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# Somatosensory cortical plasticity in carpal tunnel syndrome—A cross-sectional fMRI evaluation

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**Carpal tunnel syndrome (CTS) is a common entrapment neuropathy of the median nerve characterized by paresthesias and pain in the first, second, and third digits. We hypothesize that aberrant afferent input in CTS will lead to cortical plasticity. Functional MRI (fMRI) and neurophysiological testing were performed on CTS patients and healthy adults. Median nerve innervated digit 2 (D2), and digit 3 (D3) and ulnar nerve innervated digit 5 (D5) were stimulated during fMRI. Surface-based and ROI-based analyses consistently demonstrated more extensive and stronger contralateral sensorimotor cortical representations of D2 and D3 for CTS patients as compared to healthy adults ($P < 0.05$). Differences were less profound for D5. Moreover, D3 fMRI activation in both the contralateral SI and motor cortex correlated positively with the D3 sensory conduction latency. Analysis of somatotopy suggested that contralateral SI representations for D2 and D3 were less separated for CTS patients (3.8 ± 1.0 mm) than for healthy adults (7.5 ± 1.2 mm). Furthermore, the D3/D2 separation distance correlated negatively with D2 sensory conduction latency—the greater the latency, the closer the D2/D3 cortical representations ($r = -0.79$, $P < 0.05$). Coupled with a greater extent of SI representation for these CTS affected digits, the closer cortical representations can be interpreted as a blurred somatotopic arrangement for CTS affected digits. These findings provide further evidence that CTS is not manifest in the periphery alone. Our results are consistent with Hebbian plasticity mechanisms, as our cohort of CTS patients had predominant paresthesias, which produce more temporally coherent afferent signaling from affected digits.**


*Keywords:* Somatotopy; Nerve entrapment; Neuropathy; Hebbian plasticity; Disinhibition

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. A recent cross-sectional study revealed a prevalence in the United States of 3.72% (Papanicolaou et al., 2001). CTS etiology is characterized by compression of the distal median nerve by an elevated pressure in the carpal tunnel. Ischemic injury to the median nerve induces a range of symptoms primarily in the first through fourth digit, including paresthesias, pain, and weakness. Paresthesias represent the most common symptom (Nora et al., 2005) and result from ectopic impulse activity generated by ischemic nerve damage (Ochoa and Torebjork, 1980; Mogyoros et al., 2000).

In CTS, median nerve injury leads to altered afferent processing throughout the somatosensory system (e.g., peripheral and central nervous systems), as measured in the spinal cord, brainstem, and primary sensorimotor cortex (SMC) by somatosensory evoked potentials (Tinazzi et al., 1998). CTS manifestations in the contralateral SMC have also been studied by magnetoencephalography (MEG). A case study report suggested that the primary sensory representation of ulnar nerve innervated digit 5 (D5) may shift laterally into median nerve innervated digit territory (Druschky et al., 2000). Another MEG study of CTS found that the digit 1 (D1) to D5 cortical representation distance depended on the patients' qualitative symptomatology—expansion when paresthesias prevailed and contraction when pain prevailed (Tecchio et al., 2002). Furthermore, this study found an amplified response for median nerve innervated digit 3 (D3) as compared to ulnar nerve innervated D5, and interpreted this result as cortical amplification of a reduced amount of specific tactile information from affected digits.

The digits occupy a significant portion of the somatotopic map in the primary somatosensory cortex and are represented in consecutive order along the post-central gyrus, with D1 most ventrolateral and D5 most dorsomedial (Penfield and Boldrey, 1937). Cortical plasticity in digit somatotopy has been investigated following experimentally induced decreased, increased, and aberrant afferent signaling. Decreased afferent input has been induced by digit amputation or median nerve section, producing invasion of deafferentated primary sensory cortical fields by adjacent fields from intact digits (Merzenich et al., 1983, 1984). Conversely, electro-

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physiology and fMRI studies have shown that increased afferentation by tactile stimuli enlarges the SI cortical receptive field (Jenkins et al., 1990; Hodzic et al., 2004). Electrophysiology studies of atypical afferent signaling have demonstrated that surgically fusing adjacent digits produces blurred cortical representations of the affected digits (Allard et al., 1991). A similar result is also obtained by training a monkey with temporally coherent multi-digit stimulation (Wang et al., 1995).

As CTS is characterized by dysesthesias, or unpleasant atypical sensations, and pain, we hypothesize that this aberrant afferent input will lead to cortical plasticity. While previous studies of CTS-induced cortical plasticity have utilized MEG, CTS has never been studied with fMRI. This imaging modality has improved spatial resolution, whole brain coverage, and can provide important complementary information. For example, the extent of cortical field representations for individual digits cannot be detected by somatosensory evoked field amplitudes or equivalent current dipole moments. fMRI has been used to non-invasively map digit somatotopy (Gelnar et al., 1998; Kurth et al., 1998; McGlone et al., 2002), and we have adopted this modality to study central reorganization associated with CTS.

## Methods

This cross-sectional study was completed in conjunction with a pilot clinical trial of acupuncture for the treatment of CTS, though the data used in this study were taken before any treatment had occurred. All participants in the study provided written informed consent in accordance with the Human Research Committee of the Massachusetts General Hospital.

### *Subject recruitment and evaluation*

A total of 25 subjects were enrolled in this study; 13 adults affected by CTS, and 12 healthy adults. Clinical evaluation was completed for both groups by an experienced physician [JA] at the Spaulding Rehabilitation Hospital, and included medical history, nerve conduction studies (Cadwell Sierra EMG/NCS Device, Kennewick, WA), grip strength (BTE Work Simulator, Hanover, MD), sensory threshold testing using Semmes Weinstein monofilaments, and testing for Phalen's and Tinel's sign. Nerve conduction studies (NCS) using the method described by Ma and Liveson (1983) were performed with stimulation at the 2nd wrist crease on both the median and ulnar nerves of the most symptomatic hand (based on subject history). Both groups also completed the Boston Carpal Tunnel Syndrome Questionnaire (Levine et al., 1993). Subjects were screened and excluded for psychiatric and neurological disorders, head trauma with loss of consciousness, or other serious cardiovascular, respiratory or renal illness. CTS patients were included if they had experienced pain and/or paresthesias for greater than 3 months in the median nerve distribution of the affected hand—D1, D2, D3, and the radial aspect of D4. Furthermore, NCS findings needed to be consistent with mild to moderate CTS. Mild CTS was defined by delayed distal latency of median sensory nerve conduction across the wrist (>3.7 ms and/or >0.5 ms compared to ulnar sensory nerve conduction) with normal motor nerve conduction (Stevens, 1997; You et al., 1999). Moderate CTS was defined by mild CTS and with delayed distal latency of median motor nerve conduction across the wrist (>4.2 ms), but with normal motor amplitudes. Patients with severe CTS, defined by prolonged median sensory and motor latencies with either absent sensory nerve action potentials and/or reduced (50%) median motor amplitudes, were excluded. Patients were also excluded if they demonstrated any sign of generalized peripheral neuropathy or localized ulnar nerve entrapment.

fMRI data analysis was completed on a total of 10 CTS patients (6 female, 4 male; mean age: 51.1, range 31–60) and 9 age and gender-matched healthy adults (6 female, 3 male; mean age: 46.9, range 32–59). Of the 13 CTS patients initially studied, one was removed for excessive motion during fMRI scanning, and two were removed because they dropped out of the study immediately after the initial clinical and fMRI evaluation and did not complete adequate structural scans for surface reconstruction. Of the 12 healthy adults initially studied, one subject was removed from the fMRI analysis due to excessive motion artifact, one for lack of somatosensory response, and one for an acute finger injury (unrelated to the study). Five patients presented with CTS symptoms in both hands, while 5 presented with only unilateral symptomatology. For patients with bilateral CTS, testing was done on the more affected hand (self report). In all cases, the more affected hand was also the patient's dominant hand. The chronicity of symptoms (self reported) ranged from 4 months to 10 years, with 8 of 10 patients having symptoms for longer than 1 year. While patients reported both pain and paresthesias, a pain/paresthesia ratio was calculated from subjective responses to individual questions of the BCTSQ (pain: Q1–Q5, paresthesia: Q6–Q10).

### *fMRI image acquisition and stimulation protocol*

Functional scans were acquired using a 3.0 T Siemens Allegra MRI System equipped for echo planar imaging with quadrature head coil. The subject lay supine in the scanner with the head immobilized using a cushioned support.

Two sets of structural images were collected using a T1-weighted MPRAGE sequence (TR/TE = 2.73/3.19 ms, flip angle = 7°, FOV = 256 × 256 mm; slice thickness = 1.33 mm). Blood oxygenation level-dependent (BOLD) functional imaging was performed using a gradient echo T2*-weighted pulse sequence (TR/TE = 3000/30 ms, flip angle = 90°, FOV = 200 × 200 mm, 38 sagittal slices, slice thickness = 3.0 mm with 0.6 mm interslice gap, 90 image volumes per slice, matrix = 64 × 64). Image collection was preceded by 4 dummy scans to allow for equilibration of the MRI signal.

During an fMRI session, three digits were individually stimulated in a pseudo-randomized manner, for 3 scan runs each. Digits were chosen from the more affected hand of CTS patients (right hand: $n = 8$) and on the dominant hand of healthy adult volunteers (right hand: $n = 8$). The stimulated digits included D2, D3, and D5; thereby testing the somatosensory response for affected (*median n.*, D2, D3) and non-affected (*ulnar n.*, D5) digits in CTS patients. A single fMRI scan run consisted of a block design protocol with four 30-s blocks of stimulation (ON-block), alternating with five 30-s blocks of no stimulation (OFF-block). Pad electrodes were attached to the volar aspect (glabrous skin) of the middle and distal phalanx of D2, D3, and D5. The stimulus consisted of 100 Hz constant current electrostimulation (HANS LH202H, Neuroscience Research Center, Peking University, Beijing, China). In order to avoid habituation, the peak amplitude of the 100 Hz electrostimulation was modulated ±25% by a slow varying sinusoidal envelope (0.2 Hz) throughout each 30 s ON-block. The current strength of stimulation during each scan was