

Impaired Recognition of Social Emotion in Patients With Complex Regional Pain Syndrome

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Abstract: Multiple brain areas involved in nociceptive, autonomic, and social-emotional processing are disproportionately changed in patients with complex regional pain syndrome (CRPS). Little empirical evidence is available involving social cognitive functioning in patients with chronic pain conditions. We investigated the ability of patients with CRPS to recognize the mental/emotional states of other people. Forty-three patients with CRPS and 30 healthy controls performed the Reading Mind in the Eyes Test, which consists of photos in which human eyes express various emotional and mental states. Neuropsychological tests, including the Wisconsin Card Sorting Test, the stop-signal test, and the reaction time test, were administered to evaluate other cognitive functions. Patients with CRPS were significantly less accurate at recognizing emotional states in other persons, but not on other cognitive tests, compared with control subjects. We found a significant association between the deficit in social-emotion recognition and the affective dimension of pain, whereas this deficit was not related to the sensory dimension of pain. Our findings suggest a disrupted ability to recognize others' mental/emotional states in patients with CRPS.

Perspective: This article demonstrated a deficit in inferring mental/emotional states of others in patients with CRPS that was related to pain affect. Our study suggests that additional interventions directed toward reducing distressful affective pain may be helpful to restore social cognitive processing in patients with CRPS.

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Key words: Complex regional pain syndrome, chronic pain, emotion, cognitive function, social cognition, social perception.

Complex regional pain syndrome (CRPS) is a chronic neuropathic pain condition characterized by spontaneous pain, hyperalgesia, allodynia, and motor dysfunction that hampers quality of life and social functioning of patients.²⁷ There is evidence that functional reorganization in pain-related brain regions occurs in patients with CRPS.²³ Imaging studies have shown that multiple brain areas involved in nociceptive, autonomic,

and emotional processing are disproportionately changed in patients with this syndrome.^{10,21,22} It is interesting that the altered cortical areas in patients with CRPS encompass the ventromedial prefrontal cortex, insula, amygdala, and anterior cingulate cortex, which are engaged in emotional processing,^{10,26} understanding of others' affective mental states,³⁰ and empathy for pain of other persons.³¹ The abnormalities in these neural regions suggest a possible deterioration of social cognitive and emotional functioning in patients with CRPS.^{9,18} However, few studies have considered social cognitive and emotional functioning in CRPS. A single study observed specific cognitive disability when performing an emotionally laden task that involves loss and gain in patients with CRPS.¹ No study investigates social cognitive function in chronic pain, including CRPS.

In the present study, we explored the ability of patients with CRPS to perceive another person's mental and

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emotional states. On the basis of the neurobiological evidence and a limitation in social functioning in patients with CRPS,²⁷ we hypothesized that the ability to recognize mental states from subtle emotional and social cues may be impaired in patients with CRPS. Additionally, we assessed other cognitive function that has been found to be deficient in chronic pain patients²⁵ to investigate whether the deficit is specific to social-emotional skill or generalized to other cognitive domains.

Methods

Subjects

Forty-three patients with CRPS were recruited from the outpatient clinic at the Seoul National University Hospital. The patients (26 men and 17 women) fulfilled the research criteria of the International Association of Study of Pain for CRPS I (n = 35) or CRPS II (n = 8). The mean age of the patients was 38.8 ± 11.9 years (range, 20–59 years), and the mean years of education was 12.4 ± 2.7 years. The mean duration of the disease was 46.5 ± 42.3 months. The upper limbs were affected in 14 patients, the lower limbs in 15, and both in 14 patients. Thirty-two patients (74%) had comorbid Axis I psychiatric disorders: major depressive disorder (n = 19), other mood disorders (n = 12), and anxiety disorders (n = 1). One patient did not use any drugs, but the others were taking various analgesic drugs including opioids (n = 20), nonsteroidal anti-inflammatory drugs (n = 10), anticonvulsants (n = 37), antidepressants (n = 36), antipsychotics (n = 13), and anxiolytics (n = 33). Exclusion criteria for patients included intellectual disabilities, neurologic disorders, history of head injuries, and substance abuse.

Thirty healthy control subjects (22 men, 8 women) with a mean age of 29.9 ± 7.8 years (range, 19–48 years) and a mean educational level of 15.0 ± 1.9 years were recruited from the community through internet advertisements. These participants had no history of hospitalization due to any kind of disease and were screened for psychiatric disorders using the Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition*, nonpatient version. Exclusion criteria for controls were intellectual disabilities, psychiatric illnesses, history of head injury, and neurologic disorders. This study was approved by the institutional review board of the Seoul National University Hospital, and written informed consent was obtained from all subjects before testing.

Measurements

Clinical Assessment

The Korean version of the short-form McGill Pain Questionnaire^{20,28} was employed to quantify patient pain. This questionnaire measures sensory (11 items) and affective (4 items) dimensions of pain, which are self-rated on a Likert-type scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). This scale also includes the single-item present pain intensity scale (0 = none, 1 = mild, 2 = discomfort, 3 = distressing, 4 = horrible,

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5 = excruciating) and the visual analog scale (0 = no pain; 10 = maximum imaginable pain) to evaluate pain intensity. The 21-item clinician-rated Hamilton Rating Scale for Depression (range, 0–66)¹³ and the 14-item clinician-rated Hamilton Rating Scale for Anxiety (range, 0–44)¹² were used to evaluate the levels of depressive and anxiety symptoms in patients, respectively. In addition, the self-reported Beck Depression Inventory⁶ and Beck Anxiety Inventory,⁵ which are composed of 21 items (range, 0–63), were administered to all subjects to measure depressive and anxiety symptoms.

Neurocognitive Tests

Trained researchers administered the following neuropsychological tests during a single session in a quiet room: 1) The Reading Mind in the Eyes test (RMET)⁴ was administered to evaluate the ability to infer another person's emotional and mental state from eye expressions. Thirty-seven photographs (including 1 practice item) depicting the eye region of human faces were presented. Participants were asked to select the word that best described the mental state from among 4 choice words. A preliminary study showed overall accuracy of 74.8% in 110 Korean undergraduate university students, which was comparable to that previously reported in a study by Baron-Cohen et al.⁴ The RMET items were classified as positive (8 items), neutral (16 items), or negative (12 items) to examine a role of emotional valence on the performance.¹⁴ 2) The reaction time (RTI) test from the Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition, Cambridge, United Kingdom) was used to measure psychomotor speed and attention. The subjects were asked to release a pad button (reaction time) or touch a stimulus after button release (movement time) in response to the onset of a stimulus in a single location (simple) or in 1 of 5 locations (5-choice) as quickly as possible. 3) The stop-signal test from the Cambridge Neuropsychological Test Automated Battery was employed to evaluate the ability to inhibit an ongoing motor response. The subjects were instructed to press the right or left button, depending on the direction of the arrow, and to suppress their response when an auditory signal (beep) occurred. The stop-signal reaction time, an estimate of the time taken to withhold a response, was measured. 4) The Wisconsin Card Sorting Test (WCST)¹⁶ was used to measure cognitive flexibility. Subjects were given 4 stimulus cards with symbols differing in color, form, and number and were asked to match 128 response cards to one of the stimulus cards according to color, form, or number. The criterion shifted after 10 consecutive correct selections. This procedure was repeated until 6 criteria were completed. The number of perseverative errors and the number of categories completed, which are sensitive to frontal lobe damage,³² were used for the analysis.

Statistical Methods

Analysis of covariance (ANCOVA) was performed, with RMET accuracy rate and the stop-signal test scores as dependent variables, the CRPS patient and control

groups as the independent variables, and age and years of education as the covariates. A multivariate ANCOVA with a subsequent ANCOVA for each variable was performed for the WCST and the RTI variables. Sample size was determined by power analysis with the power of .95, alpha of .05 (2-tailed), and effect size of approximately .8. To examine if the findings are confirmed in a demographically matched sample, 20 patients and 20 control subjects who were matched for sex, age, and education were randomly selected from the total sample. For the cognitive variables in this subsample, t-test or a multivariate analysis of variance with a subsequent analysis of variance was performed. A repeated measures ANCOVA was used to explore the differential effect of the emotional valence on the RMET performance. Significant interaction was evaluated with simple main-effect test ($P < .05$). Demographic data were compared using chi-square or independent t-tests. Eta-squared was calculated as an estimate of effect size. Pearson's correlation and multiple-parameter linear regression analyses were used to assess the relationships among clinical variables and the neuropsychological data.

Results

Demographic and Clinical Characteristics

Table 1 provides the basic demographic and clinical characteristics of the whole sample. We found no significant differences in gender ($\chi^2 = 1.30$, $P > .4$), but we found significant differences in age ($t = -3.87$, $df = 70$, $P < .005$) and years of education ($t = 4.59$, $df = 71$, $P < .001$) between the patient and control groups. Thus, age and years of education were controlled in all analyses comparing neuropsychological performance between the groups. Gender had no effect on cognitive function in each group and on clinical symptoms in patients. For the Beck Depression Inventory and Beck Anxiety Inventory, 4 patients and 3 control subjects did not complete questionnaires. In the rest of the sample, significant differences were found between the 2 groups

in the Beck Depression Inventory ($t = -10.53$, $df = 52$, $P < .001$) and Beck Anxiety Inventory ($t = -9.06$, $df = 43.5$, $P < .001$).

Neuropsychological Performance

The ANCOVA revealed that the patients with CRPS were significantly more inaccurate in recognizing another's emotional and mental states compared with healthy controls on the RMET task ($73.0 \pm 9.6\%$ vs $61.6 \pm 14.0\%$; $F_{1,69} = 4.22$, $P < .05$, $\eta_p^2 = .06$) (Fig 1). A repeated measures 2 (group) \times 3 (emotional valences) ANCOVA yielded significant main effect of group ($F_{1,69} = 6.94$, $P < .01$) and interaction for group \times emotional valence ($F_{1,69} = 5.65$, $P < .02$). Post hoc simple main effect analysis showed significant difference between the groups in the positive valence ($F_{1,69} = 9.82$, $P < .003$, $\eta_p^2 = .13$; $71.7 \pm 15.4\%$ for controls, $52.9 \pm 24.7\%$ for patients), but not in the negative ($F_{1,69} = .85$, $P > .3$, $\eta_p^2 = .01$; $67.5 \pm 13.9\%$ for controls, $57.0 \pm 19.9\%$ for patients) or neutral valence ($F_{1,69} = 1.81$, $P > .1$, $\eta_p^2 = .03$; $77.7 \pm 13.8\%$ for controls, $68.6 \pm 14.4\%$ for patients) conditions. No significant difference in the stop-signal reaction time on the stop-signal test task ($F_{1,69} = .50$, $P > .5$, $\eta_p^2 = .01$; 157.2 ± 63.8 ms for controls, 203.4 ± 90.8 ms for patients) was observed between the groups. The multivariate ANCOVA showed no significant overall group effect on the WCST ($F_{2,68} = 2.25$, $P > .1$, $\eta_p^2 = .06$; perseverative errors, 11.5 ± 7.5 for controls, 20.5 ± 17.6 for patients; categories completed, $5.7 \pm .9$ for controls, 4.9 ± 1.7 for patients) or the RTI ($F_{2,66} = 1.15$, $P > .3$; simple reaction time, 301.2 ± 45.4 for controls, 363.4 ± 100.7 for patients; 5-choice reaction time, 320.1 ± 53.1 for controls, 365.6 ± 66.6 for patients; simple movement time, 357.6 ± 96.2 for controls, 469.2 ± 178.8 for patients; 5-choice movement time, 349.1 ± 103.1 for controls, 403.9 ± 145.9 for patients). Although the overall effects were not significant in the WCST and RTI variables, a separate ANCOVA yielded a significant difference in the categories completed of the WCST ($F_{1,69} = 4.22$,

Table 1. Demographic and Clinical Characteristics in Subjects

| | HEALTHY CONTROLS (N = 30) | CRPS (N = 43) | STATISTICS χ^2 OR T | DF | P |
|-----------------------------|---------------------------|---------------|--------------------------|------|-------|
| Male/female | 22/8 | 26/17 | $\chi^2 = 1.30$ | 1 | .32 |
| Age (year) | 29.9 (7.8) | 38.8 (11.9) | $t = -3.87$ | 70 | <.005 |
| Education (year) | 15.0 (1.9) | 12.4 (2.7) | $t = 4.59$ | 71 | <.001 |
| Duration of illness (month) | | 46.5 (42.3) | | | |
| SF-MPQ | | | | | |
| Sensory pain | | 20.5 (9.1) | | | |
| Affective pain | | 6.2 (3.7) | | | |
| VAS | | 6.6 (2.5) | | | |
| PPI | | 3.4 (1.1) | | | |
| HAM-D | | 16.7 (9.8) | | | |
| HAM-A | | 16.6 (12.2) | | | |
| BDI* | 4.5 (4.9) | 28.4 (12.9) | $t = 4.59$ | 52 | <.001 |
| BAI* | 3.3 (3.5) | 26.5 (15.5) | $t = 4.59$ | 43.5 | <.001 |

Abbreviations: SF-MPQ, short form of McGill Pain Questionnaire; VAS, visual analog scale; PPI, present pain intensity; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

NOTE. Data are presented as mean (SD).

*Not included in the main analysis because of missing data.

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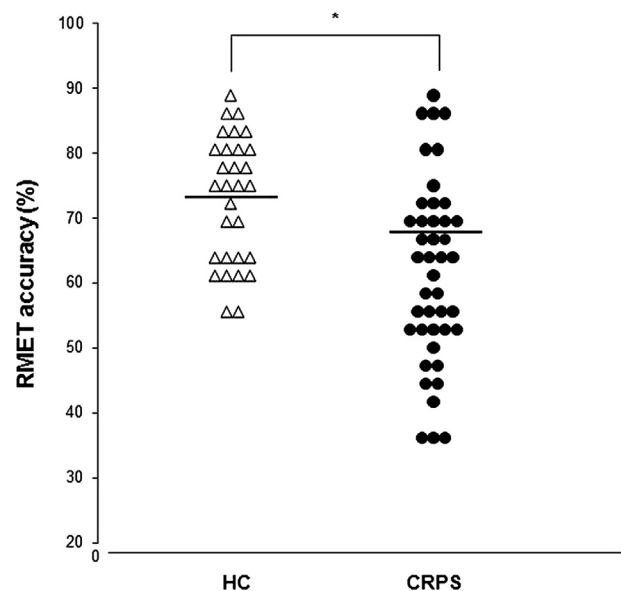


Figure 1. Performance of the RMET task in patients with CRPS and healthy controls. * $P < .05$.

$P < .05$, $\eta_p^2 = .06$). There was no significant difference between the groups in other variables of the WCST and RTI. The results on cognitive function were similar in the sex-, age-, education-matched subsample.

Relations Between the RMET and Clinical Characteristics

The Pearson's correlation analysis revealed a significant negative correlation between RMET accuracy and the score on the affective pain subscale of the short-form McGill Pain Questionnaire ($r = -.35$, $P < .03$) (Fig 2), indicating that higher affective pain was associated to poorer performance on the RMET. Multiple regression analysis showed that the affective dimension of pain score was a significant predictor of the RMET performance after adjusting for age, education, and duration of illness ($\beta = -.30$, $t = -2.04$, $P < .05$). The correlations between the RMET and Hamilton Rating Scale for Depression ($r = -.21$, $P > .2$) or Hamilton Rating Scale for Anxiety ($r = -.25$, $P > .1$) were relatively weak and not significant. No significant relationship was observed between the RMET score and the sensory pain dimension ($r = -.05$, $P > .7$), visual analog scale ($r = -.10$, $P > .5$), present pain intensity ($r = -.05$, $P > .7$), or illness duration ($r = -.01$, $P > .9$). The results of correlation analysis were similar in the sex-, age-, and education-matched subsample.

Discussion

The patients with CRPS exhibited moderate level of impairment in inferring another person's mental/emotional states. The impairment was more prevalent when decoding mental states that have the positive valence than negative or neutral emotion. There was no deficit in executive function such as set shifting, inhi-

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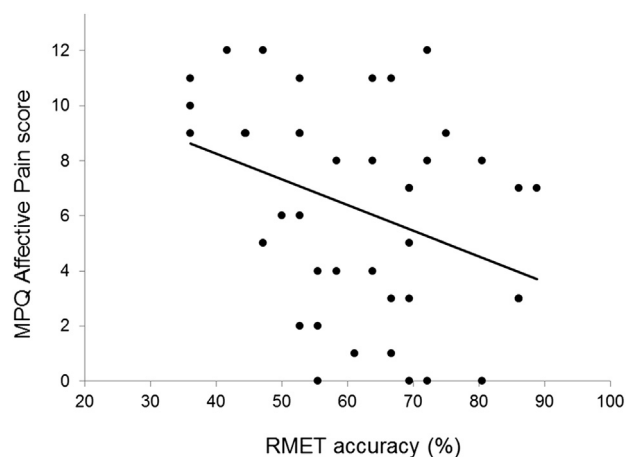


Figure 2. Correlation between affective pain score and RMET accuracy. Abbreviations: MPQ, McGill Pain Questionnaire; RMET, Reading Mind in the Eyes Test.

bitation, or psychomotor speed compared with healthy control subjects who had no psychiatric or medical illnesses. These findings suggest social cognitive deficits in patients with CRPS, particularly a disrupted ability to recognize mental/emotional states of others. Furthermore, our data showed that this deficit was associated with the affective dimension of pain. These findings suggest that unpleasant emotional feelings associated with pain are linked to disrupted recognition of mental states expressed by another person's eyes. The levels of depression and anxiety were not related to this deficit, indicating that these clinical symptoms may not be primary attributes of deficient social cognitive information processing in patients with CRPS.

It has been proposed that rewiring of pain-related neural networks in patients with chronic pain impacts cognitive functioning.¹⁵ Imaging studies have reported abnormal activation in brain regions that include the primary and secondary somatosensory cortices (S1, S2), anterior cingulate cortex, insula, ventromedial prefrontal cortex, amygdala, and superior temporal gyrus in patients with CRPS.^{10,11,19,21,22} Sensory networks appear to be related to processing the sensory discriminative components of pain, whereas other networks seem to be associated with affective aspects of pain.²⁴ Behavioral studies have shown that patients with CRPS have disturbed spatial tactile acuity and perceptual learning abilities on the affected side²⁵ as well as aberrant decision-making ability as assessed by a gambling task in which performance is affected by emotional reactions.¹ In the latter study, the authors suggested impaired emotionally relevant cognitive functioning in patients with CRPS. However, that study did not assess the emotional reactions of subjects, so whether these patients have emotional processing problems remains unresolved. The present findings offer new evidence on defective recognition of social emotion in CRPS. This finding is consistent with the notion that the CRPS is associated with abnormal activities in neural networks involving social cognitive and emotional

processing and corresponds to prior observations on impaired emotional decision making in patients with CRPS.

The RMET is widely used to measure the skill to infer another's mental and emotional states.⁴ Poor performance on this task has been identified in patients who suffer from impaired socio-emotional functioning, such as patients with autism or schizophrenia.^{3,17} Multiple brain regions are engaged when subjects infer mental states expressed in others' eyes, particularly the medial prefrontal cortex, superior temporal sulcus, frontal cortex, amygdala, and insula.^{2,29} Although whether these regions are related to aberrant mentalizing ability in patients with CRPS remains unclear because of a lack of experimental evidence, very recent studies have indicated abnormalities in regions such as the amygdala and superior temporal gyrus in this population.^{11,19} In a positron emission tomography study, patients with CRPS revealed altered opioidergic neurotransmission in the amygdala, parahippocampal gyri, and prefrontal cortex.¹⁹ A functional magnetic resonance imaging study found deactivation in several cortical areas, including the superior temporal gyrus, insula, and premotor cortex, when patients with CRPS imagined movement of their affected hand.¹¹ These findings suggest that chronic pain states in patients with CRPS are involved in the reorganization of neural networks associated with social and emotional perception. The present results provide evidence of defective socio-emotional perception in these patients at the behavioral level.

Our data show that the affective pain intensity was moderately associated with the deficit in perception of social emotion. In contrast, the sensory pain intensity was not related to the impairment. These results suggest that subjectively experienced unpleasant feelings related to chronic pain may interfere with the recognition of others' emotional states. Our findings agree with the prior observation that pain-related empathy was mediated by brain regions that represent affective dimension of pain, but not by those that represent the sensory dimension.³¹ Depression and anxiety, which are secondary pain affects, were weakly and insignificantly related to social cognitive deficit in our study. This is consistent with prior findings showing no significant relationship between depressive and anxiety symptoms and emotional decision-making performance.¹ Given that evidence of mind-reading ability in psychiatric patients with depression is mixed and that patients in our study had relatively mild depressive symptoms, it is plausible that that magnitude of the association between depression and social cognitive processing is weak in patients with CRPS.

The patients with CRPS did not exhibit a general deficit in executive functions such as set shifting and motor in-

hibition or psychomotor speed. These results are consistent with previous finding showing comparable performances in executive function tasks such as the WCST and the Stroop test between patients with CRPS and control subjects.¹ For the WCST, in our data, the patients identified fewer abstract categories than the controls, whereas they made comparable perseverative errors with the controls. These results may indicate a mild dysfunction in recruiting specific executive processing in patients with CRPS. Regarding psychomotor speed, little empirical evidence exists on this ability in patients with CRPS, although slow motor speed has been reported in chronic pain.^{25,33} Although our data showed slight decline of motor speed in patients with CRPS, additional studies are needed to confirm whether psychomotor speed is impaired in those with CRPS using various tasks.

Our study was limited in that the effects of medication and comorbid psychiatric disorders on the results could not be ruled out because many patients were taking medication and/or had coexistent psychiatric diagnosis at the time of the assessment. Additionally, although it is supposed that impairments in recognition of mental states are related to neural regions identified in previous studies, we did not investigate neural functioning associated with the deficit. Future imaging studies should apply paradigms involving social cognitive function to elucidate the neural networks associated with deficient processing in patients with CRPS. Lastly, this study did not include tasks that evaluate other components of social cognition to investigate whether the deficit is specific to recognition of social emotion or extended to other aspects of social cognitive function. It cannot be ruled out that a more generic skill such as face recognition is compromised in CRPS. Studies are needed to explore the abilities to encode, store, and process social information in CRPS.

In conclusion, social cognitive processing was moderately impaired in patients with CRPS. Given that an accurate perception of another's emotional state is crucial for social interaction and communication, this impairment may be one of the factors that hamper social functioning in patients with CRPS. Distressful emotional feelings related to ongoing pain appear to be an important contributor to the social cognitive processing deficit in patients with CRPS. Given evidence implicating affective pain reduction by hypnosis or meditation techniques,^{7,8} complementary and alternative medicine therapies directed toward reducing subjective distressful feelings on pain may be helpful to improve perceptual abilities to process social emotion in patients with this syndrome. Future studies need to clarify the behavioral and neural mechanisms underlying the disrupted perceptual ability to process social information.

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