy control subjects (49.5 ± 10.0 years) were enrolled. All subjects were examined for eligibility by a physiatrist (J.A., L.R.M.) at Spaulding Rehabilitation Hospital, which included testing of median (digits 1-3) and ulnar (digit 5) sensory nerve conduction velocities (NCVs). Nerve conduction studies (Sierra EMG, Cadwell Industries, Inc., Kennewick, WA) used previously described methods. For subjects with CTS, nerve conduction studies (NCS) inclusion criteria consisted of >3.7-millisecond sensory latency for median nerve or >0.5-millisecond sensory latency compared with ulnar sensory latency. Criteria for both CTS and healthy control subjects consisted of contraindications for magnetic resonance imaging (MRI), history of diabetes mellitus, cardiovascular, respiratory, or neurological illnesses, rheumatoid arthritis, wrist fracture, current usage of prescriptive opioid medication, thenar atrophy, nerve entrapment other than median nerve, cervical radiculopathy or myelopathy, generalized peripheral neuropathy, blood dyscrasia or coagulopathy, or current use of anticoagulation therapy. All study protocols were approved by Massachusetts General Hospital and Partners Human Research Committee. Written informed consent was obtained from all subjects before enrollment.

2.2. Clinical data

Nerve conduction studies were used to calculate relative median NCV, by subtracting ulnar (digit 5) from median (digit 2) sensory velocity. Although studies have used both raw and unnormalized median sensory velocities as outcomes, the relative measures may demonstrate higher diagnostic accuracy, as they control for nonspecific intersubject differences, ie, they are less influenced by factors such as age, height, weight, and hand temperature.

Subjects’ symptom severity was assessed by separate 11-point (0: none; 10: very strong) Numerical Rating Scales (NRS) for pain and paresthesia (numbness/tingling). These ratings were used for subgrouping subjects with CTS: paresthesia dominance (CTS-paresthesia; n = 38, greater paresthesia than pain), pain dominance (CTS-pain; n = 11, greater pain than paresthesia), and relative pain/paresthesia equivalence (n = 10, identical pain and paresthesia ratings; data not included in further analysis). To inform whether this specific pain and paresthesia rating scale may be a stable trait of subjects’ clinical presentation, we also assessed other, more nuanced, aspects of symptom severity and functional status referring to a “typical 24-hour period during the past 2 weeks,” using the Boston Carpal Tunnel Questionnaire (BCTQ), which uses a scale of 1 through 5 (1: none; 5: severe). Pain-related questions were combined into a subscore, with averaged ratings on questions 1 through 5, whereas a paresthesia subscore averaged ratings on questions 6 through 10. Subscales scores were used to calculate a pain/paresthesia ratio, which assessed the relative contribution of pain vs paresthesia to subjects’ symptom presentation. We also assessed the separate BCTQ function scale (average score from 8 questions).

Clinical data were tested for normality (Shapiro–Wilk test) and equal variance (Levene test), significant at $P \leq 0.05$ (SPSS version 20; Chicago, IL). Nerve conduction study data and BCTQ scores were compared between CTS-paresthesia and CTS-pain subgroups using either the Student t test or Mann–Whitney U test according to statistical distribution, significant at $P \leq 0.05$.

2.3. Magnetic resonance imaging data acquisition

Structural brain MRI data were acquired with a multiecho MPRAZE T1-weighted pulse sequence (TR = 2530 millisecond, TE1/TE2 = 1.64/30.0 millisecond, TI = 1200 millisecond, flip angle = 7˚, field of view = 256 × 256, slices = 176, sagittal acquisition, spatial resolution = 1 × 1 × 1 mm3) on a 3T Siemens Trio scanner (Siemens Medical, Erlangen, Germany) equipped with a 32-channel head coil.

2.4. Magnetic resonance imaging data analysis

For cortical thickness analyses, brain MRI structural data were preprocessed with FreeSurfer (recon-all, FreeSurfer v.5.3). Preprocessing included motion correction, removal of nonbrain tissue, automated Talairach transformation, intensity normalization, tessellation of the gray matter/white matter boundary, automated topology correction, and surface deformation after intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. This method produces representations of cortical thickness calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface and has been validated against histological analysis. Surficial cortical thickness data were then smoothed using 2-dimensional surface smoothing (10 mm full width at half maximum, mris_preproc, FreeSurfer v.5.3).

For subjects with CTS whose more affected hand was the left hand, cortical thickness data were flipped across the midsagittal plane before these data were passed up to group analyses with right hand–affected subjects. This allowed for data interpretation relative to the hand demonstrating median nerve pathology and is specifically important for lateralized structures (ie, S1/M1). A nonflipped analysis explored if the main results were significantly influenced by data flipping. In the entire sample, 16 patients were
more affected on the left hand. Of these 16 patients, only 1 had unilateral CTS, whereas 15 had bilateral CTS, based on our clinical/electrodiagnostic criteria. Conversely, 33 patients were more affected on the right hand, with 11 demonstrating unilateral CTS, whereas 22 had bilateral CTS.

Preprocessed cortical thickness data were contrasted between CTS-paresthesia and CTS-pain subgroups with age as a regressor of no interest using a general linear model (mri_glmfit, FreeSurfer v.5.3) and corrected for multiple comparisons at cluster-wise $P = 0.05$ (mri_glmfit-sim, FreeSurfer). Intracranial volume did not differ between groups ($P = 0.42$). For region of interest follow-up analyses involving significant clusters within precentral and postcentral gyri, a software-generated annotation file (iaparc.annot, FreeSurfer) was used to determine precentral and postcentral gyral localizations for both hemispheres. Importantly, the number of subjects required for cortical thickness analyses is dependent on cortical location, with fewer subjects required for several regions including those adjacent to the central sulcus. This is likely due to such factors as reduced intersubject variability in cortical thickness and ease of surface topology modeling for regions adjacent to the central sulcus. Thus, fewer subjects are required because of a lower variance, which stems from greater consistency in folding across individuals and the fact that intersubject registration is based on aligning cortical folding patterns in FreeSurfer. Correlation analyses associated cortical thickness and clinical variables (NCV and BCTQ), significant at $P \leq 0.05$. In addition, as our previous study directly contrasted structural brain data from subjects with CTS (a subset, N = 20, of the larger sample, N = 59, reported herein) vs healthy controls and reported significant gray matter volume differences between patients with CTS and healthy adults, this study did not directly contrast CTS data with healthy controls. In this study, healthy control subject data from significant clusters identified above were used to descriptively aid interpretation of how differences between CTS-pain and CTS-paresthesia cortical thickness relate to cortical thickness measures in age-matched and sex-matched healthy adults.

3. Results

3.1. Demographic and clinical assessments

There were no differences in age ($t(12) = -0.93; P = 0.37$; unequal variances, Levene test) or symptom duration ($t(47) = -0.33; P = 0.74$) between CTS-paresthesia and CTS-pain subgroups (Table 1). Nerve conduction testing found reduced relative (median–ulnar) sensory median NCVs for CTS-paresthesia subgroup compared with CTS-pain subgroup ($t(46) = 1.99; P = 0.05$). Boston Carpal Tunnel Questionnaire scores reflected CTS subgroup allocation, suggesting that the ratings on our NRS reflected a stable trait of subjects’ clinical presentation. Specifically, for CTS-paresthesia subjects, NRS pain was rated as 3.8 ± 2.6 (mean ± SD), whereas NRS paresthesia was rated as 6.4 ± 2.3. Conversely, for CTS-pain subjects, NRS pain was rated as 5.4 ± 2.1, whereas NRS paresthesia was rated as 4.1 ± 2.0. The pain–paresthesia metric, which was used for subgroup classification, was significantly different between the 2 groups (CTS-pain: $1.35 \pm 0.58$, CTS-paresthesia: $-2.59 \pm 2.28$, $t(46) = -9.55$, $P < 0.001$; unequal variances, Levene test). The BCTQ-derived pain/paresthesia ratio was significantly greater for CTS-pain subgroup than for CTS-paresthesia subgroup ($t(47) = 3.16; P = 0.003$). There were no differences in overall BCTQ symptom severity ($t(47) = -0.44$, $P = 0.66$) or function scale ($t(46) = -0.71$, $P = 0.48$) scores between CTS-pain and CTS-paresthesia groups. In general, the BCTQ symptom scale score across all subjects in our study was 2.72 ± 0.66, which is highly consistent with the BCTQ symptom scale score reported in previous large sample (N = 403) studies, suggesting that our cohort was at least grossly reflective of the general CTS population.

3.2. Magnetic resonance imaging data analysis: cortical thickness

A whole-brain cortical thickness analysis demonstrated that CTS-pain subjects had significantly greater cortical thickness in a cluster covering left (contralesional to the more affected hand) precentral gyrus (putative M1), postcentral gyrus (putative S1), another cluster covering left middle temporal gyrus, and a third cluster covering right (ipsilesional to the more affected hand) precentral gyrus (M1) and superior/middle frontal gyrus (consistent with premotor cortex) (Table 2, Figure 1), similar results were also seen for a nonflipped analysis, Supplementary Figure 1, available online as supplemental digital content at http://links.lww.com/PAIN/A219). The contralesional S1/M1 cluster was localized to the hand area of the somatotopic map, as supported by overlaid outlines of finger stimulation clusters from our previous functional MRI results and more clearly presented with idealized

<table>
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<th>Table 1</th>
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<td>Demographics and clinical assessments.</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Symptom duration (yr)</td>
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<tr>
<td>Nerve conduction study</td>
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<tr>
<td>Median–ulnar sensory velocity (m/s)</td>
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<td>Symptom severity</td>
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<tr>
<td>Numerical Rating Scale (0-10)</td>
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<tr>
<td>Pain rating</td>
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<tr>
<td>Paresthesia rating</td>
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<td>Pain-paresthesia (used for classification)</td>
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<tr>
<td>Boston Carpal Tunnel Syndrome questionnaire</td>
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<tr>
<td>Symptom severity score (1-5)</td>
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<td>Function status score (1-5)</td>
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<td>Pain/paresthesia ratio</td>
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Data are shown as mean ± SD. n/a, not applicable. Bold values refer to significant $P$ at level 0.05.

CTS, carpal tunnel syndrome.
Brodmann area borders for M1 and S1, following Moore et al.\textsuperscript{36}

Cortical thickness in the left precentral and postcentral gyri (but not middle temporal gyrus) for healthy control subjects (plotted for descriptive interpretation) demonstrated an intermediate mean value, between the CTS-pain and CTS-paresthesia subgroups (Figure 2). As cortical thickness differences may have been due to differences in median nerve conduction between groups, we also ran similar analyses controlling for relative median NCV, which yielded similar results with a subset of the brain regions noted above (right/ipsilesional M1, superior frontal and temporal gyrus; contralesional superior temporal gyrus, Supplementary Figure 2, available online as supplemental digital content at http://links.lww.com/PAIN/A219).

There were no brain regions that exhibited greater cortical thickness for CTS-paresthesia subgroup than for CTS-pain subgroup.

For CTS-paresthesia subjects, contralesional precentral (M1) cortical thickness was positively correlated with median nerve sensory velocity ($r(36) = 0.51$, $P = 0.001$) and negatively correlated with BCTQ paresthesia score ($r(34) = -0.40$, $P = 0.016$, Figure 3, Table 3). Thus, for the CTS-paresthesia subgroup, worse clinical presentation, as evidenced by greater paresthesia severity, was associated with thinner gray matter in contralesional M1. Conversely, for subjects with CTS-pain, a positive correlation was found between cortical thickness in both postcentral (S1; $r(9) = 0.62$, $P = 0.042$) and precentral

### Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
<th>CTS-pain - CTS-paresthesia z-stat</th>
<th>Total cluster size (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left (contralesional to more affected hand) hemisphere</td>
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<td></td>
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<td></td>
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<tr>
<td>Precentral gyrus (M1)</td>
<td>−41.2</td>
<td>−11.9</td>
<td>59.3</td>
<td>3.86</td>
<td>829</td>
</tr>
<tr>
<td>Postcentral gyrus (S1)</td>
<td>−39.7</td>
<td>−32.5</td>
<td>47.4</td>
<td>2.56</td>
<td>829</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>−62.9</td>
<td>−35.4</td>
<td>−13.3</td>
<td>3.33</td>
<td>947</td>
</tr>
<tr>
<td>Right (ipsilesional to more affected hand) hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>19.2</td>
<td>−3.2</td>
<td>64.4</td>
<td>4.79</td>
<td>2621</td>
</tr>
<tr>
<td>Precentral gyrus (M1)</td>
<td>37.5</td>
<td>−10.8</td>
<td>61.8</td>
<td>2.67</td>
<td>2621</td>
</tr>
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</table>

Figure 1. Carpal tunnel syndrome (CTS)-pain and CTS-paresthesia cortical thickness difference map. A whole-brain cortical thickness analysis demonstrated that CTS-pain subjects had significantly greater gray matter thickness in bilateral precentral gyrus (putative M1), left (contralesional to the more affected hand) postcentral gyrus (putative S1), left middle temporal gyrus, and right (ipsilesional to the more affected hand) superior/middle frontal gyrus (consistent with premotor cortex). The S1/M1 cluster was localized to the hand area of the somatotopic map, as supported by the overlaid outline (yellow) of activation clusters for median nerve-innervated digits of the affected hand (from our previous functional magnetic resonance imaging publication\textsuperscript{29}). The cluster showed separate local maxima in both purported M1 (BA4) and S1 (BA1/BA2), more clearly presented with idealized Brodmann area borders for M1 and S1, following Moore et al.\textsuperscript{36}
(M1; r(9) = 0.61, P = 0.046) gyri and BCTQ pain score (Figure 3, Table 3). Thus, for the CTS-pain subgroup, worse clinical presentation, as evidenced by greater pain severity, was associated with thicker gray matter in contralesional S1 and M1.

For CTS-paresthesia subgroup, cortical thickness in contralesional M1 (r(36) = −0.21, P = 0.21) and S1 (r(36) = 0.07, P = 0.69) was not correlated with BCTQ pain score; whereas for CTS-pain subgroup, cortical thickness in contralesional M1 (r(9) = −0.23, P = 0.50) and S1 (r(9) = 0.34, P = 0.30) was not correlated with BCTQ paresthesia score. Furthermore, for CTS-pain subgroup, cortical thickness in contralesional M1 (r(9) = 0.12, P = 0.73) and S1 (r(9) = 0.35, P = 0.33) was not correlated with median NCV (Table 3). In addition, specificity for pain and paresthesia was highlighted by the fact that gross BCTQ symptom (SSS) and function (FSS) scale scores were not correlated with cortical thickness in contralesional S1 (BCTQ-SSS: r(36) = −0.09, P = 0.57; BCTQ-FSS: r(35) = −0.09, P = 0.59) for CTS-paresthesia subjects or in contralesional M1 (r(9) = 0.39, P = 0.23 and r(9) = −0.69, P = 0.83, respectively) or S1 (r(9) = 0.48, P = 0.13 and r(9) = −0.08, P = 0.82, respectively) for CTS-pain subjects.

4. Discussion

Our study investigated the differentiation in structural brain morphometry by CTS symptom patterns and associated median nerve function. We found a double dissociation for pain-dominant vs paresthesia-dominant CTS subgroups. First, compared with CTS-pain subjects, CTS-paresthesia subjects demonstrated worse median nerve function and reduced cortical thickness for several brain regions, including S1 (hand area, contralateral to more affected hand) and M1 (bilateral). In addition, contralesional M1 cortical thickness in CTS-paresthesia subjects was correlated with median nerve velocity and paresthesia severity, but not pain severity. Conversely, in CTS-pain subjects, contralesional S1 and M1 cortical thickness was correlated with pain severity, but not median nerve velocity or paresthesia severity. These results support the existence of dichotomous subgroups of patients with CTS based on symptomatology and suggest a neuroanatomical substrate for this dichotomy.

Although paresthesia and pain are common symptoms associated with CTS, evidence supports distinct pathophysiology underlying these different symptoms. First, a factor analysis on BCTQ found that paresthesia and pain load onto different factors and that the primary paresthesia factor was more closely correlated with nerve conduction measures. This result was recently corroborated in a large sample cohort. Both paresthesia and pain result from median nerve compression due to increased carpal tunnel pressure, leading to ischemia and pathohistochemical sequelae. However, experimentally induced ischemia produces paresthesia and numbness, not necessarily pain, in patients with CTS. Paresthesia severity has been closely linked with median nerve conduction studies. As nerve conduction studies are believed to preferentially assay large diameter, myelinated A-beta fibers, CTS-induced paresthesia has been strongly associated with damage and demyelination of nonnociceptive A-beta fibers, similar to neuropathic pain syndromes. In fact, studies of nerve compression in awake human subjects have demonstrated that ischemia is related to paresthesia, resulting from an abnormal spatiotemporal pattern of ectopic impulses from different sensory units, accompanied by prolonged bursts of high-frequency afference in the most intense stage of paresthesia. Conversely, pain in CTS has been linked with small diameter, myelinated A-delta fiber damage. Because pain severity does not correlate with nerve conduction measures, pain in CTS may arise from weaker, but still chronic, median nerve compression, which preferentially damages smaller A-delta fibers. Our results support this hypothesis, as we also found median nerve conduction to be more reduced in CTS-paresthesia subgroup, compared with CTS-pain subgroup, with no differences in disease duration or BCTQ symptom severity scores between the 2 groups. Thus, pain or paresthesia dominance in CTS is not simply a consequence of disease duration or severity and likely depends on distinct pathophysiological factors.

Compared with subjects with CTS-pain, CTS-paresthesia subjects demonstrated reduced S1 and M1 cortical thickness, which was correlated with peripheral nerve dysfunction and self-rated paresthesia severity. Our previous study used whole-brain voxel-based morphometry analysis and noted...
reduced gray matter volume in contralesional S1 hand area for subjects with CTS. In that mixed (combined paresthesia-dominant and pain-dominant) sample, reduced gray matter volume was weakly correlated with median NCV but not with symptomatology. Reduced gray matter volume is broadly consistent with our current observation of reduced S1 cortical thickness for CTS-paresthesia subgroup, as this subgroup represented most subjects with CTS previously evaluated, and paresthesia is the most common CTS symptom. Lack of significant correlation with symptom severity for the previous CTS cohort is also consistent with the double dissociation noted in this study between specific (i.e., paresthesia vs. pain) symptoms and different symptom-dominant CTS subgroups.

Interestingly, altered cortical thickness was noted not just in contralesional S1 but also in M1. Moreover, contralesional M1 thickness in CTS-paresthesia subgroup was positively correlated with NCV and negatively correlated with paresthesia severity—i.e., worse clinical presentation was associated with reduced contralesional M1 thickness. Reduced cortical thickness in contralesional M1 may be due to reduced hand and arm movement in CTS-paresthesia subjects vs CTS-pain subjects.

Figure 3. Cortical thickness correlates with clinical measures in carpal tunnel syndrome (CTS)-pain and CTS-paresthesia subjects. For CTS-paresthesia subjects, contralesional precentral (M1) cortical thickness was positively correlated with relative median sensory nerve conduction velocity ($r(36) = 0.51$, $P = 0.001$) and negatively correlated with Boston Carpal Tunnel Questionnaire (BCTQ) paresthesia score ($r(34) = -0.40$, $P = 0.016$). Thus, worse clinical presentation, as evidenced by slower median nerve sensory conduction velocity and greater paresthesia severity, was associated with thinner gray matter in contralesional M1. Conversely, for CTS-pain subjects, contralesional postcentral (S1) and precentral (M1) cortical thickness was positively correlated with BCTQ pain score (S1: $r(9) = 0.62$, $P = 0.042$; M1: $r(9) = 0.61$, $P = 0.046$, respectively) but not paresthesia severity or nerve conduction velocity (S1: $P = 0.30$, $P = 0.33$; M1: $P = 0.50$, $P = 0.73$, respectively).
In fact, patients with dystonia, whose affected hand was immobilized for 4 weeks, demonstrated reduced contralesional M1 gray matter density.\textsuperscript{20} However, CTS-paresthesia subjects did not differ in disease duration or BCTQ functional scores (which refer to hand and arm movement activities) compared with CTS-pain subjects, and M1 cortical thickness was not associated with BCTQ function scores. This suggests that neither disrupted behavioral patterns nor chronicity can explain the altered cortical thickness in contralesional M1. In addition, our previous study noted altered white matter microstructure in contralesional S1/ M1 U-fiber cortico-cortical tracts, which was also associated with NCV.\textsuperscript{30} Thus, reduced M1 cortical thickness in CTS-paresthesia subgroup may be a direct consequence of more profound peripheral nerve dysfunction and concomitant paresthesia perception in these subjects, leading to disrupted hand area S1/M1 connectivity and information transfer along fiber tracts connecting these 2 regions.

In addition to CTS, purported cortical thinning has been reported for other chronic pain populations, including temporomandibular disorder\textsuperscript{33} and fibromyalgia.\textsuperscript{25} Moreover, cortical thinning has been reported for severe peripheral nerve injury\textsuperscript{23} and diabetic neuropathy,\textsuperscript{19} where thinning was demonstrated specifically in the primary somatosensory cortex. Thus, peripheral nerve damage, secondary to trauma and/or associated with neuropathic pain, seems to be closely linked with S1 cortical thinning and/or gray matter volume reduction. Carpal tunnel syndrome–induced paresthesia is believed to result specifically from A-beta fiber damage and represents a more paroxysmal, intermittent symptom compared with pain.\textsuperscript{21} In addition, numbness is more closely linked with paresthesia than pain symptoms in CTS.\textsuperscript{56} Paroxysmal paresthesia and numbness likely result from partial deafferentation and reduced median nerve velocities, leading to S1/M1 cortical thinning when paresthesia predominates over pain in patients with CTS. In our data, S1/M1 thinning may have resulted from differences in median NCVs between groups (and not symptom dominance per se). Thus, we repeated our analyses, controlling for relative median NCV, and demonstrated that several previously identified regions (eg, ipsilateral S1/M1) did indeed still demonstrate significantly reduced cortical thickness (Supplementary Figure 2, available online as supplemental digital content at http://links.lww.com/PAIN/A219).

In contrast, CTS-pain subjects not only demonstrated greater S1/M1 cortical thickness than CTS-paresthesia subjects but also showed a positive association between cortical thickness in the hand representation area and self-rated pain (but not paresthesia) severity. Thus, greater pain severity was associated with greater cortical thickness in these regions. Increased gray matter volume or cortical thickness has been reported in other chronic pain disorders.\textsuperscript{20} Specifically for S1/M1 regions, patients with low-back pain exhibit increased S1 (low back representation) cortical thickness,\textsuperscript{54} whereas patients with trigeminal neuropathic pain\textsuperscript{8} and migraine\textsuperscript{7} also demonstrate increased cortical thickness in somatosensory cortices. In addition, greater thermal and pain sensitivity correlates with cortical thickness in somatosensory cortex.\textsuperscript{11} Thus, chronic ongoing pain in patients with CTS suffering with predominant pain symptomatology in the hand/wrist, secondary to A-delta fiber damage,\textsuperscript{55} also leads to experience-dependent cortical thickening in hand area S1 regions. Consequently, such A-delta fiber damage may heighten inflammatory response and central sensitization with upregulated afferent input to the somatosensory cortex,\textsuperscript{3} resulting in experience-dependent thickening of these and closely associated (eg, M1) brain regions.

The direct physiological linkage between peripheral nerve pathophysiology in CTS and purported structural brain neuroplasticity is not well understood. Median nerve compression results in ischemia, inflammation, and elevated tunnel pressure, thereby producing altered afferent input from affected digits and decreased nerve conduction along median nerve sensory fibers. Thus, S1 cortical thickness changes may result from partial deafferentation or desynchronization in S1 input. Cortical thinning and gray matter reduction may be mediated by neuronal or glial death,\textsuperscript{31} or loss of dendritic spine density.\textsuperscript{83} Ultimately, neuronal, synaptic, glial, and even vascular remodeling can influence macroscopic MRI-based markers of plasticity.\textsuperscript{57} Furthermore, as structural plasticity after chronic pain may be reversible,\textsuperscript{48} future longitudinal studies should evaluate whether effective treatment that ameliorates symptomatology and improves median NCVs can also normalize gray matter volume and/or cortical thickness.

Limitations of our study should also be noted. For instance, the number of subjects in CTS-paresthesia subgroup was significantly greater than in CTS-pain subgroup. To address this potential bias, we performed additional analyses using the same number of age-matched and sex-matched subjects in both groups (the reduced CTS-paresthesia subgroup was extracted from the main subgroup by highest BCTQ paresthesia scores, yielding otherwise matched demographics, Supplementary Table 1, available online as supplemental digital content at http://links.lww.com/PAIN/A219, and an otherwise identical analysis). We found very similar cortical thickness differences compared with the whole group

<table>
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<th>Correlations between cortical thickness and clinical measures.</th>
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<tr>
<td><strong>CTS-paresthesia subgroup</strong></td>
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<td><strong>Left precentral gyrus (contralesional M1)</strong></td>
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<td>Correlation coefficient R</td>
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<td><strong>Left postcentral gyrus (contralesional S1)</strong></td>
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BCTQ, Boston Carpal Tunnel Questionnaire; CTS, carpal tunnel syndrome; NCV, nerve conduction velocity. Bold values refer to significant P at level 0.05.

Table 3
analysis (Supplementary Table 2, available online as supplemental digital content at http://links.lww.com/PAIN/A219), suggesting that sample size differences did not contribute significantly to our neuroimaging results. Furthermore, we should note that the number of subjects required for cortical thickness analyses is dependent on cortical location, with fewer subjects required for several regions including those adjacent to the central sulcus, where our key findings were localized.

In conclusion, we found a double dissociation for pain-dominant vs paresthesia-dominant CTS subgroups. CTS-paresthesia subjects demonstrated worse median nerve function and reduced S1/M1 cortical thickness, with the latter associated with median nerve velocity and paresthesia severity, but not pain severity. Conversely, in CTS-pain subjects, S1/M1 cortical thickness was correlated with pain severity, but not median nerve velocity or paresthesia severity. Thus, dichotomous symptom-based CTS subgroups may be supported by distinct neuroplasticity in S1/M1. More refined subgrouping for CTS and other chronic neuropathic pain disorders based on objective measures of neuroplasticity may lead to improved, personalized therapy that may focus on central (S1/M1) and also peripheral (median nerve) targets. Future longitudinal studies should evaluate whether changes in cortical thickness precede or follow changes in symptom severity, specific to paresthesia and pain, to help determine such therapeutic targeting.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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Appendix A. Supplemental Digital Content
Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A219.

Supplemental media
A video abstract accompanying this article can be found online at available online as supplemental digital content at http://links.lww.com/PAIN/A220.

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References


