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Brain Alterations and Neurocognitive Dysfunction in Patients With Complex Regional Pain Syndrome

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Abstract: Few studies have examined the involvement of specific subregions of the prefrontal cortex in complex regional pain syndrome (CRPS). We analyzed cortical thickness to identify morphologic differences in local brain structures between patients with CRPS and healthy control subjects (HCs). Furthermore, we evaluated the correlation between cortical thickness and neurocognitive function. Cortical thickness was measured in 25 patients with CRPS and 25 HCs using the FreeSurfer method. Pain severity and psychiatric symptoms were assessed using the Short Form McGill Pain Questionnaire and the Beck Depression and Anxiety Inventories, respectively. Neurocognitive function was assessed via the Wisconsin Card Sorting Test and the stop-signal task. The right dorsolateral prefrontal cortex and left ventromedial prefrontal cortex were significantly thinner in CRPS patients than in HCs. CRPS patients made more perseveration errors on the Wisconsin Card Sorting Test and had longer stop-signal task reaction times than HCs. Although the Beck Depression Inventory and the Beck Anxiety Inventory differ significantly between the groups, they were not correlated with cortical thickness. Our study suggests that the pathophysiology of CRPS may be related to reduced cortical thickness in the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex. The structural alterations in dorsolateral prefrontal cortex may explain executive dysfunction and disinhibited pain perception in CRPS.

***Perspective:** The present study reports decreased cortical thickness in the prefrontal cortex and neurocognitive dysfunctions in patients with CRPS. These findings may contribute to the understanding of pain-related impairments in cognitive function and could help explain the symptoms or progression of CRPS.*

***Key words:** Complex regional pain syndrome, cortical thickness, neurocognitive function, prefrontal cortex.*

Complex regional pain syndrome (CRPS) is a rare chronic pain disorder with a lifetime prevalence of approximately 26 per 100,000 person years.[10,14] Characteristically, the pain of CRPS is disproportionate in intensity to the initial triggering event. Furthermore, CRPS patients experience a spectrum of painful sensations such as mechanical, cold, and heat allodynia or hyperalgesia.[36] Unlike in other chronic pain disorders, most patients with CRPS have an abnormal sudomotor activity, edema, and trophic skin changes.[15] These distinct sympathetic, sensory, and somatomotor abnormalities indicate that CRPS is a systemic disease involving the peripheral and central nervous systems.[36]

Though differences in brain morphology between chronic pain patients and healthy controls have been examined, no consistent patterns have been identified.[2,5,11] Decreased density of prefrontal cortex (PFC) and thalamic gray matter (GM), which are involved

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with pain, have been reported in patients with chronic back pain (CBP).[2] Fibromyalgia patients showed significantly less GM density in the cingulate cortex, insula, medial PFC, and parahippocampal gyri.[37] A review of structural changes in phantom pain, irritable bowel syndrome, fibromyalgia, and headaches suggests that cortical changes in these disorders overlap, which include areas involving the cingulate cortex, orbitofrontal cortex, insula, and dorsal pons.[45] Several studies examining CRPS patients have provided evidence of structural brain changes. Geha et al[22] reported GM atrophy in the ventromedial prefrontal cortex (VMPFC), anterior insula, and nucleus accumbens, as well as abnormal connectivity of these regions. Similarly, a recent study found decreased GM volume in the dorsal insula, orbitofrontal cortex, and cingulate cortex in CRPS patients.[7] However, another study using voxel-based morphometry (VBM) found increased GM density in the dorsomedial PFC and primary motor cortex in patients with CRPS type I.[51] These studies mainly revealed abnormalities in the prefrontal area, but with inconsistent results.

Chronic pain appears to impair executive function and response inhibition.[48] Patients with fibromyalgia showed lower activation in the inhibition and attention networks, suggesting that inhibition and pain perception may use overlapping networks.[23] Research in chronic noncancer pain reported a significant correlation between pain rating and Stroop interference performance.[55] Poor performance on working memory tests was shown in patients with chronic visceral muscular pain.[49] Considering the severity of CRPS, we hypothesize that these patients would suffer from similar disabilities.[1] However, few studies have assessed neurocognitive dysfunction in CRPS. Apkarian et al[1] demonstrated a poor performance on the Iowa gambling test in CRPS patients. More recently, significant neuropsychological deficits were observed in 65% of CRPS patients.[39] However, little research has been performed on the relationship between structural changes in the brain and neurocognitive function.

Previous structural imaging studies in CRPS were performed using VBM analysis. However, VBM-based assessment of GM is affected not only by cortical thickness but also by cortical surface area and folding.[13] VBM analysis involves smoothing the cortical/subcortical patterns of brain GM segments to make normally distributed fields, and warping the images through a stretching and compressing algorithm to compare different subjects.[34] Thus, VBM's accuracy for measuring cortical morphology is low, and its results are sensitive to the level of smoothing.[60] Unlike VBM, cortical thickness reflects the size, density, and arrangement of cells by extracting the distance between the GM/white matter surface and the GM/cerebral spinal fluid interfaces.[44] Cortical thickness measures an absolute distance in millimeters between interfaces within the cortex rather than on the surface. Therefore, microscopic alterations in cortical thickness or GM atrophy may represent abnormal changes in dendrites and specific brain systems.[17,35] Measurement of cortical thickness is an alternative approach that provides a direct measure of GM thickness,[13] and combined with measures of neurocognitive dysfunction, it may provide a clearer understanding of how pain is processed in the brain.

In this study, we analyzed cortical thickness to identify potential structural cortical changes in CRPS patients, and evaluated executive function and response inhibition. Considering the severity and duration of pain in CRPS patients, we hypothesized that the thickness of their prefrontal cortices would be reduced and that these morphologic differences would be correlated with the severity of executive dysfunction.

Methods

Subjects

Twenty-five patients with CRPS (12 men, 13 women) who had no psychiatric treatment history before diagnosis with CRPS were recruited from the Pain Clinic of Seoul National University Hospital. All patients were evaluated by a board-certified anesthesiologist to confirm the diagnosis of either CRPS type I (n = 23) or CRPS type II (n = 2) based on the International Association for the Study of Pain criteria.[21] The right lower limbs were affected in 4 patients (16%), the left lower limbs in 2 (8%), and the left upper limbs in 6 (24%), and 13 patients (52%) had multiple lesions. Seven patients reported multiple lesions involving deficits with the right hand and an additional body location. The Structured Clinical Interview for DSM-IV Disorders[19] was used to identify neuropsychiatric comorbidities. Nineteen patients (76%) had comorbid Axis I psychiatric disorders, including major depressive disorder (n = 11), other mood disorders (n = 7), and anxiety disorder (n = 1). Patients were taking various forms of analgesic medication, including opioids (n = 13), nonsteroidal anti-inflammatory drugs (n = 12), anticonvulsants (n = 23), antidepressants (n = 20), antipsychotics (n = 10), and anxiolytics (n = 19). Patients were asked not to change their medications before neurocognitive tasks and magnetic resonance imaging (MRI) acquisition. We excluded subjects with a medical history of neurologic disease or substance abuse.

Twenty-five age- and sex-matched healthy controls (14 men, 11 women) were recruited through Internet advertisements. All healthy subjects had no history of hospitalization and were not taking medications for medical conditions. Basic demographic and neuropsychiatric characteristics of all subjects are provided in Table 1. We found no significant differences in demographic characteristics.

Pain severity was assessed using the Short Form McGill Pain Questionnaire.[46] The Beck Depression Inventory[9] and the Beck Anxiety Inventory,[8] each composed of 21 items (score range = 0–63), were used to evaluate the severity of depressive and anxiety symptoms, respectively. The study was approved by the institutional review board at Seoul National University Hospital, and written informed consent was obtained from all subjects after procedures were fully explained.