

## Complex Regional Pain Syndrome (CRPS) Impairs Visuospatial Perception, whereas Post-Herpetic Neuralgia does not: Possible Implications for Supraspinal Mechanism of CRPS

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### Abstract

**Introduction:** Complex regional pain syndrome (CRPS) patients show impaired visuospatial perception in the dark, as compared to normal patients with acute nociceptive pain. The purpose of this study is 2-fold: (i) to ascertain whether this distorted visuospatial perception is related to the chronicity of pain, and (ii) to analyse visuospatial perception of CRPS in comparison with another neuropathic pain condition. **Materials and Methods:** We evaluated visual subjective body-midline (vSM) representation in 27 patients with post-herpetic neuralgia (PHN) and 22 with CRPS under light and dark conditions. A red laser dot was projected onto a screen and moved horizontally towards the sagittal plane of the objective body-midline (OM). Each participant was asked to direct the dot to a position where it crossed their vSM. The distance between the vSM and OM was analysed to determine how and in which direction the vSM deviated. **Results:** Under light condition, all vSM judgments approximately matched the OM. However, in the dark, CRPS patients, but not PHN patients, showed a shifted vSM towards the affected side. **Conclusion:** We demonstrated that chronic pain does not always impair visuospatial perception. The aetiology of PHN is limited to the peripheral nervous system, whereas the distorted visuospatial perception suggests a supraspinal aetiology of CRPS.

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**Key words:** Cognitive dysfunction, Higher brain function, Multimodal disturbance, Neuropathic pain

### Introduction

Some of our patients with pathologic pain reported that when groping for the light switch in a dark room, they often misjudge its location even though they seem to be able to visualise the surrounding space accurately in other situations in their daily life. This phenomenon led us to examine whether patients with pathologic pain have impaired spatial perception, focusing on (i) the multimodal nature of spatial perception and (ii) the representation of one's own body in space.

Human beings and other primates are endowed with a proper visual system, and other sensory modalities for spatial perception.<sup>1,2</sup> Spatial perception is achieved by integrating information from vision as well as other

sensory modalities. Different sensory space maps are integrated to create a single unified map of space.<sup>3,4</sup> For example, somatosensory stimulation includes vibrotactile stimulation and transcutaneous electrical nerve stimulation can affect visuospatial perception in both normal subjects and hemineglect patients.<sup>5-7</sup> Therefore, we hypothesised that pathologic pain can affect spatial perception because pain is a type of somatosensory stimulus.

In the representation of one's own body in space, hand representation is particularly considered to be a visuomotor transformation device which provides an arm-centred reference frame for space perception.<sup>8</sup> Furthermore, hand representation has an inherent condition in which the right hand occupies the right side of space and the left hand

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occupies the left side of space.<sup>9</sup> These suggest that body representation greatly affects spatial perception. Moreover, findings from several studies on subjectively perceived hand size,<sup>10,11</sup> motor imagery of rotating hands<sup>12</sup> and somatotopy in the primary somatosensory cortices<sup>13</sup> suggest that body representation of patients with unilateral pain is asymmetrical. These observations led us to hypothesise that asymmetry of body representation can induce an asymmetric perception of the left and right hemispaces.

Based on these 2 aspects, we previously conducted studies on visuospatial perception and found that unilateral pathologic pain in complex regional pain syndrome (CRPS) patients produced exaggerated somatosensory information, shifting the subjectively perceived midline of the sagittal axis of visuospace towards the affected side. Deafferentation by local anaesthetics in normal and CRPS patients, in contrast, diminished the somatosensory information and caused transient analgesia and a shift of the midline towards the unaffected side. Furthermore, we revealed that the midline shift of visuospace is not relevant to cross-modal linkage in spatial attention between vision and the somatosensory system.<sup>14,15</sup>

Based on these findings, we designed this study to investigate the following 2 issues. First, after lesions in somatosensory pathways, the sensory input from a portion of the body is partially or completely lost. Such pathologic deafferentation (by nerve injury) is frequently accompanied by pathologic pain, which is clinically defined as deafferentation pain. Do patients with deafferentation pain show a shift of the midline in visuospatial perception?

Second, do patients with overall chronic pain show distorted visuospatial perception in the dark, as CRPS patients do? In other words, the second aim was to ascertain whether the distorted visuospatial perception is related to the chronicity of pain.

## Materials and Methods

### Participants

Twenty-seven patients with post-herpetic neuralgia (PHN) and 22 with CRPS participated in this study. CRPS patients suffered unilateral pathologic pain in a limb and fulfilled the International Association for the Study of Pain (IASP) diagnostic criteria.<sup>16</sup> None of them showed any clinically apparent cerebral dysfunction, and none were excluded from the study population. The patients were divided into 4 groups on the basis of their affected side: the first group was 10 left-sided CRPS patients (Lt-CRPS), the second was 12 right-sided CRPS patients (Rt-CRPS), the third was 13 left-sided PHN patients (Lt-PHN) and the last was 14 right-sided PHN patients (Rt-PHN). Tables 1 to 4 provide demographic and clinical information on the patients. All participants had normal or corrected-to-normal eyesight and

each gave their informed consent to participate in the study. The local ethics committee also approved the procedures.

### Procedures

A visual subjective body-midline judgment task (vSMJ-task) was performed by each participant while sitting upright in a chair with their head in a chin-rest so that their head and body axes were aligned. Participants faced straight ahead towards a screen that was 200 cm away. A small red laser dot was projected onto the screen at eye level. Each trial started when a single red dot appeared between 20° and 30° to the right or left of the participants' objective body-midsagittal plane, which was aligned with the 0 position of the red dot. The red dot moved towards the sagittal plane of the objective body-midline (OM) at a constant speed (3°/s). The participants were asked to direct the red dot, using verbal commands, to a position that crossed their precise subjective body-midsagittal plane with binocular vision, which was defined as the visual subjective body-midline (vSM) position. We asked them to use verbal commands, to eliminate possible confounding influences of visuomotor impairment. The vSMJ-task was performed in both light and complete dark conditions even though this kind of experiment is typically used to assess hemineglect in the dark. The vSMJ-task consisted of 20 trials, in which random starting positions of the red dot (10 right and 10 left) were counterbalanced, and 4 sets of 5 trials were conducted under light or dark conditions in an alternating order. Each participant's vSM position was determined by taking the average of 10 position judgments from each of the light and dark conditions. The distance between vSM and OM was measured to determine how and in which direction the vSM position deviated towards the right (positive values) or towards the left (negative values), measured in degrees of visual angle. The results across the 4 patient groups were analysed for light and dark conditions separately using the Kruskal-Wallis test ( $P < 0.05$ ) and then the multiplicative Bonferroni correction ( $P < 0.0083$ ).

## Results

Demographic data were compared among the 4 groups. The vSMJ-task results for all participants were analysed for the 2 different conditions and are expressed as median values with 25th and 75th percentiles given in parentheses. Under light condition, no significant difference was observed among the groups [Lt-CRPS 0.08° (-0.04; 0.17); Rt-CRPS 0.10° (-0.08; 0.27); Lt-PHN 0.09° (-0.46; 0.18); Rt-PHN -0.01° (-0.41; 0.91), Kruskal-Wallis test:  $P = 0.51$ ]. In the dark condition, there was a significant difference between vSM judgments of Lt-CRPS [-2.33° (-2.89; -1.60)], Rt-CRPS [2.19° (0.90; 2.91)], Lt-PHN [1.20° (-1.06; 1.50)] and Rt-PHN [0.27° (-0.93; 1.15)] (Kruskal-Wallis test:  $P = 0.0024$ ) (Fig. 1). Bonferroni post-hoc test revealed

Table 1. Clinical Details of Patients with Left-sided Complex Regional Pain Syndrome

Patient	Age (y)	Sex	Dominant hand	Affected side	Affected limb	Duration (week)	NRS	
1	74	F	Rt	Lt	Upper limb	8	4	
2	69	M	Rt	Lt	Upper limb	14	5	
3	32	M	Rt	Lt	Lower limb	60	6	
4	61	F	Rt	Lt	Lower limb	20	7	
5	68	F	Rt	Lt	Upper limb	10	8	
6	66	F	Rt	Lt	Upper limb	9	7	
7	59	F	Rt	Lt	Lower limb	228	7	
8	67	F	Rt	Lt	Upper limb	29	8	
9	67	F	Rt	Lt	Lower limb	3	7	
10	70	F	Rt	Lt	Upper limb	43	8	
Mean (SD)						63.3 (11.8)	42.4 (67.6)	6.7 (1.3)

F: female; Lt: left; M: male; NRS: numerical rating scale; Rt: right; SD: standard deviation

Table 2. Clinical Details of Patients with Right-sided Complex Regional Pain Syndrome

Patient	Age (y)	Sex	Dominant hand	Affected side	Affected limb	Duration (week)	NRS	
1	44	F	Rt	Rt	Upper limb	75	7	
2	51	M	Rt	Rt	Upper limb	4	4	
3	74	M	Rt	Rt	Upper limb	5	6	
4	43	F	Rt	Rt	Upper limb	20	6	
5	41	M	Rt	Rt	Lower limb	50	5	
6	71	F	Rt	Rt	Upper limb	3	6	
7	81	F	Rt	Rt	Upper limb	12	7	
8	65	F	Rt	Rt	Lower limb	100	6	
9	62	M	Rt	Rt	Upper limb	361	10	
10	69	F	Rt	Rt	Upper limb	9	7	
11	60	F	Rt	Rt	Lower limb	46	4	
12	54	F	Rt	Rt	Lower limb	82	5	
Mean (SD)						59.6 (13.1)	63.9 (99.5)	6.08 (1.6)

F: female; Lt: left; M: male; NRS: numerical rating scale; Rt: right; SD: standard deviation

significant differences between Lt-PHN and Lt-CRPS ( $P = 0.0059$ ) and between Lt-CRPS and Rt-CRPS ( $P = 0.0001$ ). The magnitude of the deviation of the vSM judgments (namely, absolute values of the results) among the groups was not significantly different in either condition by the Kruskal-Wallis test (light,  $P = 0.31$ ; dark,  $P = 0.15$ ). Pain intensities were compared among the groups (Kruskal-Wallis test,  $P = 0.55$ ). In all groups, we found no significant correlation (Spearman rank correlation test) between pain intensity and the amount of deviation in vSM position judgments in the light (Lt-PHN,  $P = 0.53$ ; Rt-PHN,  $P = 0.43$ ; Lt-CRPS,  $P = 0.52$ ; and Rt-CRPS,  $P = 0.08$ ) or the dark (Lt-PHN,  $P = 0.28$ ; Rt-PHN,  $P = 0.62$ ; Lt-CRPS,  $P = 0.19$ ; and Rt-CRPS,  $P = 0.98$ ). There was no significant

correlation between pain duration and the amount of vSM deviation in the light (Lt-PHN,  $P = 0.83$ ; Rt-PHN,  $P = 0.21$ ; Lt-CRPS,  $P = 0.52$ ; and Rt-CRPS,  $P = 0.73$ ) or the dark (Lt-PHN,  $P = 0.26$ ; Rt-PHN,  $P = 0.23$ ; Lt-CRPS,  $P = 0.18$ ; and Rt-CRPS,  $P = 0.83$ ).

## Discussion

To determine whether chronic pain distorts visuospatial perception, we evaluated vSM representation in patients with CRPS and PHN under light and dark conditions. In the light, each vSM position approximately matched the OM position. In the dark, the vSM position of CRPS patients deviated towards the affected side. The vSM position of

Table 3. Clinical Details of Patients with Left-sided Post Herpetic Neuralgia

Patient	Age (y)	Sex	Dominant hand	Affected side	Affected body part	Duration (week)	NRS	
1	84	M	Rt	Lt	face (V1)	150	8	
2	65	F	Rt	Lt	body trunk (Th10)	30	5	
3	41	M	Rt	Lt	upper limb (C7)	4	6	
4	81	M	Rt	Lt	lower limb (S2)	44	5	
5	58	M	Rt	Lt	lower limb (S2)	15	5	
6	72	F	Rt	Lt	body trunk (Th2)	21	4	
7	68	M	Rt	Lt	face (V1)	12	5	
8	66	M	Rt	Lt	lower limb (L1)	20	6	
9	79	F	Rt	Lt	body trunk (Th12)	200	7	
10	44	F	Rt	Lt	body trunk (Th12)	150	9	
11	41	M	Rt	Lt	body trunk (Th3)	14	8	
12	20	F	Rt	Lt	upper limb (C8)	3	8	
13	53	M	Rt	Lt	body trunk (Th10)	24	4	
Mean (SD)						59.4 (18.9)	52.8 (66.8)	6.15 (1.68)

F: female; Lt: left; M: male; NRS: numerical rating scale; Rt: right; SD: standard deviation

C for cervical, Th for thoracic, L for lumbar, and S for sacral. The trigeminal nerve is the fifth cranial nerve, represented by V.

Table 4. Clinical Details of Patients with Right-sided Post-herpetic Neuralgia

Patient	Age (y)	Sex	Dominant hand	Affected side	Affected limb	Duration (week)	NRS	
1	88	M	Rt	Rt	face (V1)	180	8	
2	64	M	Rt	Rt	upper limb (C6)	20	6	
3	40	F	Rt	Rt	body trunk (Th10)	40	6	
4	68	F	Rt	Rt	body trunk (Th3)	4	5	
5	51	F	Rt	Rt	body trunk (Th10)	60	5	
6	56	M	Rt	Rt	body trunk (Th8)	12	6	
7	44	F	Rt	Rt	face (V2)	3	8	
8	69	M	Rt	Rt	face (V1)	60	7	
9	81	F	Rt	Rt	upper limb (C6)	18	6	
10	70	M	Rt	Rt	upper limb (C8)	39	5	
11	81	M	Rt	Rt	body trunk (Th3)	70	4	
12	48	F	Rt	Rt	upper limb (C5)	50	6	
13	77	F	Rt	Rt	body trunk (Th2)	16	7	
14	21	F	Rt	Rt	face (V1)	24	6	
Mean (SD)						61.3 (18.8)	42.6 (45.1)	6.07 (1.14)

F: female; Lt: left; M: male; NRS: numerical rating scale; Rt: right; SD: standard deviation

PHN patients did not, however, deviate towards the affected side in the dark, even though the disease durations were similar between CRPS and PHN patients. Therefore, our results suggest that the deviation of vSMJ in CRPS patients would not be related to the chronicity of their pain. This is supported by our findings that the deviation of vSMJ did not show a linear correlation with disease duration.

#### *Pathologic Pain in One Extremity of CRPS Impairs Egocentric Reference Frame*

Concerning the different aspects of spatial coordinate frames, a distinction should be made among allocentric, egocentric, and object-centred (environment-centred) reference frames.<sup>17</sup> Visuospatial information is provided to the neural substrate for space perception in different reference frames according to the specific task demands.

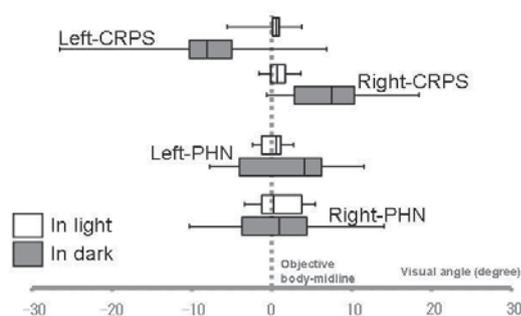


Fig. 1. The subjective body-midline (SM) representation of respective groups in light and dark conditions is expressed in degrees of visual angle.

The dotted line represents the objective body-midline. White (light condition) and gray (dark condition) boxes represent the 25th to 75th percentiles, with the vertical black line showing the median SM judgment, under the light and dark conditions, respectively. The extended bars represent the 10th to 90th percentiles. Positive values indicate a rightward shift of SM representation and negative values indicate a leftward shift. The results across the 4 patient-groups were analysed for light and dark conditions separately using the Kruskal-Wallis test ( $P < 0.05$ ) and then the multiplicative Bonferroni correction ( $P < 0.0083$ ).

Left-CRPS: left-sided complex regional pain syndrome (CRPS) patients; Right-CRPS: right-sided CRPS patients; Left-PHN: left-sided post-herpetic neuralgia (PHN) patients; Right-PHN: right-sided PHN patients.

When we determine the spatial location of visual stimuli, we roughly capture the position of visual stimuli in the environment (object-centred reference frame). Allocentric reference frame is defined as relative spatial relations between 2 or more stimuli in three-dimensional space, independent of the self-body. Meanwhile, egocentric reference frame absolutely relates the subjective direction of the sagittal midline of the body with the location of the visual stimuli. The present vSMJ-task performed in the dark evaluated the egocentric reference frame, as participants could not code the spatial position of the visual stimuli with reference to other visible objects. They, therefore, must have specified a subjective direction to the visual stimuli in relation to their own body. Our finding that vSM representation of CRPS patients deviated only in the dark suggests that unilateral pain of CRPS has an influence on the egocentric reference frame. Meanwhile, CRPS patients (and PHN patients) demonstrated an approximately correct vSM position in the light. There is a strong likelihood that the patients used visible objects (e.g., edges of the screen, borders of walls) as references in order to judge the location of the visual stimuli correctly. Humans are able to perceive the surrounding space properly by integrating and transforming all of these reference frames, and hence we considered that CRPS patients are compensated for the impaired egocentric reference frame with intact allocentric and/or object-centred (environment-centred) reference frames. This finding is consistent with a previous report<sup>17</sup> that CRPS patients showed no typical abnormalities in a

visual line bisection task which primarily evaluates the allocentric and object-centred reference frames.<sup>18</sup> Thus, consistent with our previous report,<sup>15</sup> we demonstrated that unilateral pain of CRPS distorts visuospatial perception, shifting the egocentric reference frame towards the affected side. However, unilateral pain of PHN did not distort the egocentric reference frame. CRPS patients suffered pain in a limb, whereas most of our PHN patients suffered pain in the face or body-trunk. Somatosensory inputs from the face and body-trunk usually project into bilateral primary and secondary somatosensory cortices. Since unilateral somatosensory information from the face or body-trunk is processed in both right and left cerebral hemispheres, the laterality of the somatosensory information might not have any impact on egocentric reference frame, hence resulting in covert distortion of vSM judgments in PHN patients.

#### *Pathologic Pain Relates to Cognitive and Multimodal Disturbances in CRPS*

Thus far, we suggest that unilateral pain in a limb induces the imbalance of somatosensory information from the right and left hemibodies, resulting in the deviation of the egocentric reference frame. Although the number of PHN patients suffering pain in a limb was limited, they did not show any trends to shift the vSM judgments in the dark (not shown in data). This is a significant difference between CRPS and PHN patients. To elaborate this difference, we consider the following ideas: The aetiology of PHN is limited in the peripheral nervous system, whereas the aetiology of CRPS is in both the peripheral and central nervous systems. In particular, a series of reports has suggested the involvement of supraspinal mechanisms in CRPS.<sup>19-21</sup> These reports show that an incongruent sensorimotor loop between motor output and sensory feedback results in the pathologic pain of CRPS. The results of our present study thus suggest that the underlying mechanism of CRPS, different from that of PHN, is associated with not only peripheral and somatosensory abnormalities but also cognitive and multimodal abnormalities such as visuospatial deviation. Conventional physiotherapy modalities for CRPS patients mainly aim to improve the impaired range of motion and strength of the affected limb. Our present findings suggest that we should also address higher-order brain function associated with space perception and sensorimotor processing in future treatment strategies for CRPS. Actually, we have treated CRPS successfully by means of prism adaptation to optical deviation in which prism adaptation could neutralise the deviation of vSM representation.<sup>14,22</sup> Since prism adaptation is known to have the potential to realign the coordinative spatial relationship between visual-motor reference (the action expected from a visual feed forward movement plan) and proprioceptive-motor reference (the action achieved under somatosensory

feedback control),<sup>18</sup> we assume that prism adaptation may be a viable cognitive treatment for CRPS to retrieve congruent sensorimotor integration.

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