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Complex Regional Pain Syndrome Is Associated With Structural Abnormalities in Pain-Related Regions of the Human Brain

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Abstract: Complex regional pain syndrome (CRPS) is a chronic condition that involves significant hyperalgesia of the affected limb, typically accompanied by localized autonomic abnormalities and frequently by motor dysfunction. Although central brain systems are thought to play a role in the development and maintenance of CRPS, these systems have not been well characterized. In this study, we used structural magnetic resonance imaging to characterize differences in gray matter volume between patients with right upper extremity CRPS and matched controls. Analyses were carried out using a whole brain voxel-based morphometry approach. The CRPS group showed decreased gray matter volume in several pain-affect regions, including the dorsal insula, left orbitofrontal cortex, and several aspects of the cingulate cortex. Greater gray matter volume in CRPS patients was seen in the bilateral dorsal putamen and right hypothalamus. Correlation analyses with self-reported pain were then performed on the CRPS group. Pain duration was associated with decreased gray matter in the left dorsolateral prefrontal cortex. Pain intensity was positively correlated with volume in the left posterior hippocampus and left amygdala, and negatively correlated with the bilateral dorsolateral prefrontal cortex. Our findings demonstrate that CRPS is associated with abnormal brain system morphology, particularly pain-related sensory, affect, motor, and autonomic systems.

***Perspective:** This paper presents structural changes in the brains of patients with CRPS, helping us differentiate CRPS from other chronic pain syndromes and furthering our understanding of this challenging disease.*

***Key words:** Voxel-based morphometry, complex regional pain syndrome, neuroimaging, chronic pain.*

Complex regional pain syndrome (CRPS) is a neurologic illness characterized by spontaneous pain that is out of proportion to the inciting event and that extends beyond the sensory distribution of any single nerve. Swelling (edema), temperature changes, and excess sweating are commonly observed, distinguishing CRPS from other neuropathic pain disorders. Motor dysfunction is observed in 80% of patients.[4,13] The majority of patients are female and with upper extremity pain.[4]

CRPS may involve abnormalities in the central nervous system. Magntoencephalography[14] and somatosensory evoked potentials[27] have shown reorganization of the contralateral primary somatosensory cortex. Functional magnetic resonance imaging (MRI) has identified widespread somatotopic alterations during mechanical stimulation[18,19] in several areas of the brain, including the primary motor and sensory cortices, bilateral secondary sensory cortex, cingulate cortex, and parietal association cortex. Functional MRI of a finger tapping task of the affected limb has also demonstrated reorganization of the motor circuits and increased

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activation in the bilateral primary motor cortices and the contralateral supplementary motor cortex.[17]

In this study, we characterized gray matter abnormalities in CRPS patients using structural MRI. A previous structural MRI study of CRPS patients identified less gray matter in a single, large cluster encompassing the right insula, ventromedial prefrontal cortex, and nucleus accumbens.[11] The previous study, however, used a heterogeneous population. We therefore recruited only females, all of whom were right-handed and had right upper extremity CRPS. We hypothesized that these patients would demonstrate gray matter volume abnormalities in areas of the brain commonly seen in chronic pain patients, including the somatosensory cortex, anterior cingulate cortex, and insula.[30,37] We also hypothesized that we would observe gray matter volume abnormalities in the motor system of these patients, because previous nonstructural imaging studies and clinical examination criteria have suggested that these abnormalities would help differentiate CRPS from other pain syndromes.

Methods

Subjects

After institutional review board approval was received, 15 right-handed women with right upper extremity CRPS were recruited from the Stanford University Pain Clinic and surrounding community (see Supplementary Table 1 for demographic information). Fifteen aged-matched, right-handed female controls were also recruited via community outreach and advertisements. Written consent was obtained from all study participants. The CRPS group had an age range from 20 to 68, with a mean age of 44.0. Controls were matched to within 2 years, with an age range of 20 to 68, and a mean age of 44.1. All individuals were examined and had their CRPS diagnosis confirmed by a board-certified pain specialist at Stanford using the standard diagnostic criteria of the International Association for the Study of Pain. All patients also met the clinical criteria as outlined by the Budapest Research Criteria.[13] Pain duration ranged from 2 to 206 months. Subjects were not asked to change their treatment regimen during their participation in the study. The inclusionary criteria for the CRPS group were as follows: 1) at least 18 years of age and 2) a diagnosis of CRPS with an examination by a Stanford pain specialist. The exclusionary criteria were as follows: 1) pregnancy, 2) claustrophobia, 3) MRI incompatibility, and 4) psychiatric disorders that would interfere with the participant's ability to complete study tasks.

Procedures

After signing informed consent, disease severity was assessed using the McGill Pain Questionnaire.[23] The average McGill questionnaire score for patients was 24.2, with the average visual analog scale (VAS) score reported for 14/15 patients at 7.25. The average McGill score for 11/15 controls was 6 and average VAS was .7. Because of the severity of their pain, CRPS patients were not asked to stop their medications, which are listed in Supplementary Table 1. Only 2 of the controls were taking any medication (birth control and antihypertensive medication). Following the pain questionnaire, participants completed the structural imaging protocol. Because the protocol involved only structural imaging, participants were instructed simply to keep their heads still for the duration of the scanning, which totaled approximately 60 minutes.

MR Data Acquisition and Processing

High-resolution T1-weighted anatomic images were acquired using a 3D IR-FSPGR sequence, 28 slices, and 4-mm slice thickness with 1-mm skip; voxel size was $1.5 \times 1.5 \times 1.5$ mm. Scans were conducted at Stanford University using a 3.0 Tesla MRI system (General Electric Healthcare Systems, Milwaukee, WI) and a transmit-receive, end-cap, single-channel head coil (Pathway Medical, Seattle, WA). All image analysis and processing was performed using SPM8 (Wellcome Trust Centre, University College London, London, United Kingdom).

Anatomic images from all subjects were first segmented into gray matter, white matter, and cerebrospinal fluid images. Next, the DARTEL toolbox was used to normalize the anatomic images into a common stereotactic space. DARTEL was chosen because it has been shown to provide improved image normalization relative to many other common algorithms.[15] Finally, each gray matter image was spatially smoothed with an 8-mm Gaussian kernel.

Statistical Analysis

Whole brain statistics were computed using an independent Student t-test, with healthy controls in one group and CRPS patients in the other group. Participant age and total gray matter volume were regressed out, to remove effects of noninterest. A gray matter mask was applied to eliminate voxels not containing gray matter, thus reducing the number of statistical tests being conducted. To control for the incidence of false positives, 2 corrections for multiple comparisons were applied. First, a false discovery rate-controlled, voxel-level height threshold was calculated, yielding a corrected P value of .0005 (t = 3.71). Second, a cluster-level extent-threshold of 30 contiguous voxels was applied, using a priori information regarding our smallest structure of interest. The cluster threshold of 30 contiguous voxels yields a volume of 45 mm^3 and was based on the approximate size of the caudate nucleus as well as of the nucleus accumbens region, which is commonly reported in imaging studies and was the seed region used in the Geha paper.[11]

Secondary analyses were performed on the patient group only, to determine if there was a relationship between gray matter volume and disease severity. Using a 1-sample t-test, gray matter volume values were tested for correlations with disease duration (n = 15) and pain severity (n = 14). The P value was set to .001 for these analyses to maintain a t-value threshold of 3.71 (comparable to the main analysis threshold). The 30 consecutive voxel-extent threshold was retained.