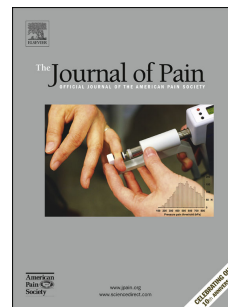


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Brain alterations and neurocognitive dysfunction in patients with complex regional pain syndrome

Running title: Brain structural alterations and cognition in CRPS

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Disclosures

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Abstract

Few studies have examined the involvement of specific sub-regions of the prefrontal cortex in complex regional pain syndrome (CRPS). We analyzed cortical thickness to identify morphological 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 (BDI and BAI), respectively. Neurocognitive function was assessed via the Wisconsin Card Sorting Test (WCST) and the stop-signal task (SST). The right dorsolateral prefrontal cortex (DLPFC) and left ventromedial prefrontal cortex (VMPFC) were significantly thinner in CRPS patients than in HCs. CRPS patients made more perseveration errors on the WCST and had longer SST reaction times compared with HCs. Although BDI and BAI 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 DLPFC and VMPFC. The structural alterations in DLPFC 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 complex regional pain syndrome. These findings may contribute to the understanding of pain-related impairments in cognitive function and could help explain the symptoms or progression of complex regional pain syndrome.

Key words

complex regional pain syndrome, cortical thickness, neurocognitive function, prefrontal cortex

ACCEPTED MANUSCRIPT

Introduction

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 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 system.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 prefrontal cortex (PFC) and thalamic gray matter (GM) density, which are involved 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 prefrontal cortex (MPFC) and parahippocampal gyri.³⁷ A review of structural changes in phantom pain, irritable bowel syndrome, fibromyalgia, and headaches suggest 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 non-cancer 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 Yet, 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 morphological 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%), the left upper limbs in 6 (24%) and 13 patients (52%) had multiple lesions. Seven patients reported multiple lesion involving deficits with the right hand and an additional body location. The Structured Clinical Interview for DSM-IV Disorders¹⁹ was used to identify neuropsychiatric comorbidities. Nineteen patients (76%) had comorbid Axis I psychiatric disorders, including major depressive disorder ($n = 11$), or 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 neurological 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 (SF-MPQ).⁴⁶ The Beck Depression Inventory (BDI)⁹ and Beck Anxiety Inventory (BAI)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.

MR Data Acquisition and Processing

MR images were acquired on a 3-T MRI scanner (GE Medical Systems, Milwaukee, WI, USA) fitted with a 12-channel phased-array head coil. A high-resolution anatomical whole-brain scan (180 axial slices; 256×256 matrix; 25.6-cm field of view; $1 \times 1 \times 1$ -mm voxels) was acquired using a T1-weighted inversion recovery three-dimensional fast-spoiled gradient echo (IR-FSGPR) sequence (flip angle = 15° , TE = 3 ms, TR = 7.8 ms, TI = 450 ms).

To estimate cortical thickness, we used the FreeSurfer software (Version 5.3) (<http://surfer.nmr.mgh.harvard.edu>), an automated program for the analysis of brain structures.²⁰ In short, a 1-mm triangular grid was used to establish numerous vertices across

the cortical mantle, and the distance between vertices was used to calculate cortical thickness (the distance between the GM/white matter boundary and the pial surface).

Neurocognitive Tasks

To evaluate neurocognitive function, we used the Wisconsin Card Sorting Test (WCST) and the stop-signal task (SST).^{30,58} We implemented a computerized version of the WCST in which subjects were given four reference cards with differing colors, forms, and numbers and asked to respond to stimulus cards presented on a computer screen. After 10 consecutive correct selections, the rules changed; the task continued until 128 cards were selected. The number of perseverative errors in categorization, which is sensitive to frontal lobe dysfunction, was used for the analysis.

The SST was used to assess response inhibition. Subjects were instructed to press the same direction button but suppress their response if an auditory signal (beep) appeared. This task is sensitive to inhibitory control; reaction time reflects the time taken to withhold a response.

Statistical Analysis

Statistical analysis of demographic and clinical data was performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL). Differences in age, education, and neurocognitive tests between each group were evaluated using Student's two-tailed *t*-test for independent samples, and those in gender and handedness were assessed using the chi-square test for independent samples. The significance of interaction was evaluated using a simple main effect test ($p < 0.05$). A GLM was used to evaluate effects of each variable of interest at each vertex on the cortical surface, with cortical thickness as the dependent variable. The overall difference in cortical thickness was compared using simple factorial ANOVA adjusted for

the presence of neuropsychiatric symptoms, opioids, and antidepressant medication. Differences in cortical thickness between patients and controls, and the effect of age were removed by using them as covariates. We applied a threshold of $p < 0.05$ (corrected for multiple comparisons using the false discovery rate (FDR) permutation with 5000 iterations) across the whole brain. Pearson's correlation coefficients were calculated to evaluate the relationship of mean cortical thickness at each region of interest with demographic characteristics, severity of symptoms, and neurocognitive function.

Results

First, we compared neurocognitive function between CRPS patients and controls. Patients with CRPS made significantly more perseveration errors on the WCST (16.7 vs. 9.1, $p = 0.013$) and had significantly longer stop-signal response times (SSRT) (193.6 ms vs. 150.4 ms, $p = 0.016$) compared with healthy controls (Table 1). Also, as expected, baseline depressive and anxiety symptoms, as evaluated by the BDI and BAI, were significantly higher in patients with CRPS.

The overall cortical thickness of the whole brain in CRPS patients was 1.92 ± 0.19 mm, compared with 2.00 ± 0.20 in the control group ($p = 0.120$). No effect modification on the overall cortical thickness was seen from the presence of neuropsychiatric symptoms ($F = 0.007$, $p = 0.935$), opioids ($F = 0.016$, $p = 0.900$) and antidepressant medications ($F = 1.066$, $p = 0.308$). As shown in Figure 1, the right dorsolateral prefrontal cortex (DLPFC) (peak coordinate: 26.2, 72.7, -3.9; $p = 0.026$) and left VMPFC (peak coordinate: -6.2, 54.9, -33.9; $p = 0.021$) were significantly thinner in patients with CRPS compared with healthy controls.

Correlations between cortical thickness and demographic and neurocognitive variables

were also examined (Figure 2). The thickness of the right DLPFC was negatively correlated with perseveration errors on the WCST (Pearson's $r = -0.525$, $p = 0.007$) in healthy controls, and positively correlated with reaction times on the SST in CRPS patients (Pearson's $r = 0.484$, $p = 0.014$). Cortical thickness was not correlated with duration of treatment, age, pain severity, BDI, or BAI.

Discussion

To our knowledge, this study is the first to compare cortical thickness in CRPS patients with that of healthy controls. Based on previous investigations showing that the PFC has an important role in the central modulation of pain,^{23,57} we expected that the PFC morphology in CRPS patients would differ significantly from that of controls. After correcting for age, we found a significant reduction in cortical thickness in the right DLPFC and left VMPFC in CRPS patients. Neurocognitive tests identified significant differences in cognitive function between CRPS patients and controls, as well as a negative correlation between right DLPFC thickness and perseverative errors on the WCST in controls.

The DLPFC is responsible for executive function and its reciprocal connections enable it to modulate several brain regions associated with motor control, error monitoring, and higher-order sensory processing.^{25,61} Investigations of chronic pain disorders have suggested that the DLPFC is associated with top-down inhibition of the nociceptive transmission system.⁴² Application of painful stimuli to the skin by capsaicin resulted in activation of the medial thalamic pathway to the frontal lobe, including the DLPFC.⁴¹ Similarly, impairment of this pathway caused sustained pain and was hypothesized to be involved in the pathophysiology of chronic pain.⁴⁷ Structural MRI studies of CBP have reported reduced

density in the DLPFC,² with similar observations having been made in fibromyalgia patients.⁴³ Although the mechanism underlying this atrophy remains to be elucidated, these results imply that CRPS is accompanied by cerebral atrophy and that morphological changes in the DLPFC may contribute to the pathophysiology of this disorder. Specifically, we observed decreased thickness in the right DLPFC. Studies concerned with laterality of pain processing have consistently reported that the right hemisphere is more involved.⁵⁰ Repetitive transcranial magnetic stimulation of the right, but not the left, DLPFC in healthy subjects increased pain tolerance.²⁴ These results agree with our findings of both morphological differences in the right DLPFC and functional impairments in pain processing among CRPS patients.

In this study, the left VMPFC appeared thinner in CRPS patients than in healthy controls. Neuroimaging studies have shown that the VMPFC is involved in the integration of emotion, memory, and environmental stimuli, and damage to this area can lead to impairments in decision-making and social behavior.^{18,56,61} Existing evidence suggests that the VMPFC is also involved in pain networks. The functional MRI study of patients with a CBP indicated that the MPFC was significantly associated with severity of pain compared to other regions.⁶ Similar results have been reported in other CBP^{28,29} studies and chronic pain disorders including fibromyalgia⁴⁵ and hip osteoarthritis.⁵³ Recently, CRPS studies using VBM have also identified decreased GM volume in several pain affect regions including the left VMPFC.⁷ A longitudinal study of CBP suggested that brain activity related to back pain shifts in location from regions involved in acute pain to engage emotion related circuits encompassing the MPFC as the condition persists.²⁸ The role of the VMPFC in the pain network remains unclear. However, previous studies suggest that this area is involved in pain anticipation, which plays an important role in modulating acute and chronic pain^{32,52} and could be a specific transitional marker from acute to chronic pain.²⁸ Notably, these

findings are also similar to functional changes found by functional MRI in CRPS patients.⁵⁹ Thus, the morphological differences in VMPFC between CRPS patients and controls that we observed suggest a shared mechanism with other pain disorders.

Patients with CRPS made significantly more perseverative errors on the WCST and had longer SSRT. These findings are consistent with the notion that chronic pain may affect the PFC, which is in line with evidence showing that chronic pain patients perform poorly on neurocognitive tests.^{1,23,48,57} WCST is the most widely used test to evaluate executive function and is sensitive to frontal lobe dysfunction.^{23,48,57} The greater number of perseverative errors indicates that CRPS patients suffer from cognitive inflexibility, using limited solutions in problem solving tasks.^{40,48} Response inhibition is also one of the core executive functions, and is believed to be associated with the PFC.^{4,26,58} Increased SSRT is considered to reflect dysfunction in cognitive control, implying a need for more time to inhibit off-target responses.⁵⁸ Therefore, our neurocognitive results indicated that CRPS affects the frontal lobe.

The relationship between cortical thickness and neuropsychiatric function was assessed by correlation analysis, which revealed a significant negative correlation between perseverative errors and right DLPFC thickness, only in healthy controls. No significant relationship between cortical thickness and psychiatric symptoms were identified. Although the results are not always consistent, previous studies have proposed that patients with right DLPFC damage are more impaired on the WCST than are patients with other lesions.⁴⁰ The present results are consistent with prior imaging studies demonstrating a correlation between the amount of GM and cognitive ability.²⁷ Although no significant negative correlation was found in CRPS patients, the lower cortical thickness of CRPS patients may reflect a neuroanatomical alteration that could be associated with functional impairments. Interestingly, we found that cortical thickness in the right DLPFC was positively correlated

with SSRT in CRPS patients. Previous studies have shown that response inhibition is impaired in patients with lesions to the right, but not the left, hemisphere; moreover, the severity of right inferior frontal gyrus lesions was negatively correlated with SSRT.^{4,26,58} These results are not easily reconciled with our observation of longer SSRT in CRPS patients compared with controls. One interpretation is that a relatively decreased cortical thickness in CRPS patients could explain their delayed response time, but the correlation analysis suggests that other factors or interactions modulate or compensate response inhibition. As several functional MRI studies have proposed various areas of brain activation during successful response inhibition including the DLPFC, and VMPFC.^{3,12,33,62} Furthermore, response inhibition is the most extreme and straightforward form of inhibitory control and is generally required in all types of cognitive control, such as stimulus recognition, attention, and error detection.⁶² Difficulties in performing neurocognitive tests are expected due to pain itself, it is possible that poorer motor skills or a patient's disability may have contributed to the insignificant findings.

There are several limitations of this study. First, this study was cross-sectional, preventing inferences regarding whether the identified structural brain changes are the cause or the result of CRPS. That is, these morphological changes may not result from a direct effect of the pain, but from an indirect effect of functional impairments by disabilities, and/or lifestyle changes. A variety of psychiatric symptoms were reported, even though all CRPS subjects had no previous history of psychiatric treatments at the time of study. Therefore, it is possible that psychiatric symptoms and other impairments are likely to have affected the structural changes in the subjects. Long term, repetitive structured research will be required to elucidate the potential causal relationship between the neural structural changes and the development of CRPS. Second, brain imaging was not synchronized with neurocognitive tasks, though we attempted to acquire imaging data and neurocognitive

tasks in a very short interval. Additionally, we did not confirm the difference in motor functioning between the healthy controls and CRPS patients as mentioned in discussion. Medications may also influence brain activity and hence cortex thickness. A previous animal study reported that morphine reduced neuronal packing density and the number of neurons without affecting cortical thickness.⁵⁴ The neurotropic effect of antidepressants on limbic structures have been reported in human studies.¹⁶ In elderly patients with depression, antidepressants were associated with larger orbitofrontal regional volume as compared with medication-naive patients.³⁸ It must be acknowledged that most patients in this study were taking opioids, antidepressants, and/or anxiolytics, raising the possibility of a medication confounder. Finally, head motion significantly affects measures acquired using a T1-weighted anatomical brain scan.³¹ Motional effects should be considered when interpreting these results, and strategies to reduce artifacts are needed for future studies.

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Figure legends

Figure 1. Analysis of differences in cortical thickness between CRPS (n=25) and matched control subjects (n=25). All results are significant at $P < .05$, corrected for multiple comparisons.

Abbreviations: CRPS, chronic regional pain syndrome; DLPFC, dorsolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; R, right; L, left

Figure 2. Correlation between cortical thickness and neurocognitive tasks. Cortical thickness in right dorsolateral prefrontal cortex (R. DLPFC) was positively correlated with stop signal response time in patients with CRPS (A) and negatively correlated with perseveration errors in control group (B).

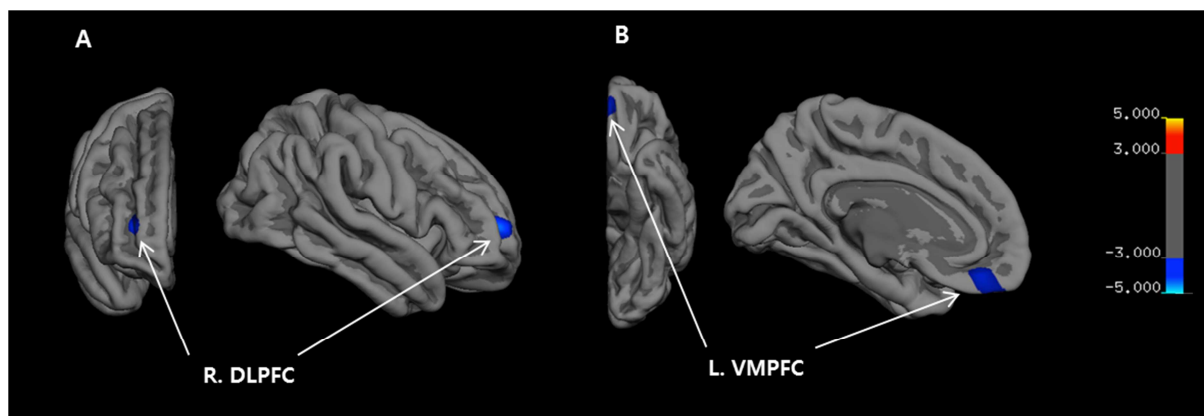
Abbreviations: CRPS, chronic regional pain syndrome; DLPFC, dorsolateral prefrontal cortex; R, right; SSRT, stop-signal response time; PE, perseveration error

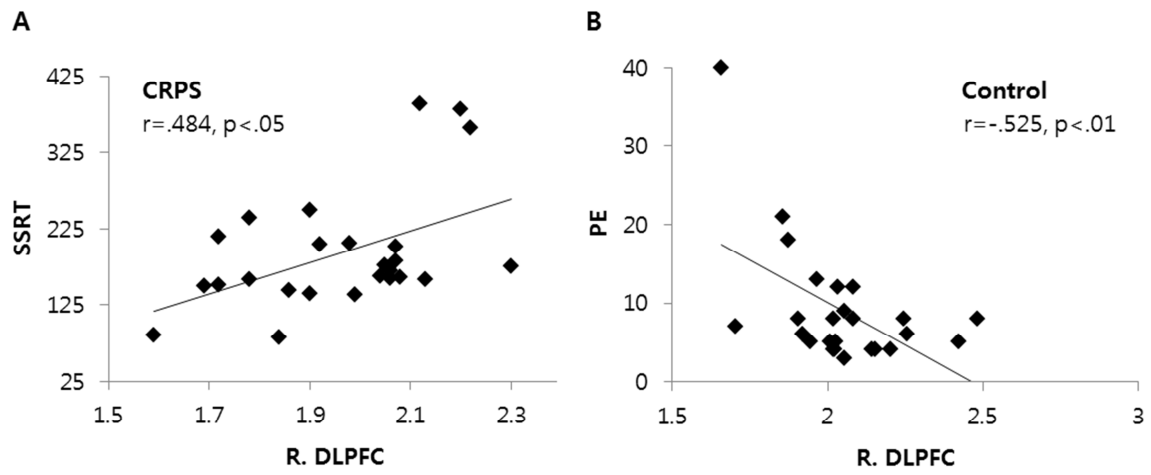
Demographics	CRPS(N=25)	HC(N=25)	χ^2 or T	df	p
Sex(M/F)	12/13	14/11	0.32	1	0.571
Age(Mean \pm SD)	36.1 \pm 11.4	31.7 \pm 6.7	1.66	48	0.119
Handedness(Right/Left)	23/2	22/3	0.22	1	0.637
Duration of illness (Mean \pm SD)	2.8 \pm 3.0	-	-	-	-
WCST(Mean \pm SD)					
Perseveration errors	16.7 \pm 12.3	9.1 \pm 7.8	2.61	40.8	0.013*
Categories	5.1 \pm 1.4	5.8 \pm 0.9	-1.94	40.5	0.059
SSRT	193.6 \pm 78.8	150.4 \pm 31.7	2.54	31.6	0.016*
BDI	28.0 \pm 13.7	3.0 \pm 3.3	8.45	25.3	<0.001*
BAI	29.1 \pm 16.1	2.4 \pm 3.6	7.72	24.9	<0.001**

Table 1. Demographic characteristics and Neuropsychological assessments of the subjects.

Abbreviations: WCST, Wisconsin Card Sorting Test; SSRT, stop-signal response time; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CRPS, complex regional pain syndrome; HC, healthy controls

*p < 0.05, **p < 0.01.





Highlights

- Significant cortical thinning in the prefrontal cortex was observed in CRPS patients.
- Patients with CRPS made significantly more perseverative errors on the WCST.
- Patients with CRPS showed significantly longer stop-signal response time.
- The alterations may explain executive dysfunction and disinhibited pain perception.