Why do people with complex regional pain syndrome take longer to recognize their affected hand?

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Abstract—*Background:* People with complex regional pain syndrome (CRPS) take longer to recognize the laterality of a pictured hand when it coincides with their affected hand. The author explored two aspects of this phenomenon: whether the duration of symptoms relates to the extent of the delay and whether guarding-type mechanisms are involved. *Methods:* Eighteen patients with CRPS type 1 of the wrist and 18 matched control subjects performed a hand laterality recognition task. McGill pain questionnaire, Neuropathic Pain Scale, and response time (RT) to recognize hand laterality were analyzed. Regressions related 1) mean RT for patients to the duration of symptoms and to pain intensity; and 2) mean RT for each picture to the predicted pain on executing that movement as judged by the patient, and to the awkwardness of the movement that would be required. *Results:* For patients, the duration of symptoms correlated with mean RT (Spearman rho = 0.44; $p = 0.02$). Predicted pain rating explained 45% of the variance in RT for each picture for each patient ($p < 0.01$). *Conclusions:* The results suggest that in patients with complex regional pain syndrome type 1, delayed recognition of hand laterality is related to the duration of symptoms and to the pain that would be evoked by executing the movement. The former is consistent with chronic pain and disuse and may involve reorganization of the cortical correlate of body schema. The latter is consistent with a guarding-type response that probably occurs upstream of the motor cortex at a motor planning level.

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When we recognize a pictured hand as being either a left or right hand, we confirm the accuracy of that choice by mentally maneuvering our own hand to match the position shown in the picture.[1,2] Therefore, response time (RT) for that task depends on the angular rotation and range of the mental movement, the so-called "awkwardness" of the movement.[3] The RT is proportional to the time required to actually move one's hand into the pictured position and to the time required to imagine doing so.[3] This phenomenon reflects similarities between imagined and actual movements in brain activity,[4-8] changes in excitability of the spinal motoneuron pool,[9] and EMG activity.[10] Like imagined and executed movements, recognition of hand laterality relies on the body schema—a real-time dynamic representation of one's own body in space, which is derived from sensory input and is integrated with motor systems for the control of action.[11]

Accordingly, disruption of the body schema is thought to underlie the delay in recognition of a pictured hand's laterality.[12,13] Those authors proposed that because body schema is an on-line representation of the body, the severity of pain should affect RT. In short, their results supported their proposal: it took patients longer to recognize the hand that corresponded to their affected limb,[13] but responses were quicker when pain had been reduced via music therapy.[12] This proposal is consistent with studies that have demonstrated an impact of disrupted body schema and altered sensory input on mental and executed movement (e.g., delayed recognition of hand laterality in people with parietal damage,[14] perceived movement of stationary body segments during experimental stimulation of proprioceptive structures).[15,16]

However, two other mechanisms may contribute to a delay in hand recognition in people with complex regional pain syndrome type 1 (CRPS1): 1) a neglect-like effect of chronic disuse; and 2) disruption of motor processes via a protective response. Chronic pain and disuse is known to change cortical and perceptual aspects of body sense. For example, cortical reorganization has been documented in amputees with chronic phantom pain[17] and in chronic low back pain patients, in whom the extent of cortical reorganization is proportional to the duration of symptoms.[18] Chronic pain patients demonstrate reduced proprioceptive acuity that is not explained by the severity of their pain[19-22] and can persist beyond the resolution of symptoms.[23] These data raise the possibility that chronic disuse may have a similar impact on the mental movements associated with hand laterality recognition in much the same manner as neglect,[14] which has already been offered as a potential explanation for the signs and symptoms associated with CRPS.[24]

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Table Patient data

Affected limb	Prescribed medications (other medications)	Age, y/Sex/Dom	Duration CRPS1, weeks	MPQa	MPQs	MPQe	MPQm	MPQ PPI	NPS
L	Morphine, amytryptiline, tramadol (paracetamol, codeine)	32/F/R	87	12	13	3	9	7	50
L	Morphine, tramadol, paracetamol, codeine, vitamin C	45/F/L	58	11	11	1	8	6	49
L	Gabapentin, amytryptiline (paracetamol, codeine)	37/F/R	29	11	7	2	8	7	49
L	Amytryptiline, zoloft	42/M/R	21	11	8	4	10	5	40
R	Morphine, amytryptiline, tramadol (act 3, aspirin)	20/M/R	34	14	6	1	13	6	40
R	Gabapentin, zoloft	38/F/R	16	10	6	4	7	3	39
L	Morphine, amytryptiline, tramadol (neurofen, topical voltaren)	54/M/R	21	16	4	3	6	5	40
L	Morphine, tramadol	46/F/R	7	8	4	1	7	4	37
R	Morphine, naprogesic	32/M/R	3	20	7	1	4	6	44
L	Morphine (cannabis, paracetamol, codeine)	27/M/L	33	15	11	3	8	7	49
R	Morphine, amytryptiline, tramadol	22/F/R	21	16	8	2	12	7	41
R	Gabapentin, zoloft (cannabis)	18/F/R	42	11	9	3	5	6	44
L	Morphine, amytryptiline, tramadol	37/F/R	60	11	10	1	8	6	46
L	Gabapentin, amytryptiline (paracetamol, codeine)	38/M/R	75	13	12	3	8	5	46
L	Gabapentin, amytryptiline (paracetamol, codeine, cerebrex, aspirin)	49/F/R	43	12	9	1	10	4	46
R	Gabapentin, zoloft	57/F/L	25	11	4	4	17	6	45
R	Morphine, amytryptiline, tramadol (paracetamol)	30/F/R	30	11	7	1	12	6	44
L	Morphine, tramadol (paracetamol, neurofen, digesic)	62/M/R	38	11	5	1	10	3	35
	Mean (SD)	38.1 (12.6)	8.7 (5.2)	12.4 (2.8)	7.8 (2.8)	2.1 (1.2)	9.0 (3.1)	5.5 (1.3)	43.6 (4.4)

Dom = dominant hand; CRPS1 = complex regional pain syndrome type 1; MPQ = McGill Pain Questionnaire, affective (a); sensory (s); evaluative (e); miscellaneous (m) factors; PPI = present pain intensity; NPS = neuropathic pain scale.

There are no data that suggest disrupted hand laterality recognition in people with CRPS1 also reflects alterations in motor processes associated with a protective response. In previous work, pain inhibition or guarding was excluded as a cause of delayed responses because patients did not describe the task as painful nor did the task actually involve movement.[12] However, guarding serves primarily to avoid provocation of a painful body part and as such does not necessarily involve movement or pain nor does it require conscious control.[25,26] Absence of movement also does not imply absence of the cortical motor processes that underlie movement. Therefore, it remains possible that altered motor processes that are attempting to guard the (painful) hand from provocation may cause delayed recognition of hand laterality. If so, there should be a relationship between the impact on RT and the pain that would be evoked if the mental movement were executed.

The current study tested two hypotheses in patients with CRPS1. First, if protective motor processes aimed at guarding the affected hand contribute to delayed RT to recognize the affected hand, RT then should be related to the pain that would be evoked by executing the mental movement. Second, if a longer RT to recognize the affected hand reflects the effect of chronic pain and disuse, RT then should be related to the duration of symptoms.

Methods. *Participants.* Eighteen patients (three left handed) with CRPS1 of the wrist and/or hand, diagnosed according to Bruehl et al.,[27] participated in the study. The table presents patient data including prescribed and nonprescribed medications. No attempt was made to control medication intake. Eighteen control participants were matched for age, sex, and hand preference (mean ± SD age, height, and weight was 36 ± 10 years, 170 ± 19 cm, and 72 ± 16 kg, respectively; three were left handed). Informed consent was obtained, and all procedures were approved by the institutional ethics committee and conformed to the Declaration of Helsinki.

Before data collection, patients completed the McGill pain questionnaire, which has sensory, affective, and evaluative subscales,[28] and the Neuropathic Pain Scale (NPS), which has numerous subscales, including pain intensity and pain unpleasantness.[29] Both measures have established validity and reliability.

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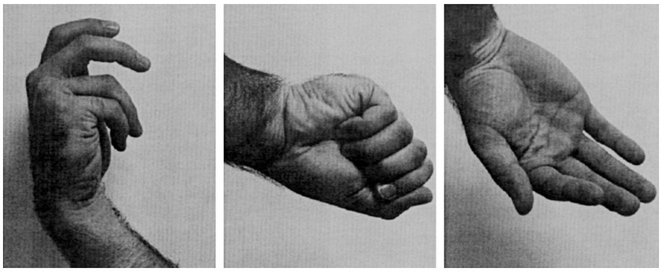

Figure 1. Example photographs of right hand in a variety of postures.

Visual stimuli. Twenty-eight photographs of a right hand in a variety of postures were obtained (figure 1) and were digitally mirrored to construct otherwise identical pictures of a left hand. Using Matlab 6.5 (release 13, Mathworks, Natick, MA), all 56 pictures were randomly presented on a monitor in front of the sitting subject. Participants sat with forearms horizontal and palms down. They responded as quickly as possible to each picture according to whether they recognized the picture to be a left or right hand. Using their nonaffected hand (dominant hand for control subjects), they pressed one of two buttons on a keyboard with either their index or middle finger. RT and accuracy were recorded, and RT for correct responses was used for analysis.

Movement duration for each picture: awkwardness. To quantify the awkwardness of each picture, we have previously used the mean duration of the movement required to adopt the hand posture shown. Duration of movement is considered to be advantageous over an awkwardness measure defined by the direction and orientation of the picture because 1) duration of movement reflects the awkwardness and range of movement required to adopt the posture; and 2) the hand postures were of greater complexity and variability than those used in previous work, which made classification problematic.[3] Previous data from 30 asymptomatic and healthy control subjects were pooled with data from the current sample of 18 control subjects. The hand pictures were displayed quasi-randomly such that each picture was shown to each participant three times. The participant was advised to adopt the position shown "as quickly as possible." By videotaping (100 Hz) performance of each movement, the period from initiation of movement to final position was determined as the number of frames × 0.01 seconds. The mean duration of each movement was calculated for each participant and then for the group. These data were used as the awkwardness measure for each picture.

Predicted pain rating for each picture. After the reaction time task, each patient was presented with hard copies of all the pictures. Patients estimated how painful it would be to adopt the hand position shown in each picture, and then they ordered pictures into four groups from least painful to most painful. To determine whether those movements that are predicted to be painful also take longer, movement duration was recorded for a subset of four patients according to the protocol outlined previously. This was not undertaken for all patients because it exacerbated symptoms.

Statistical analysis. All statistics were performed using Statistica 5.1 (Statsoft Inc., Tulsa, OK). Two 2 (group) × 2 (hand) multivariate analyses of variance compared RT and accuracy between limbs and between patients and control subjects. Post hoc Scheffé tests were used.

For control subject data, a regression analysis evaluated the relationship between mean RT and awkwardness measure of each picture. To test the hypothesis that delay in RT is caused in part by guarding-type mechanisms, a multiple regression analysis evaluated in patients the relationship between RT for each picture for each patient (dependent variable), the awkwardness measure of each picture, the predicted pain rating for each picture for each patient, and the present pain intensity (independent variables). To test the hypothesis that a delay in RT is reflective of the effects of chronic pain and disuse aside from an effect of pain, a further regression evaluated the relationship between mean RT to recognize the affected limb (dependent variable) and the duration of symptoms, pain intensity, and unpleasantness (independent variables). Tolerance was set at 0.20 for all regressions. Because these data were not normally distributed, nonparametric correlations were obtained (Spearman rho).

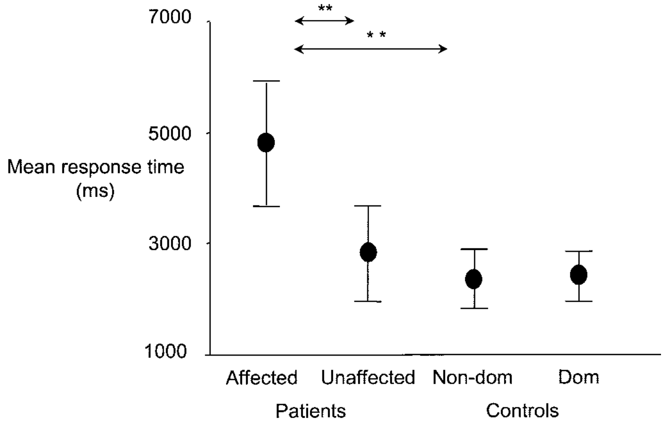

*Figure 2. Mean (circles) and SD (error bars) response time to recognize the affected and unaffected limbs for patients and nondominant and dominant hand for control subjects (*p < 0.05; **p < 0.01).*

Finally, to estimate whether predicted pain rating simply reflects the awkwardness measure, a 1 (movement duration) × 4 (predicted pain rating) analysis of variance and a regression between the awkwardness measure and RT were undertaken on the data collected from four patients.

Although multiple measures elevate the probability of a type I error, a Bonferroni correction would elevate the probability of a type II error and reduce significance to $p < 0.008$, which was considered to be too conservative. In light of criticism in the literature of Bonferroni and other corrections (e.g., Perneger[30]), significance was maintained at $\alpha = 0.05$.

Results. *RT and accuracy in control subjects.* The mean ± SD RT and accuracy were 2,310 ± 680 ms and 94% ± 4.5%, respectively. There was no difference in RT or accuracy between recognition of dominant and nondominant hands ($p > 0.4$ for both; figure 2), and there was no speed-accuracy trade off. The awkwardness score for each picture was strongly related to the mean RT for that picture ($F(1,26) = 351.7$; $p < 0.001$; adjusted $R^2 = 0.93$).

RT and accuracy in patients vs control subjects. Patient characteristics, McGill pain questionnaire, and NPS data are shown in the table. There were main effects of pictured hand ($F(1,71) = 29.6$; $p < 0.001$) and group ($F(1,71) = 53.2$; $p < 0.001$) on RT. There was a hand × group interaction ($F(1,71) = 14.6$; $p < 0.001$) such that in patients recognition of the affected side was slower than recognition of the unaffected side (see figure 2).

Duration of symptoms, but not pain intensity or unpleasantness, correlated with mean RT to recognize the affected hand (figure 3; Spearman rho = 0.44; $p = 0.02$ for duration of symptoms; $p > 0.18$ for pain intensity and unpleasantness). Tolerance for each independent variable was >0.6, and there was no relationship between duration and either pain intensity or unpleasantness ($p > 0.28$ for both).

In the regression on RT for each picture for each patient, the awkwardness measure and predicted pain rating explained 46% of the variance in RT for each picture ($F(2,53) = 24.3$; adjusted $R^2 = 0.46$; $p < 0.001$). However, predicted pain rating alone explained 45% of the variance in RT ($F(1,54) = 46.6$; adjusted $R^2 = 0.45$; $p < 0.001$). Present pain intensity did not relate to RT for individual

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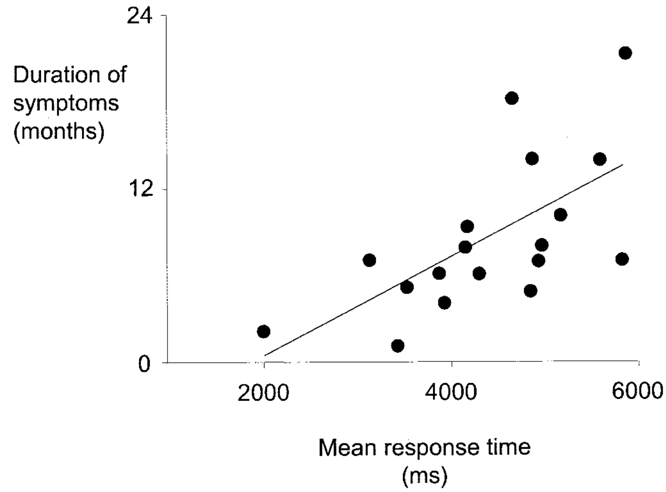

Figure 3. Plot of duration of symptoms in months (y-axis) and mean response time for the group (x-axis). Note a relatively linear relationship (Spearman rho = 0.44; p = 0.02).

pictures. Figure 4 shows RT for pictures according to predicted pain rating.

For four patients for whom an awkwardness measure was calculated for each picture, there was no difference in mean awkwardness measure for each category of predicted pain ($F(3,79) = 0.90$; $p = 0.45$), and there was no relationship between awkwardness measure and RT ($p = 0.22$).

Discussion. These results from control subjects and patients with CRPS1 corroborate previous work. In control subjects, the RT was strongly related to the awkwardness measure, which reflects the proportional relationship between duration to recognize hand laterality and imagined and actual movement

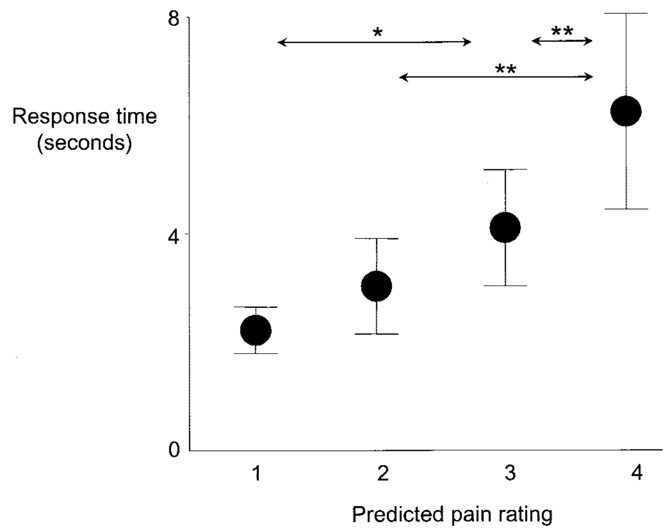

Figure 4. Mean (circles) and SD (error bars) response time to recognize the laterality of individual pictures of the affected limb for patients only, grouped according to the predicted pain that would be evoked if the movement was executed; 1 = least painful, 4 = most painful ($p < 0.05$; **$p < 0.01$).*

of the hand to the position shown.[3] In patients with CRPS1, RT was longer for responses involving recognition of their affected side than it was for recognition of their unaffected side as shown previously.[12,13] The novel findings of the current work are that in patients with CRPS1: 1) the mean RT to recognize the laterality of a pictured hand varies according to the duration of symptoms independent of pain intensity; and 2) the RT to each picture varies primarily according to the pain that would be evoked by executing the mental movement rather than simply as a function of the awkwardness of that movement.

It has been proposed that a longer RT to recognize the affected side is reflective of the impact on the body schema of moment-to-moment changes in nociceptive input.[13] That proposal is open to question because the patients did not report pain during testing. However, a second study using music therapy demonstrated marked reductions in pain and RT after therapy, which does appear to support their proposal.[12] The present results are not corroborative because there was not a significant relationship between the intensity or unpleasantness component of the NPS and the mean RT nor was there a relationship between present pain intensity and RT for individual pictures.

The observation that duration of symptoms was related to mean RT implicates long-term changes associated with pain and disuse in the delayed RT demonstrated by patients. This observation may reflect reorganization of the primary sensory and motor cortices, which has been observed in various chronic pain states[31,32] in which extent of reorganization seems to depend on the duration of symptoms[18] and the level of pain.[32] However, extrapolation of those data to the current findings is problematic because the hand laterality recognition does not consistently activate the primary motor and sensory areas but is thought to primarily involve the dorsolateral frontal and posterior parietal cortex, which supposedly holds the neural substrate for the body schema.[33] Perhaps reorganization also occurs in these cortical areas. A lack of data to this effect in people with chronic pain may reflect limitations of measurement rather than a lack of effect. In light of substantial data that imply a disrupted body schema in those with chronic pain (e.g., reduced body position sense), reorganization of the neural correlates of body schema seems feasible.[23,34]

The other main finding of the present work is that when the hand is painful, the RT is more dependent on the predicted pain associated with the movement that would be required to adopt the position than on the awkwardness of that movement. A possible explanation for this finding is that painful movements take longer to perform, which would mean that the relationship between duration of executed and imagined movements might be preserved. Data from four patients suggested that this is unlikely. An alternative explanation is that guarding-type processes occur at an intention to move level, which involves the

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planning of movements and prediction of their sensory consequences. Evidence that motor imagery and motor execution activate similar cortical networks offers support to this possibility.[4-8] This is important clinically because most data concerning alterations in motor output associated with pain suggest change in the excitability of spinal motor processes[25,35] or primary motor cortex,[36] but the current data suggest for the first time that the impact of predicted pain may occur upstream from the primary motor cortex at a motor planning level. This has implications for our understanding and management of motor disorders associated with pain.

The main findings of the current work cast some light on recent attempts to treat patients with acute CRPS1 via mirror therapy.[37] Mirror therapy is thought to reconcile motor output and sensory feedback[38] and activate premotor cortices,[39] which have intimate connections with visual processing areas.[40] Regarding the present results, it is likely that mirror therapy would reduce guarding responses via exposure to movement and promote reorganization of cortical changes via activity of the affected limb.

Although the current findings relate most obviously to CRPS1, they may apply to any chronic pain state of one upper limb. However, this needs to be verified because CRPS1 is associated with many peripheral and central changes (see Janig and Baron[41]) that are not observed in other chronic pain states, and it is possible that mechanisms underlying the current findings are not simply a consequence of chronic pain.

Interpretation of the current results should consider that movements that the patient expects to be painful are probably also movements that are most often avoided. Therefore, the mechanism underlying increased RT for those pictures may reflect prolonged and specific disuse, which would be in line with the neglect-like theory mentioned earlier. However, we would also expect to see longer RT for recognizing positions that were not commonly adopted regardless of the predicted pain rating, which we did not observe.

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