


## NEUROPATHIC PAIN SECTION

# Impaired Performance in Mental Rotation of Hands and Feet and Its Association with Social Cognition in Patients with Complex Regional Pain Syndrome

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### Abstract

**Objectives.** . So far, dysfunction in mental rotation has been assessed in relation to the left- or right-sided CRPS. Here we examined mental rotation in patients with upper or lower limb CRPS. Considering the potential role of socio-emotional functioning on the perception of body image, we further investigated the association between performance on mental rotation and socio-emotional characteristics. **Methods.** . We examined the performance of 36 patients with upper or lower limb CRPS on the limb laterality recognition. Accuracy and response times for pictures of hands and feet at 4 rotation angles were evaluated. Socio-emotional functioning was measured by the Interpersonal Reactivity Scale and the Toronto Alexithymia Scale. **Results.** . Patients with upper limb pain showed longer RTs to recognize the laterality of hands than feet ( $P=0.002$ ), whereas patients with lower limb pain showed longer RTs for feet than hands ( $P=0.039$ ). Exploratory correlation analyses revealed that RTs for feet were negatively correlated with the levels of empathic ability to take another's perspective ( $P=0.006$ ) and positively correlated with the level of emotional difficulty in identifying feelings ( $P=0.006$ ). **Conclusions.** . This study is the first to report selectively impaired mental rotation of hands vs feet in patients with upper or lower limb CRPS. The findings suggest that impaired mental rotation derives from relative deficits in the representation of the affected limb. Correlations between impaired mental rotation and socio-emotional inability indicate that an altered body schema may be closely associated with impaired social cognitive aspects in CRPS patients.

**Key Words:** Alexithymia; Body Schema; Complex Regional Pain Syndrome; Empathy; Mental Rotation

### Introduction

Complex regional pain syndrome (CRPS) is a chronic pain disorder that accompanies broad sympathetic, sensory, and somatomotor abnormalities [1]. Recently, there has been growing interest in altered cognitive functions of patients with CRPS, and related studies have found that some patients can present with complex

neuropsychological changes, such as deficits in differentiating between the left and the right side of the body, comprehending arithmetic, writing, repeating others' speech, and/or imitating gestures [2, 3].

Impaired body schema is one of the well-characterized neuropsychological changes in CRPS. Body schema, the representation of one's own body in space in a real-time

dynamic manner, derives from multimodal sensory information and its interactions with the motor system [4]. Studies on body schema in CRPS evaluated patients' ability to mentally rotate the image of a body part, commonly measured by the limb laterality recognition task (LLRT) [5–11]. The LLRT entails viewing images of hands and feet at various rotation angles and judging whether those images belong to the left or right side of the body. The LLRT measures accuracy and response times (RTs) which are interpreted to reflect acuity and capacity to process the body schema, or proprioceptive representation [6]. Previous results show that patients with CRPS demonstrate selectively impaired performance in laterality recognition; they took longer to recognize the hand that corresponded to their affected limb compared with the unaffected limb [6, 8, 12]. One possible explanation is that persistent pain may affect the perception of painless sensations and result in the distortion of the body schema [8], which is consistent with evidence of an altered functional organization of the S1 in patients with CRPS [13, 14] (cf [15, 16]). Alternatively, the distortion of the body schema may be attributed to reduced sensory input to the somatosensory cortex [17], underuse of a limb [18, 19], or problems with updating body representations [20].

So far, most studies investigating mental rotation in CRPS recruited patients with upper limb pain and used LLRT with the image of hands only [6, 8, 10, 11], whereas few studies recruited patients with lower limb pain [5] and employed the LLRT with images of both hands and feet [7]. One study conducted a between-group comparison of the performance of the hand laterality judgement task in patients with upper vs lower limb pain and found no difference in RTs between the two groups [5]. The authors interpreted this result as implying nonspecific, general cognitive deficits rather than impaired body representation in CRPS. However, no studies have conducted within-group comparisons. Given that the body schema can be updated and this process might be different between the affected and unaffected limb [2, 20], there would be different patterns in mental rotation of hands vs feet as well as left vs right according to the region of pain.

Dysfunction in mental rotation has rarely been assessed in relation to social or emotional aspects in CRPS. A recent neuroimaging study demonstrated that patients with CRPS have reduced access for mental resources modulating arousal, emotional response, and subcortical sensorimotor integration during mental rotation [9]. A wealth of literature indicates that CRPS is associated with emotional dysfunction such as alexithymia (the inability to identify and label emotions) and difficulties in differentiating emotional arousal from bodily sensations [21]. Considering that alexithymics show increased neural activity in areas responsible for physical sensation [22], emotional functioning may play a potential role in modulating intrinsic physiological reactions to

painful stimuli. In addition, when investigating the relationships between neurocognitive changes and psychological symptoms in CRPS, the severity of self-reported neglect-like symptoms (i.e., detachment of the affected limb) was positively associated with depression, anxiety, somatization, and depersonalization (i.e., experiences of emotional detachment and disembodiment) [23]. Although it remains unclear whether these factors are outcomes or determinants of CRPS, the results suggest the possibility that emotional and psychological distress may play a part in disturbances in body perception in CRPS.

The present study examines performances on the LLRT by patients with CRPS affecting their upper or lower limb using pictures of hands and feet positioned at a variety of rotation angles. Participants were expected to be slower and/or less accurate when the type of stimuli (i.e., hands vs feet) corresponds to the specific location of pain. We also explored whether impairment in LLRT was associated with clinical and socio-emotional variables, such as duration of illness, alexithymic symptoms, and empathic abilities.

## Methods

### Participants

In total, 36 patients with CRPS (mean age  $\pm$  SD:  $42.9 \pm 9.8$  years) participated in the study. Patients were recruited from the pain clinic at Seoul National University Hospital and met the criteria of the International Association for the Study of Pain for CRPS I ( $n = 33$ ) or CRPS II ( $n = 3$ ) [24]. Patients were excluded from enrollment if they could not understand or perform the task due to severe pain. Patients were divided into two groups according to their initial CRPS diagnosis (i.e., upper vs lower limb CRPS). Pain was localized in the left upper limb in 3 patients, in the right upper limb in 7 patients, in the left lower limb in 12 patients, and in the right lower limb in 14 patients. The mean duration of illness was  $60.7 \pm 44.6$  months (range: 8–205 months). This study was approved by the Institutional Review Board of Seoul National University Hospital. All methods were performed in accordance with the relevant guidelines and regulations. All participants provided written, informed consent. The participants took part in our previous study, using a different methodology, to investigate hypotheses different from those involved in the present study [25]. We calculated that this study would have 85% power to detect an effect size of 0.6 (Cohen's  $d$ ) using F tests on the within-between interaction with an alpha level = 0.05, and a sample size of  $n = 9$  per group. Effect size was estimated from a previous study reporting the difference in reaction times for laterality judgment of hands vs feet stimulus in patients with impaired working body schema of lower limbs [26].



**Figure 1** Example of stimuli used in the limb laterality recognition task. Right hands (**A**) and right feet (**B**) in two different perspectives (top, bottom) and in four orientations ( $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ , and  $270^\circ$ ). Left stimuli were mirror images of right stimuli.

### Clinical Assessments

The short-form McGill Pain Questionnaire (SF-MPQ) was employed to evaluate pain severity [27]. This self-rated questionnaire measures 11 sensory and 4 affective dimensions of pain on a Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The Interpersonal Reactivity Index (IRI), a 28-item self-report scale, was administered to assess the multidimensional components of empathy, including empathic concerns, perspective taking, fantasy, and personal distress [28]. The Toronto Alexithymia Scale (TAS) was used to assess the abilities to identify and describe and process emotions, which is composed of *difficulty in identifying feelings*, *difficulty in describing feelings*, and *externally oriented thinking* [29].

### Limb Laterality Recognition Task

The LLRT was used to measure each participant's mental rotation ability. Images of left and right hands were presented in two views (i.e., palm-down and palm-up) with four rotation angles ( $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ ,  $270^\circ$ ). Images of the left and right foot were presented with two views (i.e., the dorsal and the sole) and four rotation angles ( $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ ,  $270^\circ$ ) (Figure 1). According to a viewpoint consistent with looking at one's own body in a sitting posture with both hands on a keyboard, the image of palm-down and the top of the foot are categorized as "from the top view," whereas palm-up and the sole of the foot are categorized as "from the bottom view." A total of 16 pictures of hands and 16 of feet were presented once within a block and repeated across three blocks. In total, there were 96 trials. Fixation cross-hairs were presented for 1 sec at the center of the screen between stimuli. Blocks were presented in a pseudorandom order.

Participants were asked to press the "z" key with their left index finger in response to a left image and the "m" key with their right index finger in response to a right image as quickly and accurately as possible. A practice trial of 10 pictures was administered to familiarize participants with the procedure. On average, it took about 5 minutes to complete the task. RTs and accuracy were the primary outcomes measured.

### Statistical Analysis

For quality control, the analysis included participants whose RTs for correct responses and accuracy were within  $\pm 2.5$  standard deviations from the mean. Six participants were excluded from the analysis on this basis. The mean RTs of excluded patients were not significantly different from patients included in analyses for both types of stimuli (hands:  $t = -0.89$ ,  $P = 0.38$ ; feet:  $t = -0.73$ ,  $P = 0.50$ ). An independent  $t$ -test was used to compare the ages and clinical characteristics of patients with upper limb vs lower limb pain, and the Chi-square test was used to compare gender ratios.

The common logarithm of RTs for the LLRT was taken for statistical analysis. As linear mixed model and log-transformed RTs yielded the same pattern of results and a comparable level of significance, descriptive statistics and figures were constructed based on RTs for consistency with previous research. To determine if the performances differed in response to stimuli corresponding to the affected (e.g., *hand* stimuli for patients with *upper* limb pain) versus unaffected limb, a linear mixed model was conducted. Independent variables included the stimulus type (hand, foot), side (left, right), perspective (top, bottom), rotation angle ( $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ ,  $270^\circ$ ), and their interactions with the region of pain (upper limb/lower limb pain patients). Participants were considered to contribute to the model as random effects. Residual-versus-fits plots and normality plots for log-transformed RTs did not reveal any obvious deviation from homoscedasticity or normality. Post hoc analyses for statistically significant main effects and interaction effects were performed with paired  $t$ -tests. Partial  $\eta^2$  was used to calculate Cohen's  $f$  to estimate the effect size.

Accuracy for LLRT was negatively skewed due to general high levels of performance and was therefore non-parametrically analyzed using a generalized estimating equation with stimulus type (hand, foot), side (left, right), perspective (top, bottom), rotation angle ( $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ ,  $270^\circ$ ), and the interaction between stimulus type  $\times$  and the region of pain as independent variables.

Pearson or Spearman correlation analyses were conducted to explore the potential association of clinical factors (duration of illness and MPQ pain score) and

psychological factors (IRI and TAS) with RTs and accuracy of patients (upper-limb and lower-limb patients pooled together). For all statistical analyses, a bilateral  $P$  value of 0.05 was used as the criterion for statistical significance. The Bonferroni correction was applied for multiple comparisons and correlations. All analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS, ver. 25).

## Results

### Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patient groups are presented in Table 1. There were no significant differences in the mean ages, gender distributions, and other clinical and psychological

characteristics between patients with upper vs lower limb pain.

### RTs According to Group, Stimulus Type, Side, Perspective, and Rotation Angle

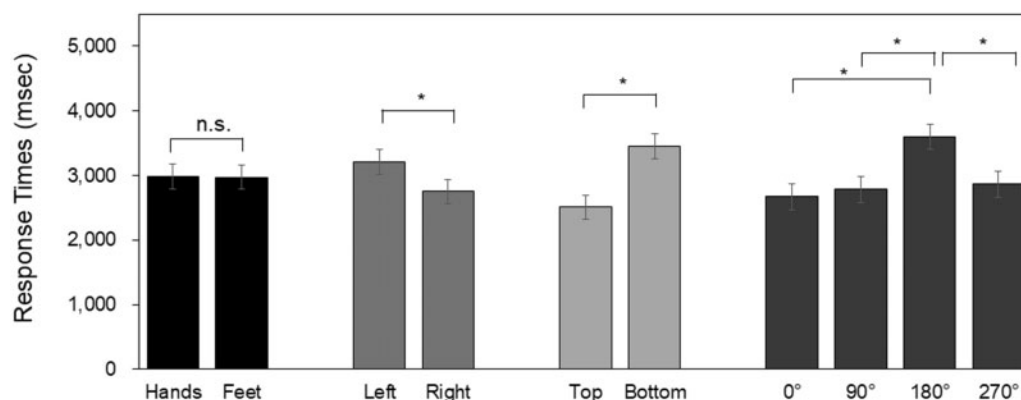
A main effect of stimulus type was not significant ( $F = 1.88$ ,  $P = 0.17$ ) (Figure 2): RTs for the images of hands ( $2,985.39 \pm 188.73$  ms) were comparable to those of feet ( $2,975.58 \pm 189.48$  ms). However, there was a significant interaction of stimulus type and the region of pain ( $F = 34.13$ ,  $P < 0.001$ ,  $f = 0.19$ ): patients with upper limb pain showed slower responses to mentally rotating the image of the hand (mean  $\pm$  SD:  $3,271.15 \pm 872.34$  msec) compared with that of the foot ( $2,754.62 \pm 594.49$  ms) ( $t = 2.41$ ,  $P = 0.039$ ), while patients with lower limb pain showed slower responses to mentally rotating the image of the foot

**Table 1** Demographic, clinical, and psychological characteristics in patients with upper and lower limb CRPS

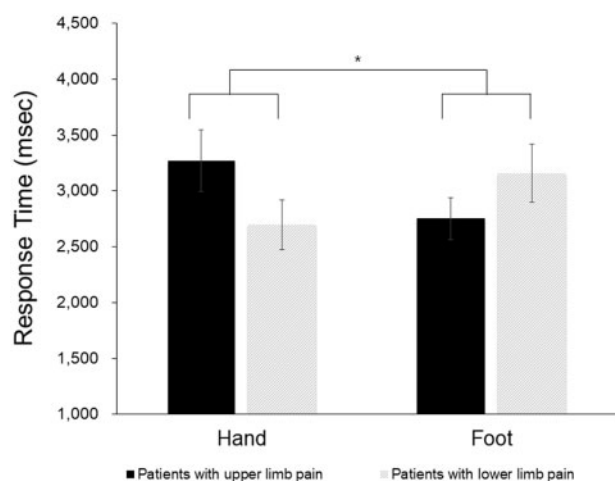
Variables	Upper limb pain	Lower limb pain	Statistics
Age, years	42.8 (12.09)	42.8 (8.17)	$p = 1.00$
Gender (male, female)	7M, 3FM	15M, 5FM	$p = 1.00$
Duration of illness, months	34.9 (23.32)	61.65 (37.58)	$p = 0.05$
SF-MPQ			
<i>physical</i>	18.2 (8.60)	23.6 (5.01)	$p = 0.09$
<i>affective</i>	6.9 (3.04)	7.25 (2.63)	$p = 0.75$
<i>pain severity</i>	2.9 (0.99)	3.55 (0.76)	$p = 0.06$
IRI			
<i>perspective taking</i>	14.10 (6.23)	14.10 (5.90)	$p = 1.00$
<i>fantasy</i>	11.1 (5.69)	13.75 (4.71)	$p = 0.19$
<i>empathic concern</i>	17.4 (5.95)	17.1 (5.12)	$p = 0.89$
<i>personal distress</i>	15.5 (5.99)	13.6 (5.86)	$p = 0.41$
TAS-20			
<i>difficulty identifying feelings</i>	24.8 (5.29)	27.5 (4.72)	$p = 0.17$
<i>difficulty describing feelings</i>	16.2 (3.91)	17.0 (3.83)	$p = 0.60$
<i>externally-oriented thinking</i>	21.3 (3.89)	21.7 (3.59)	$p = 0.78$

Data are given as the mean (standard deviation) except for gender.

SF-MPQ = Short form of McGill Pain Questionnaire; IRI = Interpersonal Reactivity Index; TAS-20 = Toronto Alexithymia Scale-20.



**Figure 2** Reaction times according to stimulus type, side, perspective, and rotation angle. Bar graph displaying mean reaction times in milliseconds to hands vs feet, left vs right stimuli, presented at different views (top vs bottom), orientations ( $0^\circ$  vs  $90^\circ$  vs  $180^\circ$  vs  $270^\circ$ ). Error bars represent standard errors. Participants were significantly slower at making laterality judgements about left-sided stimuli ( $P < 0.001$ ), from the bottom view ( $P < 0.001$ ), at 180 degrees ( $P_s < 0.001$ ), while response times were comparable between the type of stimulus ( $P = 0.17$ ).



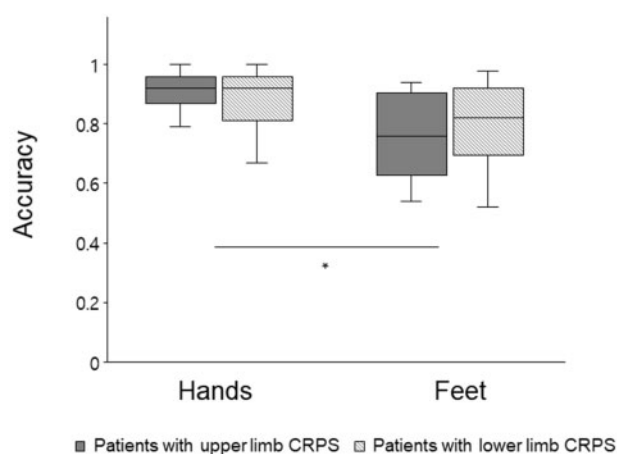
**Figure 3** RTs of patients with upper limb CRPS (black) and with lower limb CRPS (gray) by stimulus type. Bar graph displaying mean reaction times in milliseconds for both stimulus types per group. Error bars represent standard errors. Patients with upper limb CRPS showed slower responses to hands stimuli ( $P=0.039$ ) while those with lower limb CRPS showed slower responses to feet stimuli ( $P=0.002$ ). \*  $P<0.05$ .

( $3,158.26 \pm 1163.47$  ms) compared with that of the hand ( $2,697.56 \pm 1,000.69$  ms) ( $t = -3.69$ ,  $P=0.002$ ) (Figure 3). That is, patients with upper limb pain take 19% longer to recognize the laterality of the hand image than that of the foot, whereas patients with lower limb pain take 17% longer to recognize the laterality of the foot image than that of the hand.

A main effect was significant for the side ( $F=29.80$ ,  $P<0.001$ ,  $f=0.20$ ), perspective ( $F=170.59$ ,  $P<0.001$ ,  $f=0.47$ ), and rotation angle ( $F=32.75$ ,  $P<0.001$ ,  $f=0.36$ ) (Figure 2). Regarding side, the post hoc paired  $t$ -test indicated that RTs for right-sided stimuli were faster ( $2,752.98 \pm 189.40$  ms) compared with left-sided stimuli ( $3,207.99 \pm 188.80$  ms) ( $P<0.001$ ). Regarding perspective, RTs for stimuli from the top view were faster ( $2,509.61 \pm 188.77$  ms) compared with stimuli from the bottom view ( $3,451.37 \pm 189.43$  ms) ( $P<0.001$ ). Regarding rotation angle, RTs for  $180^\circ$  stimuli was slower ( $3,599.37 \pm 201.84$  ms) compared with  $0^\circ$  ( $2,673.38 \pm 201.96$  ms),  $90^\circ$  ( $2,784.02 \pm 202.60$ ), and  $270^\circ$  ( $2,865.19 \pm 202.06$ ) stimuli ( $P_s < 0.001$ ).

#### Accuracy According to Group, Stimulus Type, Side, Perspective, and Rotation Angle

The main effect of stimulus type was significant ( $\chi^2(1) = 28.74$ ,  $P<0.001$ ). Patients showed poorer performance on mentally rotating the image of the foot (median  $\pm$  interquartile ranges:  $0.80 \pm 0.68$ – $0.92$ ) compared with the hand ( $0.92 \pm 0.83$ – $0.96$ ) ( $P<0.001$ ) (Figure 4). The interaction of stimulus type and the region of pain was not significant ( $\chi^2(1) = 0.95$ ,  $P=0.33$ ). A main effect was significant for perspective ( $\chi^2(1) = 39.58$ ,  $P<0.001$ ) and rotation angle ( $\chi^2(3) = 12.57$ ,  $P=0.006$ ) but not for side ( $\chi^2(1) = 0.91$ ,  $P=0.34$ ). Regarding perspective, the



**Figure 4** Accuracy of patients with upper limb CRPS (black) and with lower limb CRPS (gray) by stimulus type. Box plot displaying median accuracy and interquartile range for both stimulus types per group. The whiskers represent maximum (above box) and minimum (below box) values. Patients were more accurate for laterality judgements for hands compared with feet stimuli ( $P<0.001$ ). \*  $P<0.05$ .

accuracy for stimuli from the top view was higher ( $0.94 \pm 0.87$ – $0.98$ ) compared with stimuli from the bottom view ( $0.77 \pm 0.67$ – $0.92$ ) ( $P<0.001$ ). Regarding rotation angle, accuracy for  $180^\circ$  stimuli was lower ( $0.85 \pm 0.70$ – $0.96$ ) compared with  $0^\circ$  ( $0.90 \pm 0.79$ – $0.92$ ),  $90^\circ$  ( $0.85 \pm 0.79$ – $0.96$ ),  $270^\circ$  ( $0.90 \pm 0.79$ – $0.96$ ) stimuli ( $p_s < 0.05$ ). The main effect of stimulus side and group was not significant ( $P_s > 0.05$ ).

#### Correlation of Performance on the LLRT with Patients' Clinical Characteristics

Correlation analyses were conducted on the task performance and clinical characteristics of patients. No significant correlation was observed for duration of illness with RTs for both hands ( $r = -0.11$ ,  $P=0.57$ ) and feet ( $r = -0.13$ ,  $P=0.49$ ) stimuli; however, the results showed a significant association between duration and accuracy for hands ( $\rho = -0.39$ ,  $P=0.04$ ) (but not for feet stimuli,  $\rho = -0.21$ ,  $P=0.28$ ). MPQ pain scores were not correlated with both RTs and accuracy ( $P_s > 0.05$ ).

#### Correlation of Performance on the LLRT with Patients' Psychological Characteristics

We found no significant associations of IRI and TAS with overall RTs and accuracy for both hands and feet stimuli ( $P_s > 0.05$ ). For exploratory purposes, we tested the existence of a linear relationship between these psychological factors and RTs for rotated ( $90^\circ$ ,  $180^\circ$ ,  $270^\circ$ ) minus unrotated ( $0$  degrees) stimuli, which reflect the amount of mental rotation [9]. Correlation coefficients are shown in Table 2. Of the 84 comparisons, five yielded significant outcomes (mostly observed in the  $0^\circ$  vs  $90^\circ$  condition), two of which survived the Bonferroni correction; RTs for left foot were negatively correlated

**Table 2** Spearman-rho Correlation coefficients of IRI and TAS subscales and RTs for the rotated (90°, 180°, 270°) minus unrotated (0 degrees) hand and foot stimuli

	IRI-PT	IRI-FS	IRI-EC	IRI-PD	TAS-DIF	TAS-DDF	TAS-EOT
0 vs 90°							
L Hand	0.009	-0.353	-0.060	-0.100	-0.296	-0.095	0.200
R Hand	-0.203	-0.442*	-0.176	-0.020	-0.163	-0.266	-0.082
L Foot	-0.489**	-0.076	0.001	-0.182	-0.039	0.020	0.187
R Foot	-0.067	-0.053	-0.169	-0.142	<b>0.490**</b>	0.073	0.230
0 vs 180°							
L Hand	-0.104	-0.121	0.208	-0.152	-0.210	-0.089	0.046
R Hand	0.096	-0.256	-0.014	-0.024	0.011	0.004	-0.224
L Foot	-0.052	0.089	0.145	-0.072	-0.130	-0.081	-0.109
R Foot	-0.160	-0.055	0.020	-0.035	<b>0.423*</b>	0.242	0.167
0 vs 270°							
L Hand	0.146	-0.047	0.015	-0.084	0.013	-0.086	0.011
R Hand	0.089	-0.041	0.111	0.165	0.028	-0.251	-0.174
L Foot	-0.347	-0.018	0.084	0.130	0.106	0.032	0.082
R Foot	-0.109	0.085	0.000	-0.171	<b>0.388*</b>	0.105	0.168

\*  $P < 0.05$ .\*\*  $P < 0.007$ .

IRI = Interpersonal Reactivity Index; PT = perspective taking; FS = fantasy scale; EC = empathic concern; PD = personal distress; TAS = Toronto Alexithymia Scale; DIF = difficulty identifying feelings; DDF = difficulty describing feelings; EOT = externally oriented thinking; L = left; R = right.

with the level of *perspective taking* ( $\rho = -0.489$ ,  $P = 0.006$ ) on the IRI, while RTs for right foot were positively associated with *difficulty in identifying feelings* on the TAS ( $\rho = 0.490$ ,  $P = 0.006$ ). Correlation results for accuracy are described in [Supplementary Data Table 1](#).

## Discussion

The present results firstly demonstrate that patients with upper limb pain take longer to recognize the laterality of the images of hands than those of feet, whereas patients with lower limb pain take longer to recognize the laterality of the images of feet compared with those of hands. These results suggest that the performance of CRPS patients on the LLRT was particularly diminished in response to stimuli that corresponded to their affected limb. Although the overall RTs and accuracy were not significantly correlated with patients' psychological factors, an exploratory correlation analysis revealed that the increased RTs for specific conditions (i.e., 0° vs 90°) were significantly correlated with a deterioration in their ability to understand emotions and demonstrate empathy.

The process of mental rotation has four sequential phases including initial visual encoding; analysis of the orientation difference between the target and the mental template; mental rotation of the corresponding body part from the current to the target position; and laterality judgment and response [30, 31]. The observed longer RTs and poorer accuracy with increasing rotation angle in the present study demonstrate that our LLRT did induce implicit motor imagery in patients. Selectively increased RTs in response to stimuli corresponding to patients' affected limb may reflect a disruption of mental template, i.e., body schema. Patients with CRPS often

describe their affected limb as foreign and exhibit reduced spatial acuity in relation to their affected limb [32, 33], demonstrating particularly impaired performance in laterality recognition when the presented stimulus corresponded to their affected (i.e., left or right) limb [6, 8, 12]. However, there exist contradictory findings as well; a number of studies have reported comparable RTs for pictures corresponding to patients' affected vs unaffected limbs [9, 10], and no differences in performance on LLRT between the patients with CRPS and the control group [11]. In the study of Bultitude and colleagues, the authors compared RTs on mental rotation of hands for patients with upper and lower limb CRPS and found no difference between these groups, which can be interpreted as evidence against impaired bodily-specific representation [5]. However, results from within-group comparison in the present study showed particularly impaired performance in laterality recognition when the presented stimulus corresponded to their affected (i.e., upper or lower) limb. Our results add to the previous findings that impaired mental rotation is attributed to relative deficits in the representation of the affected limb rather than nonspecific cognitive deficits.

The primary sensory cortex (S1) plays a critical role in cortical representations of body parts (i.e., body schema). S1 holds the somatotopic body map, and the insula and secondary somatosensory cortex are associated with similar body maps [34–36]. There is evidence indicating an altered functional organization of the S1 in patients with CRPS [13, 14]. However, recent fMRI studies have failed to replicate somatotopic abnormalities of S1 [15, 16], yielding further hypotheses of deficits in higher order mechanisms to explain sensory symptoms in CRPS [17, 37]. Brown et al. have shown the potential cognitive mechanism underlying tactile sensory deficits in CRPS;

that is, knowledge learned from constantly changing internal sensations or the environment may be impaired in this population [37]. Viewed in this light, our findings can be interpreted as indicating that prior knowledge learned from persistent pain in the affected body part may hamper patients' performance on the mental rotation of body image corresponding to their affected limb. Given that simply imagining movement results in pain and swelling in patients with CRPS [38], pain expectation itself may negatively affect top-down processing of hand and foot representation. Although our study did not evaluate changes in pain intensity before and after the mental rotation task, previous research reported the relationship between pain expectation and limb laterality judgments; RTs on the LLRT task were significantly accounted for by the predicted pain associated with the movement (i.e., how painful it would be to adopt the hand position shown in a picture) [6].

Neuroimaging studies have demonstrated activation of the anterior cingulate cortex (ACC) and insula in response to cues related to a person's experience of pain [39, 40]. These brain abnormalities are reported to worsen as pain becomes chronic [41]. Our findings are consistent in that we demonstrated a significant negative correlation between duration of illness and accuracy on the mental rotation of hand stimuli. With respect to patients' social function, the same analysis demonstrated that RTs were negatively correlated with their empathic ability to take another person's perspective. A body-related stimulus, such as body image, biological motion, or gesture, often includes social information in the context of interpersonal interaction. The ability to perceive biological motion has been associated with social functioning, including empathy [42]. Given that mental rotation of hands or feet includes simulating the process of body gestures in social inference, these findings may suggest that deficits in simulating bodily image are associated with impaired inferential ability in social context. Empathy is known to rely on a common representation held by the self and others [43]. Perceiving others' behavior automatically activates self-representations of the behavior [44]. Understanding and responding to the feelings of others, and also understanding and expressing one's own feelings, are critical components of empathy. Both components were found to be significantly related to the capacity to process body image, which can be a potential social cue in patients with chronic pain. In this vein, we suspect a potential linkage between body schema and social cognition in patients with CRPS. Future studies should further explore the role of higher-order social cognition in CRPS. Regarding patients' emotional function, we demonstrated that RTs were positively correlated with the severity of alexithymic symptoms. Alexithymia is prevalent in people with CRPS; among 34 patients, 88% met the clinical diagnosis criteria of alexithymia [45]. In a cross-sectional study, patients with CRPS exhibited significantly higher scores

of alexithymia compared with patients with lower back pain [21], and the levels of alexithymia were positively correlated with the severity of pain. The observed relationships between the level of alexithymia and delays in limb laterality judgments in the present study may simply reflect that more alexithymic patients have lower imaging capacity [46]. However, a previous study reporting similar associations between emotional distress and distorted body perception [23] suggest potential contributions of psychological distress to neurocognitive changes in CRPS. Future studies are needed to elucidate the role of psychological factors in the development of neurocognitive symptoms in CRPS.

This study has several limitations. Twenty patients in this study had lower limb CRPS, and 10 patients had upper limb CRPS. Due to the small sample size and imbalanced ratio between the two groups, our results should be interpreted with caution. The lack of a control group makes it difficult to determine whether the observed findings are specific to CRPS. In addition, as no information regarding the medication status and handedness/footedness of the participants was included in the analysis, we cannot ensure that patients' performance on the LLRT was not affected by psychotropic medications or hand/foot dominance. Furthermore, even though we found significant interaction between the region of pain (upper vs lower limb) and stimulus type (hand vs foot), owing to the small effect sizes and the small number of trials, the results must be interpreted cautiously and should not be regarded as conclusive evidence. Lastly, generally higher accuracy for hands compared with foot stimuli demonstrates an inherent limitation in comparing the ability to mentally rotate hands vs feet stimuli. Due to the foot's limited motion, it would have been much easier for patients to mentally rotate the images of hands (which have a greater range of motion). Nevertheless, we found no speed-accuracy trade-off, and reaction times were selectively increased in response to stimuli corresponding to patients' affected limb.

Our findings suggest some clinical implications for patients with CRPS. A graded motor imagery, an effective intervention for reducing pain and disability in patients with CRPS, consists of three successive stages: left/right limb laterality judgments, imagined movements of the affected limb, mirror therapy [47, 48]. The first stage of this intervention program involves images of the *affected* limb, and our findings with lower limb CRPS provide indirect support for its validity. Moreover, our findings suggest that patients' mental representation capacity should be considered in advance to maximize the treatment effects for intervention programs utilizing imagery.

## Conclusions

The results of this study indicate the selectively impaired mental rotation of hands vs feet in patients with upper or

lower limb CRPS. Expansions in stimulus type and patient pool in the present study provide additional evidence that impaired mental rotation derives from relative deficits in the representation of the affected limb rather than general cognitive deficits. An impaired mental rotation ability was correlated with low empathy and high alexithymia, indicating that altered body schema is closely associated with impaired social cognition in patients with CRPS. These findings may suggest that deficits in simulating body image are associated with impaired inferential ability in social context in patients with CRPS.

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## Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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