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# Impaired spatial body representation in complex regional pain syndrome type 1 (CRPS I)

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ABSTRACT

Recently, a shift of the visual subjective body midline (vSM), a correlate of the egocentric reference frame, towards the affected side was reported in patients with complex regional pain syndrome (CRPS). However, the specificity of this finding is as yet unclear. This study compares 24 CRPS patients to 21 patients with upper limb pain of other origin (pain control) and to 24 healthy subjects using a comprehensive test battery, including assessment of the vSM in light and dark, line bisection, hand laterality recognition, neglect-like severity symptoms, and motor impairment (disability of the arm, shoulder, and hand). Statistics: 1-way analysis of variance, *t*-tests, significance level: 0.05. In the dark, CRPS patients displayed a significantly larger leftward spatial bias when estimating their vSM, compared to pain controls and healthy subjects, and also reported lower motor function than pain controls. For right-affected CRPS patients only, the deviation of the vSM correlated significantly with the severity of distorted body perception. Results confirm previous findings of impaired visuospatial perception in CRPS patients, which might be the result of the involvement of supraspinal mechanisms in this pain syndrome. These mechanisms might accentuate the leftward bias that results from a right-hemispheric dominance in visuospatial processing and is known as pseudoneglect. Pseudoneglect reveals itself in the tendency to perceive the midpoint of horizontal lines or the subjective body midline left of the centre. It was observable in all 3 groups, but most pronounced in CRPS patients, which might be due to the cortical reorganisation processes associated with this syndrome.


## 1. Introduction

The human brain encodes space and spatial locations of objects in so-called reference frames [52], which are classified as allocentric or egocentric reference frames [20,35]. In an allocentric reference frame, for example, the position of a coffee cup is encoded as standing left to the milk jug. In an egocentric reference frame, the position of a the cup is perceived relative to the observer, and more specifically in relation to parts of his body, for example, the observer's hand (body referencing) [8,20,35].

The computation of an egocentric reference frame involves the continuous integration of signals from different sensory sources (visual, vestibular, proprioceptive, and somatosensory) into a postural schema of the body. This dynamic postural schema, serving as "egocentric reference", corresponds to the concept of body schema, emphasizing the close relationship between body schema and spatial perception [7,8,11,12,19].

Both motor disorders [44] and body schema distortions are well known in patients suffering from complex regional pain syndrome (CRPS), and have been linked to cortical reorganization processes in brain regions associated with body schema [29,30,45]. Visuospatial perception appears to be impaired in CRPS patients, as indicated, for example, by findings of delayed recognition of the laterality of a pictured hand [33,41,47], a process that requires mental rotation of one's own hand. Mental rotation is a core spatial ability, and mental rotation of hands is known to be associated with the egocentric reference frame [36,53]. CRPS patients also display difficulties in accurately positioning their limb in the dark [25] or in identifying which of their fingers is touched [5]. A further indication of impaired visuospatial perception was described by Sumitani et al. [51], who investigated the visual subjective body midline (vSM) in CRPS patients. Typically, a right hemispheric brain lesion can cause hemispatial neglect that may result in an

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ipsilesional deviation of vSM, reflecting an impairment of the egocentric reference frame [18,23]. Moreover, the perception of painful thermal stimuli appears disturbed in hemispatial neglect, suggesting a close connection between neglect, spatial attention, and pain perception [26].

However, Sumitani et al. found that, in contrast to patients with hemispatial neglect, the vSM shifted towards the affected side in CRPS patients despite absence of neurological injury [51]. He reasoned that unilateral CRPS pain induces a somatosensory imbalance, with pain providing "exaggerated" input from the affected side, hence distorting visuospatial perception [51]. In view of the well-known cortical and perceptual distortions of hand representation in CRPS patients [5,6,9,10,29,33,38] it might indeed be conceivable that the vSM shift is a symptom that is specific for these patients only. However, the impact of unilateral hand pain on visuospatial perception is as yet unclear. Moreover, the hand is an important visuomotor transformation device in spatial body representation, providing an arm-centred reference frame [15,48,58]. The present study therefore compared 24 CRPS patients to 21 patients with upper limb pain of other origin and to 24 age- and sex-matched healthy subjects. The vSM assessment was complemented with clinical data and other tasks commonly used to assess hand representation and spatial perception.

## 2. Method

### 2.1. Subjects

After approval by the Ethics Committee of the Ruhr-University Bochum (No. 3412-09) and after obtaining written informed consent, 24 right-handed patients with CRPS type I of the upper extremity (mean age 53.4 years, range 34–78 years), 21 patients with pain of the upper limb of other origin (pain control group) (mean age 51.8 years, range 32–71 years), and 12 male and 12 female right-handed healthy subjects, age- and sex-matched to CRPS patients (mean age 52.8 years, range 29–76 years) were included in the study. Patient characteristics are outlined in Tables 1 and 2.

In the pain control group, 14 patients suffered from neuropathic pain of the hand after peripheral injury (radial nerve: n = 2; median nerve: n = 8; ulnaris nerve = 2; all 3 hand nerves: n = 1, brachial plexus palsy: n = 1), due to carpal-tunnel syndromes (n = 5) or trauma (n = 9). The remaining 7 patients presented with painful posttraumatic arthrosis after distal radius or finger/hand fracture (n = 3), humerus fracture (n = 1), amputation (n = 1), soft tissue injury (n = 1) or thoracic outlet syndrome (n = 1). All patients in the pain control group were recruited from the Department of Pain Management or the neurological or surgical department of the Bergmannsheil University Hospital.

All CRPS patients were recruited from the Department of Pain Management of the Bergmannsheil University Hospital in Bochum. CRPS type I was diagnosed based on the modified diagnostic research criteria [17]. Additionally, all CRPS patients displayed a typical enhancement in the late phase of the 99 m-technetium-triple-phase skeleton scintigraphy [61]. Sensory abnormalities were assessed by neurological examination, which, in most patients (CRPS patients: n = 20, pain control patients: n = 10) was accompanied by quantitative sensory testing using the protocol of the German Research Network on Neuropathic Pain [42] and reference data in accordance with Magerl and Krumova, and Maier et al. [27,28]. See Table 3 for clinical signs and symptoms of all patients.

**Table 1**
Demographic data of patients.

| | | CRPS | | | Upper limb pain of other origin | | |
|---|---|---|---|---|---|---|---|
| | | Left-affected N = 12 | Right-affected n = 12 | Total n = 24 | Left-affected n = 9 | Right-affected n = 12 | Total n = 21 |
| Sex | Female | 7 | 5 | 12 | 5 | 7 | 12 |
| Handedness | Right | 12 | 12 | 24 | 8 | 11 | 19 |
| Age | Mean ± SD | 56.9 ± 9.4 | 50.2 ± 9.8 | 53.4 ± 10.1 | 56.0 ± 11.8 | 49.1 ± 10.5 | 51.8 ± 11.3 |

CRPS, complex regional pain syndrome.

**Table 2**
Summary of patients' characteristics.

| | | CRPS I | | | Upper limb pain of other origin | | |
|---|---|---|---|---|---|---|---|
| | | Left-affected n = 12 | Right-affected n = 12 | Total n = 24 | Left-affected n = 9 | Right-affected n = 12 | Total n = 21 |
| Initiating event | Hand/finger fracture | 2 | 1 | 3 | – | 1 | 1 |
| | Radius/ulna fracture | 4 | 6 | 10 | 5 | 1 | 6 |
| | Humerus fracture | – | – | – | 1 | – | 1 |
| | After surgery | 2 | 1 | 3 | – | 2 | 2 |
| | Traumatic finger amputation | 1 | - | 1 | – | 1 | 1 |
| | Tendovaginitis | 1 | – | 1 | – | – | – |
| | Soft tissue trauma without surgery | 2 | 4 | 6 | 2 | 1 | 3 |
| | Carpal entrapment syndrome | – | – | – | | 5 | 5 |
| | Thoracic outlet syndrome | – | – | – | – | 1 | 1 |
| | Brachial plexus palsy | | | | 1 | – | 1 |
| Illness duration | Months (mean ± SD) | 23.6 ± 22.7 | 14.1 ± 13.4 | 18.9[a] ± 18.8 | 51.8 ± 60.3 | 53.5 ± 44.9 | 52.8[a] ± 50.1 |
| Current medication | | | | | | | |
| | NSAID | 2 | 3 | 5 | 3 | 3 | 6 |
| | Antidepressants | 2 | 4 | 6 | 3 | 3 | 6 |
| | Anticonvulsants | 2 | 2 | 4 | 2 | 1 | 3 |
| | Opioids | 1 | 2 | 3 | 2 | 4 | 6 |
| | Other | 3 | 7 | 10 | 4 | 1 | 5 |

CRPS I, complex regional pain syndrome type I; NSAID, nonsteroidal antiinflammatory drugs.
[a] Significant difference between CRPS I and upper limb pain of other origin (analysis of variance).

**Table 3**
Frequency of sensory, sudomotor, vasomotor, trophic, and motor signs in 24 CRPS patients and 21 patients with upper limb pain of other origin.

| | | CRPS I | | | Upper limb pain of other origin | | |
|---|---|---|---|---|---|---|---|
| | | Left-affected | Right-affected | Total | Left-affected | Right-affected | Total |
| Sensory abnormalities | Hyperalgesia (e.g., tactile/ bland pressure) | 8 | 10 | 18 | 6 | 4 | 10 |
| | Tactile hypaesthesia | 7 | 11 | 18[a] | 6 | 2 | 8 |
| | Dynamic allodynia | 1 | 3 | 4 | 1 | 1 | 2 |
| | Paraesthesia | 11 | 10 | 21 | 7 | 10 | 17 |
| Sudomotor dysregulation | Oedema | 11 | 9 | 20[a] | 1 | 3 | 4 |
| | Sweating | 7 | 7 | 14[a] | 1 | 1 | 2 |
| Vasomotor dysregulation | Skin changes and/or temperature difference | 5 | 5 | 10[a] | 0 | 0 | 0 |
| Trophic dysregulation | Impaired hair and/or nail growth | 9 | 8 | 17[a] | 1 | 0 | 1 |
| Motoric impairment | Range of motion wrist (quotient of affected side to nonaffected side) | 0.6 ± 0.3 | 0.3 ± 0.3 | 0.5[a] ± 0.3 | 0.8 ± 0.3 | 0.7 ± 0.3 | 0.8 ± 0.3 |
| | Finger-to-palm distance in cm (mean ± SD) | 4.2 ± 3.1 | 4.2 ± 4 | 4.2[a] ± 3.5 | 1.6 ± 3.7 | 0.6 ± 1.3 | 1.0 ± 2.4 |

CRPS I, complex regional pain syndrome type 1.
[a] Significant difference between CRPS I and upper limb pain of other origin (analysis of variance or $\chi^2$).

Healthy subjects without history of trauma, neurological or psychiatric diseases, or medication intake were recruited among students, members of the hospital staff, or their relatives.

All patients and all healthy subjects had normal or corrected-to-normal eyesight.

### 2.2. Questionnaires

Both patient groups rated their current and average pain over the last week on an 11-point numerical rating scale (0 = no pain, 10 = worst pain imaginable). Severity of neglect-like symptoms was assessed on a 6-point Likert scale using a 5-item questionnaire by Frettlöh et al. [6] based on Galer and Jensen's self-administered patient survey [10]. The mean of the 5 items renders the total score. Furthermore, patients were asked to rate function of the affected limb using the disability of the hand, arm, and shoulder (DASH) questionnaire [13]. This instrument assesses the ability to perform daily activities on a 5-point Likert scale. Scores are summarized and standardized, and the final score indicates the degree of restriction ranging from 0 to 100, with low scores indicating a low degree of restriction.

Handedness was assessed using the Edinburgh Handedness Inventory [34], based on which, a laterality quotient (LQ) ranging from −100 to +100 (with negative values indicating left-handedness and positive values indicating right-handedness) was determined. Participants were considered left-handed if the LQ was smaller than zero and right-handed if the LQ was larger than zero. Apart from 2 patients with upper limb pain, who were determined as left-handed based on the LQ (−100 and −55.5), all participants were right-handed (CRPS LQ: 67.27 ± 36.24; upper limb pain of other origin LQ: 80.54 ± 23.06; healthy subjects LQ: 92.08 ± 21.85).

### 2.3. Experimental procedures

Prior to testing, all subjects completed a line-bisection task to control for hemispatial neglect [21]. To determine the subjective vSM, participants were seated in front of a 160-cm-wide and 200-cm-high screen at a viewing distance of 200 cm. The 0° position of a white dot on the screen was aligned with the objective body midline (OM) of the subject. The starting position of the dot was chosen to begin not from the outer border of the screen, but at eye level 20° to 30° to the left or the right of the sagittal plane of the OM to avoid screen borders serving as anchor stimuli for subjects. Subjects were asked to follow the horizontally moving dot (3°/second) with their gaze, with head and trunk remaining stable (Fig. 1). Subjects were instructed to verbally stop the dot at the point when it crossed their subjective body midline both under light and dark conditions (Fig. 1). For each of those 2 conditions, 20 trials of random starting positions of the dot were assembled, with 2 sets of 5 trials starting from the left and 2 sets of 5 trials starting from the right in counterbalanced alternating order.

The in-house developed software automatically recorded the direction of the deviation of the vSM from the OM in degrees of visual angle. Negative values indicate a leftward deviation, and positive values indicate a rightward deviation from the OM. A median over all vSM judgements was calculated to assess the direction of the deviation, with the median absolute deviation (MAD) indicating the variance in judgments.

The absolute distance between vSM and OM was assessed by calculating the median of the absolute value of all vSM judgements, independent of their sign, with MAD indicating the variance in judgements. In the results, the direction of the deviation is indicated as the raw score median, and the distance of the deviation is described as the absolute value of the median.

Participants then completed a hand laterality recognition task, which followed a previously established protocol [41]. This laterality recognition task was designed to randomly present 168 pictures of left and right hands in different positions. Subjects were instructed to press either the left or right arrow key to indicate the laterality of the hand that had just been presented. Reaction time (RT) recorded in milliseconds for each trial, and the common logarithm of RT was then calculated for statistical analysis.

### 2.4. Statistics

Statistical analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) with the significance level $\alpha$ = .05 for all analyses. The Kolmogorov-Smirnov Test was used to test for normal distribution of the data. Group differences were analysed using 1-way analysis of variance with post hoc Bonferroni correction. *T*-tests for independent samples served to calculate differences between CRPS patients or left- and right-affected pain controls. Paired *t*-tests were used to analyse differences of vSM judgment, depending on the starting position of the dot (left or right), and to compare RT between the dominant and nondominant hand, that is, affected and nonaffected hands. Pearson correlation analysis was calculated between the outcome measures of the experimental procedures and handedness (LQ), illness duration, pain intensity, motor impairment (DASH), and neglect-like severity symptom score in the respective groups.

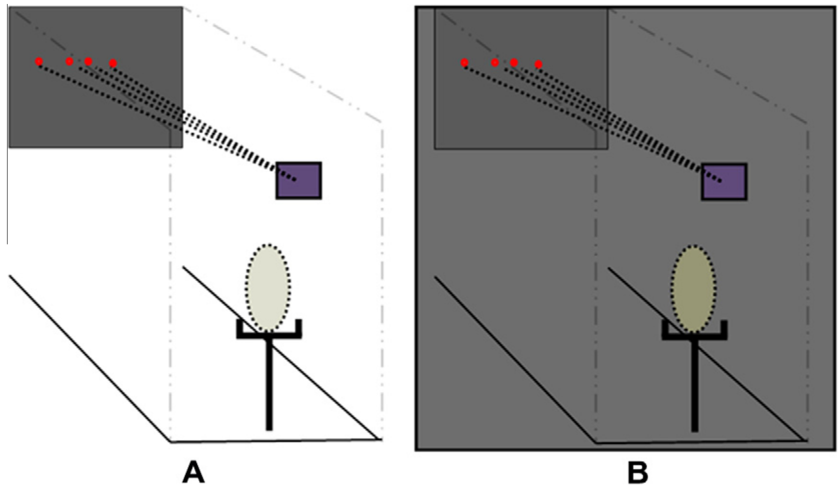


**Fig. 1.** Experimental set-up of visual body midline assessment in the light (A) and dark (B) condition. The participant was seated 200 cm away from a screen (width 160 cm, height 200 cm) with a dot appearing at eye level 20° to 30° to the left or the right of the sagittal plane of the objective body midline (OM) to avoid screen borders serving as anchor stimuli for subjects. Subjects were instructed to follow the horizontally moving dot (3°/second) with their gaze and to verbally stop the dot at the point when it crossed their subjective body midline both under light (A) and dark (B) conditions.

## 3. Results

### 3.1. Study sample

CRPS patients and patients in the pain control group did not differ regarding current or average pain intensity. In contrast, CRPS patients had a significantly shorter illness duration and larger motor impairment, as indicated by a significantly lower range of motion of the wrist, greater finger-to-palm distance, and a higher DASH score (Table 4). The severity of neglect-like symptoms in our sample of CRPS patients was, on average, higher compared to the pain control patients, but without reaching statistical significance ($P = 0.067$). However, a detailed analysis revealed that right-affected CRPS patients displayed a significantly higher severity of neglect-like symptoms than left-affected CRPS patients or left- or right-affected pain controls, and were more impaired in their wrist range of motion and finger-to-palm distance than left-affected and right-affected pain controls (Table 4).

In the line-bisection task, all participants tended to bisect the line to the left of the centre (healthy subjects: 0.4 mm ± 0.3; CRPS patients: 0.4 mm ± 0.4; upper limb pain patients of other origin: 0.4 mm ± 0.5), with no significant differences between groups ($P > 0.85$).

### 3.2. Visual subjective body midline (vSM)

One CRPS patient displayed a vSM judgment, which was 4-fold of the SD of the mean of the CRPS group. He was therefore regarded as an extreme outlier and excluded from the statistical analysis.

Only in the dark, but not in the light, condition did CRPS patients demonstrate a significantly larger absolute shift of the vSM from the objective body midline (median ± median absolute deviation [MAD]: 2.2° ± 1.1) compared to the pain control group (median ± MAD: 1.4° ± 0.6; $P < 0.01$) and to healthy subjects (median ± MAD: 0.8° ± 0.6; $P < 0.01$) (Fig. 2A). Control patients did not differ from healthy subjects ($P > 0.15$).

In contrast to previous findings, the vSM was always shifted to the left (Fig. 2B) in CRPS patients (median ± MAD: −0.7° ± 0.1), independent of the side that was affected (left-affected CRPS patients median ± MAD: −0.8° ± 0.1; right-affected CRPS patients median ± MAD: −1.0° ± 0.1). An overall leftward deviation was also seen in healthy subjects (median ± MAD: −0.1 ± 0.06) and in pain controls (median ± MAD: −0.09° ± 0.07). However, in pain controls the direction of the shift depended on the affected side, with vSM being shifted to the left on left-affected patients (median ± MAD: −0.54° ± 0.08) and to the right in right-affected patients (median ± MAD: 0.27° ± 0.06); vSM judgments were not affected by the left or right starting position of the dot in any of the 3 groups (all $P > 0.67$).

In right-affected CRPS patients, a significant correlation between the severity of neglect-like symptoms and vSM judgments was observed ($r = 0.6$; $P < 0.05$). In contrast, no correlations were observed for left-affected CRPS patients or patients with pain of other origin (all $P > 0.61$).

All other correlations between vSM judgements and illness duration, pain intensity, and DASH scores were not significant (all $P > 0.35$).

### 3.3. Hand laterality recognition task

RTs for correctly recognised pictures did not differ between CRPS patients (2235.5 ms ± 662.2) and pain controls

**Table 4**
Pain intensity, neglect-like severity score, and disability of the hand, arm, and shoulder (DASH) in CRPS patients and patients with upper limb pain of other origin (all mean ± SD).

| | CRPS I | | | Upper limb pain of other origin | | | *P*-values |
|---|---|---|---|---|---|---|---|
| | Left-affected | Right-affected | Total | Left-affected | Right-affected | Total | |
| Average pain (past 4 weeks) | 4.5 ± 2.7 | 5.1 ± 2.6 | 4.8 ± 2.6 | 4.1 ± 2.6 | 4.0 ± 2.3 | 4.5 ± 2.2 | >0.05 |
| Current pain | 3.9 ± 3.2 | 4.3 ± 2.6 | 4.1 ± 2.8 | 4.6 ± 2.3 | 4.6 ± 2.5 | 4.4 ± 2.5 | >0.05 |
| Neglect-like severity score | 1.0 ± 1.1 | 2.3[a] ± 1.2 | 1.7 ± 1.3 | 1.4 ± 1.1 | 0.8 ± 0.7 | 1.0 ± 0.9 | 0.016[a] |
| DASH | 46.6 ± 20.1 | 60.5 ± 9.1 | 53.5[b] ± 16.8 | 41.6 ± 14.7 | 40.7 ± 20.4 | 41.1 ± 17.8 | 0.021[b] |

CRPS I, complex regional pain syndrome type 1; DASH = disability of the hand, arm, and shoulder instrument.
[a] Significance between left-affected and right-affected CRPS patients.
[b] Significant difference between CRPS I and upper limb pain of other origin (analysis of variance).

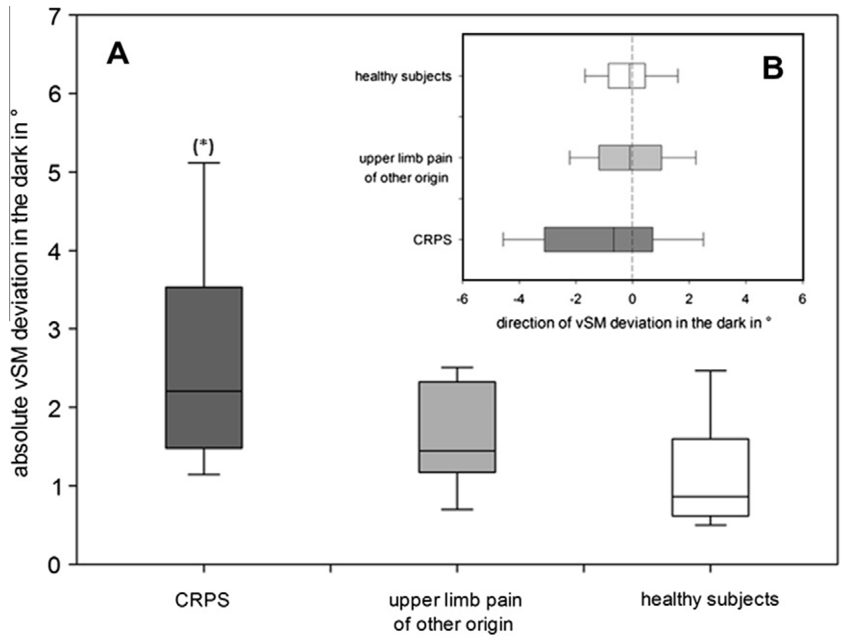


**Fig. 2.** Representation of subjective body midline in the dark. The boxes represent the 25th to the 75th percentile with the black line within the box marking the median. The extended bars above and below the box indicate the 90th and 10th percentiles. Shown are the absolute distance (A) and the direction of the vSM deviation (B) of the objective body midline expressed in degrees of visual angle (°). (B) The dotted line indicates the objective body midline, negative values indicate a shift of the vSM to the left, positive values indicate a shift of the vSM to the right. vSM, visual subjective body midline; CRPS, complex regional pain syndrome.

(2234.0 ms ± 642.8) or healthy subjects (1947.9 ms ± 664.9) ($P > 0.15$). In both patient groups, RTs did not differ between hand pictures corresponding to the affected side and hand pictures corresponding to the unaffected side (CRPS, pictures of the affected hand: 2217.74 ms ± 735.1, pictures of the unaffected hand: 2252.6 ms ± 639.8; pain controls, pictures of the affected hand: 2232.2 ms ± 658.5, pictures of the unaffected hand: 2243.6 ms ± 662.1; all $P > 0.39$). For healthy subjects and CRPS patients, there was a significant difference in RT between hands that corresponded to the dominant hand and hands that corresponded to the nondominant hand (CRPS, pictures corresponding to the dominant hand: 2146.1 ms ± 703.2, pictures corresponding to the nondominant hand: 2324.2 ms ± 662.8; healthy subjects: pictures corresponding to the dominant hand: 1877.46 ms ± 642.73, pictures corresponding to the nondominant hand: 2021.8 ms ± 701.4; $P < 0.01$). In both patient groups, no significant correlations between RTs of correctly recognised pictures and illness duration, neglect-like symptoms, or self-rated upper extremity disability and symptoms score (DASH) were found. In patients with upper limb pain of other origin, high LQs indicating a strong right-handedness were related to fast recognition scores (indicated by low RTs) of both left- and right-hand pictures (pictures of left hands: $r = -0.44$; $P < 0.05$; pictures of right hands: $r = 0.50$; $P < 0.05$). No significant correlations between LQ and right-hand or left-hand pictures were found for CRPS patients or healthy subjects. Further correlational analyses revealed significant positive correlations between age and RT in the group of CRPS patients ($r = 0.64$; $P < 0.01$) and in healthy subjects ($r = 0.54$; $P < 0.05$), but not in the group of patients with pain of other origin ($P > 0.72$).

## 4. Discussion

The present study compared spatial body representation regarding both allo- and egocentric reference frames in CRPS, upper limb pain of other origin, and age- and sex-matched healthy subjects. The results of the vSM being further shifted to the left than in pain controls or healthy subjects under dark conditions confirm previous findings of impaired visuospatial perception in CRPS, suggesting a distorted spatial body representation. Possibly, this deviation impairs CRPS patients in coding visual stimuli with respect to their own body midline (ie, the egocentric reference frame).

### 4.1. CRPS-specific impairment of the egocentric reference frame

The egocentric reference integrates different reference frames (retinotopic, somatotopic), which are constructed from somatosensory stimuli arising from both body sides [7,8]. If unilateral pain alone, as suggested [51,54], would provide exaggerated information from one body side, inducing a somatosensory imbalance between the 2 body sides, than a shift of the egocentric reference frame towards the painful side would be expected. However, this could not be confirmed in the present study. Patients with pain of origin other than CRPS did not show a deviation of the body midline in our study or in a previous report on postherpetic neuralgia [54], indicating that a shift of the egocentric reference frame is not induced by unilateral upper limb pain alone. Furthermore, the vSM deviation did not correlate with pain intensity in the present or in previous studies [50,51,54]. Particularly in CRPS, unilateral pain was demonstrated to (bilaterally) suppress the sensory processing of sensory stimuli in the somatosensory cortex from the affected hand rather than exaggerating it [16,24,29,30,38,45]. In the construction of the egocentric reference frame, the hand plays an important role as visuomotor transformation device, providing an arm-centred reference frame [15,48,54]. In CRPS, a smaller representation of the affected hand in the sensory cortex has been reported [30,38]. Moreover, the integration of visual and proprioceptive hand-related input in the posterior parietal cortex is disturbed in CRPS [29]. Thus, it can be hypothesized that in CRPS, the integration of the arm in the egocentric reference frame is compromised, probably due to the reduced tactile and proprioceptive input from the affected limb and the reduced cortical representation of the affected hand. Furthermore, the intracortical inhibition in both the motor and the sensory cortex is reduced [24,44]. While cortical disinhibition has been shown to occur also in neuropathic pain, this is observed in only the contralateral hemisphere [46]. Therefore, it is conceivable that higher-order brain functions associated with spatial perception are implicated only in the pathophysiology of CRPS.

### 4.2. Pseudoneglect and egocentric reference frame

In contrast to previous work [51,54], the present study observed a leftward deviation of the body midline for all 3 groups. Importantly, the size of this effect was most pronounced in CRPS patients and was independent of whether the left or right side was affected. These results correspond to the neurobiological model of right-hemispheric dominance for spatial tasks and point to the phenomenon of pseudoneglect that typically occurs in neurologically intact healthy subjects. Pseudoneglect should not be confused with either the (typically) ipsilesional hemispatial neglect following brain lesions nor with the neglect-like syndrome, a disturbance of body perception observed in CRPS patients [2,5,6,9,10]. Pseudoneglect has been attributed to the dominance of the right hemisphere for attentional processes, which is independent of stimulus properties and may result from an involvement of the right hemisphere in processing both the contra- and ipsilateral hemifield [3,21,32,49]. As a result, horizontal lines are typically bisected towards the left of the veridical centre on the line-bisection task, and horizontal line length is overestimated when this falls to the left of a vertical line in the horizontal vertical line illusion (an illusion of length perception) [21,22,40]. Moreover, a deviation of the egocentric midsagittal plane (or vSM) towards the left was observed [1,20,21,56]. According to some authors, the leftward bias in spatial tasks could result from scanning factors that proceed from left to right [21]. However, there was no significant influence of the starting position of the dot on vSM judgements. Moreover, eye-movements are not solely anchored to a retinotopic representation, but are further remapped into body-centred coordinates, that is, the egocentric reference frame [7,8,37].

Importantly, brain regions activated during line bisection [4,55,57,59,60] have also been suggested to contribute to the egocentric reference frame. During the setting of the body midline, bilateral activations in the posterior parietal cortex were observed, including the intraparietal sulcus, adjacent superior parietal lobule, superior occipital gyrus, and the lateral premotor cortices, with a prevailing activation of the right hemisphere [7,8,57]. A subset of these regions was also active during allocentric spatial representation, the reference frame that underlies the line-bisection task [37,40]. Notably, CRPS patients did not display an impaired allocentric reference frame, since their vSM judgements matched the OM in the light condition, and since they did not exhibit any abnormalities in the line-bisection task in the present or in previous studies [5,6].

Altogether, neuroimaging results appear to emphasize the parallels between visuospatial attention and the egocentric reference frame in which right-hemispheric dominance for spatial tasks induces pseudoneglect of the right hemispace. The supraspinal mechanisms involved in CRPS may contribute to an exacerbation of the "normal" leftward bias of visuospatial attention due to an impaired egocentric reference frame.

### 4.3. Influence of the distorted body representation in CRPS on spatial abilities

In what way might a distorted body representation be associated with impaired visuospatial perception? The hand laterality recognition, which is commonly applied to assess the body schema and requires mental rotation of the hand, was reported to be impaired in CRPS [33,41,47]. Mental rotation, as a core spatial ability, depends on the egocentric reference frame [36,53]. Although the present study failed to replicate a significant difference between CRPS patients and healthy subjects with regard to mental hand rotation, RTs of CRPS patients were comparable to those observed in a previous study [41] indicating a compromised egocentric reference frame. The RTs of healthy subjects were slightly higher in the present study than previously reported [41], which might be explained by age differences, since the present study recruited a significantly older sample of healthy adults than the previous one. Indeed, in line with previous observations [43], laterality recognition was found to correlate with age also in the present sample.

Further on, CRPS patients often report feelings of foreignness or disownership towards the affected hand that imply a distorted body representation termed neglect-like syndrome (which is an unfortunate term as it is easily confused with hemispatial neglect occurring after brain lesions) [5,6,9,10]. In the present study, the magnitude of neglect-like symptoms and vSM deviation in right-affected CRPS patients strongly correlated, in contrast to left-affected CRPS patients who presented with significantly lower neglect-like severity score. It might therefore be conceivable that a distorted hand representation contributes to a leftward bias of spatial attention allocation. Nevertheless, it has to be noted that assessment of neglect-like symptoms relied on a self-administered questionnaire which, like most self-administered questionnaires, bears limitations [6]. To the degree that is possible for lack of external measures, the questionnaire has been validated [6], but it has to be acknowledged that data about neglect-like symptoms originate from cross-sectional studies and there is no information on how these symptoms develop in the course of the disease.

### 4.4. Differences to previous studies and limitations of the present study

The difference between the present and previous findings may be explained by the recruited sample and vSM assessment. Previous studies included patients suffering from both types of CRPS (type 1 and type 2) in whom the upper or the lower limb was affected [51]. Since as yet little is known about body schema distortions of CRPS on the foot and the potential relevance to spatial body representation, we only included patients affected at the upper limb. In addition to the sensory changes in CRPS I, stronger thermal and mechanical sensory loss was demonstrated in CRPS II, and its extent was similar to that in patients with peripheral nerve injury [14]. To avoid overlapping effects of concomitant nerve lesions, we considered patients with CRPS I only. Furthermore, in contrast to previous studies [51,54], an investigator-independent approach was applied by using computer software that automatically recorded the verbally indicated position of the dot in degrees of visual angle, calculating its deviation from the OM. Finally, vSM judgments of CRPS patients were characterized by a high variability, suggesting heterogeneities within the sample. A high heterogeneity is an often-encountered characteristic of CRPS patients, possibly because of the multifactorial pathophysiology of this condition [31].

### 4.5. Conclusion

In conclusion, the present study provides further evidence for a link between impaired body representation and visuospatial attention in patients with CRPS, in addition to previously reported changes in the central nervous system in CRPS. Cortical reorganization processes in brain regions implicated in integrating visuospatial information may also play a role in this disorder. Future research should investigate if optokinetic or vestibular stimulation, which has been shown to successfully modulate perception of the body midline in hemispatial neglect, is beneficial in CRPS as well [39,40,50].

## Conflict of interest statement

There are no financial or other relationships that might lead to a conflict of interest.

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