



**Table 1****Characteristics of the CRPS participants.**

ID	Age/ sex	Handed.	Inciting injury	CRPS limb	Diagnosis	Dur.	Current treatment/medication	Other pain	Other	Task
01	62/F	R	Frac wrist	L	CRPS-R	12	Tramadol 1 × 50 mg, paracetamol 1 g, ketoprofen 1-2 × 200 mg	L shoulder, R hand when cold	—	V-SAT, P-SAT
02	56/F	R	PS hand	L	CRPS-C	4	Ibuprofen 3 × 400 mg	L Arm	R CRPS 4 y ago	V-SAT, P-SAT, VP-PT
03	55/F	L	Frac wrist	L	CRPS-C	20	/	Both feet	—	V-SAT, P-SAT, VP-PT
04	62/F	R	Frac-PS wrist	L	CRPS-R	20	Physical therapy, occupational therapy, paracetamol 3-4 × 1 g, tramadol when on pain	L Foot	—	V-SAT, P-SAT, VP-PT
05	50/F	R	STI hand	L	CRPS-R	32	Amitriptyline 1 x 25 mg	L Side of the neck	—	V-SAT, P-SAT, VP-PT
06	51/F	R	STI/PS shoulder	R	CRPS-C	6	Physical therapy, occupational therapy, amitriptyline 2 × 10 mg, bromazepam 6 mg, paracetamol 1 g or ibuprofen 600 mg/day, tramadol when on pain.	R Elbow and shoulder	Slap L shoulder	V-SAT, P-SAT, VP-PT
07	56/F	R	Frac wrist	L	CRPS-C	7.5	Physical therapy	L Elbow and shoulder	—	V-SAT, P-SAT, VP-PT
08	50/F	R	Fract forearm	R	CRPS-C	5	Physical therapy, paracetamol when on pain	R Elbow and shoulder	—	V-SAT, P-SAT, VP-PT
09	64/M	R	PS hand	L	CRPS-R	4	Physical therapy, paracetamol when on pain	R Hand	R Hand arthrosis	V-SAT, P-SAT, VP-PT
10	51/F	R	STI/PS hand	L	CRPS-R	33	Physical therapy, occupational therapy	—	—	V-SAT, P-SAT, VP-PT
11	50/F	R	Frac forearm	L	CRPS-R	5	Physical therapy, tramadol 1 × 200 mg, paracetamol 1 × 300 mg	—	—	P-SAT, VP-PT
12	60/F	R	Frac wrist	R	CRPS-R	10	Physical therapy, occupational therapy, paracetamol 1 × 1 g, formoterol 1 × 12 µg	—	—	V-SAT, P-SAT, VP-PT
13	58/F	R	Frac wrist	L	CRPS-R	8	Physical therapy, occupational therapy, paracetamol when on pain	L Calf	—	V-SAT, P-SAT, VP-PT
14	33/F	R	STI thumb and wrist	R	CRPS-R	14	Physical therapy, ibuprofen when on pain	R Arm and shoulder	Migraine	V-SAT, P-SAT, VP-PT
15	58/F	R	Frac wrist	L	CRPS-C	21	Tramadol 2 × 50 mg, paracetamol 2 × 75 mg, zolpidem 10 mg to sleep	—	—	V-SAT, P-SAT, VP-PT
16	47/M	R	Frac wrist	R	CRPS-R	16	Physical therapy, occupational therapy, paracetamol 3 × 1 g, ibuprofen 2 × 400 mg, buprenorphine 35 µg every 3 d	R Elbow	R Cubital nerve compression	V-SAT, P-SAT, VP-PT
17	55/F	R	Fract wrist	R	CRPS-C	5	Acupuncture	R elbow, shoulder and knee	Migraine	V-SAT, P-SAT, VP-PT

Age in years.

CRPS-C, Budapest clinical criteria for CRPS; CRPS-R, Budapest research criteria for CRPS; Dur, duration since inciting injury in months; F, female; Frac, fracture, PS, postsurgery; Handed, handedness; L, left; M, male; P-SAT, proprioceptive straight-ahead task; R, right; STI, soft tissue injury; VP-PT, visuoproprioceptive pointing task; V-SAT, visual straight-ahead task.

mplete data on CRPS patients' spatial cognition abilities using different sensory cues and motor responses. We compared

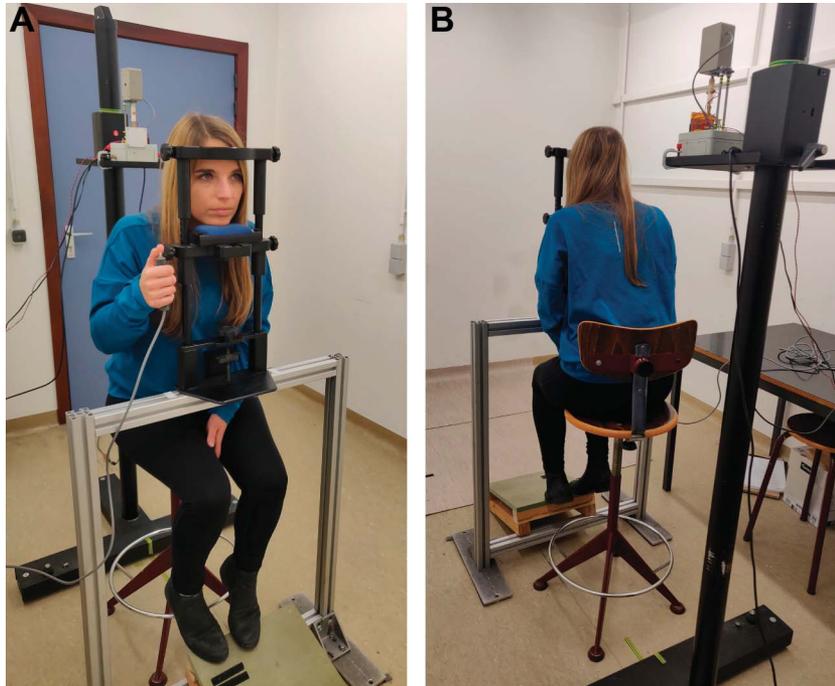
performances of patients with upper-limb CRPS and matched control participants during V-SAT to those in a proprioceptive

straight-ahead task (P-SAT) consisting in pointing towards the imaginary prolongation of one's body midline while blindfolded, and a visuoproprioceptive pointing task (VP-PT) during which participants pointed towards an object through a box preventing vision of the pointing limb.<sup>6,7,14–16,25,49,50,55</sup> Whereas performing V-SAT and P-SAT required inputs from one single sensory modality (ie, vision vs proprioception, respectively), performing VP-PT depends on the ability to coordinate visual perception of the target and proprioception of one's limb in the absence of visual feedback about limb position.

## **2. Methods**

### **2.1. Participants**

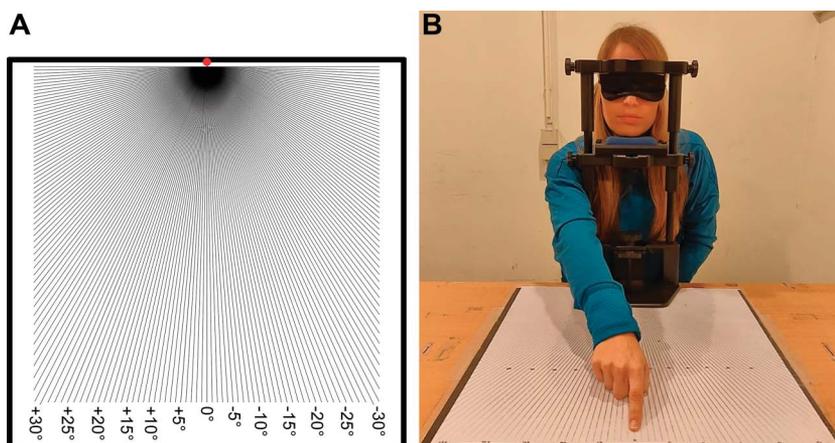
Seventeen patients with upper-limb CRPS were recruited in collaboration with the orthopaedic and physical rehabilitation departments of Saint-Luc University Hospital (Brussels, Belgium), Erasmus Hospital (Brussels) and Bois de la Pierre Clinical Centre (Wavre, Belgium). Diagnosis was made according to the research (for 10 patients) and clinical (for 7 patients) Budapest diagnostic criteria for CRPS.<sup>23</sup> Exclusion criteria were any neurological and severe psychiatric disorders, unresolved orthopaedic injuries as well



**Figure 1.** Visual straight-ahead task (V-SAT). The images illustrate the experimental setup of V-SAT from a front (A) and back (B) perspective, respectively. The robotic device holding the laser was placed on the platform fixed on the metal pole standing behind the participant. The laser flashed the red dot on the wall in front of the participant, above his/her vertex. The participant pressed a manual switch to stop the red dot at a position corresponding to the prolongation of the midsagittal plane of his/her body.

as uncorrected vision. One CRPS participant did not perform the V-SAT because of technical problems. VP-PT data from another CRPS participant were excluded from the analyses because of intense pain preventing optimal performance during the task. In the V-SAT (13 women, 3 men; 10 left hand CRPS, 6 right hand CRPS), the mean age of the CRPS participants was 54 years (SD = 5.44, range: 33–64 years). In the P-SAT (14 women, 3 men; 11 left hand CRPS, 6 right hand CRPS), mean age was 54 years (SD = 5.41, range: 33–64 years). In the VP-PT (13 women, 3 men; 10 left hand CRPS, 6 right hand CRPS), it was 53 years (SD = 5.31, range: 33–64 years). According to the Flinders Handedness Survey,<sup>44</sup> all participants were right-handed, except one who was left-handed (see details in

**Table 1**). Seventeen healthy volunteers were recruited as control participants and were individually matched to each of the CRPS patients according to their age (P-SAT: M = 54 years old, SD = 4.92, range: 35–64 years; V-SAT: M = 54 years old, SD = 4.75, range: 35–64 years; VP-PT: M = 53 years old, SD = 4.74, range: 35–64 years), sex, and handedness. Exclusion criteria for the control group were any chronic pain (diagnosed or not), head trauma, trauma of an upper limb during the past year, severe psychiatric or neurologic disorders as well as uncorrected vision. Experimental procedures were approved by the local ethic committee (Commission d’Ethique Biomédicale Hospitalo-Facultaire, Saint-Luc Hospital & Université catholique de Louvain) and conform to the Declaration of Helsinki. All



**Figure 2.** Proprioceptive straight-ahead task (P-SAT). The image A illustrates the sheet on which 181 lines radiated from  $-90^{\circ}$  to  $90^{\circ}$  with  $0^{\circ}$  having been aligned with the participant’s midsagittal plane by means of the red dot marker and the chinrest. Blindfolded, the participants pointed straight ahead with one of their index fingers towards a position on the sheet that they considered as corresponding to the prolongation of their body midline (B).

participants provided written informed consent before taking part in the study and received a financial compensation for their participation.

## 2.2. Apparatus and procedures

During V-SAT, participants were asked to stop a dot moving horizontally on a wall when it crossed the line they imagined prolonging their midsagittal plane. During P-SAT, participants were asked to point straight-ahead along their body midline. During VP-PT, they sat in front of a box and were asked to reach and point towards an object (ie, a pen) placed on the other side of the box, either straight-ahead in front of them or on the left and or right side. Conversely to V-SAT, P-SAT and VP-PT required movements with one of the upper limbs to reach and point the target. Participants were blindfolded during P-SAT, and the box prevented them from seeing the moving limb in VP-PT. For these 2 latter tasks, CRPS patients were tested with both the affected hand and unaffected hand in separate blocks. Performances of each control participant were coded according to the hands of the CRPS participant to

whom they were matched (eg, results of a control participant having performed the task with the left hand were coded as “affected hand” if matched to a CRPS participant with CRPS affecting the left hand). The tasks were performed in a randomized order. The experimenter (C.V.) was not blinded with regard to the group status of the participants.

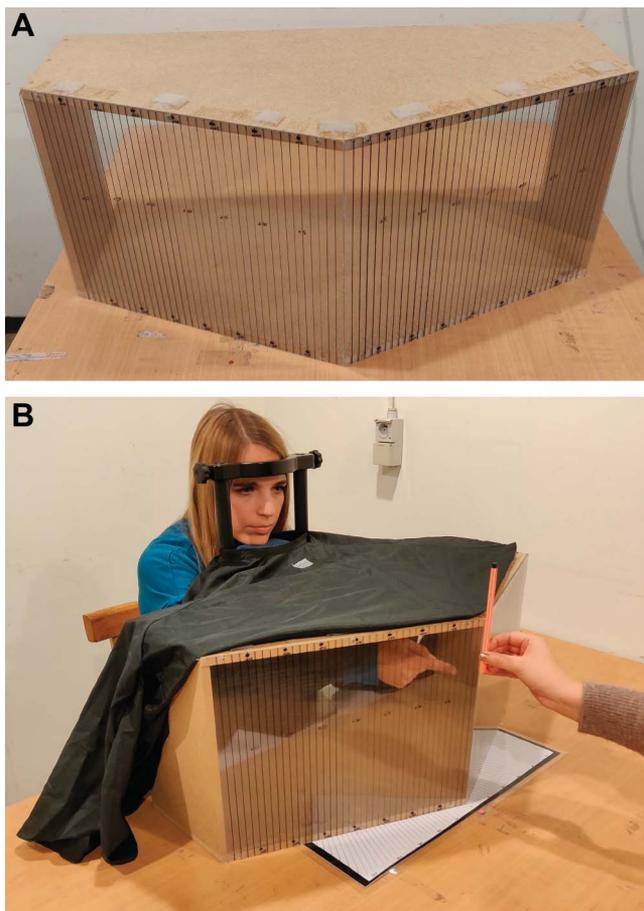
### 2.2.1. Visual straight-ahead task

Participants sat on a height-adjustable stool with their head stabilized on a chinrest to prevent any head movement, holding a manual switch in one of their hands (CRPS participants with their unaffected hand; each control participant with the same hand as the CRPS participant to whom he/she was matched, regardless of the handedness). The other hand rested in a comfortable position on the leg. The chinrest was placed on a fixed metallic support (94 cm height) 200 cm away from a white wall. A light dot was projected on the wall (0.25 cm diameter at target area) by means of a red laser (PICOTRONIC, 650 nm, 1 mV, LFD650-1-12(9x20)). The laser was rotated horizontally by a robotic device remotely controlled by a single-board microcontroller (Arduino Uno, Arduino.cc, Milan, Italy). Rotation speed of the laser was 3°/second. Devices were placed on a tray fixed on a metal pole and positioned behind the participants so that the laser was located at 159 cm high and at 260 cm from the wall. To ensure that the laser dot was projected at eye level on the wall, the height of the stool was adjusted so that the laser was located right above the participant’s vertex (**Fig. 1**). The laser position was calibrated before each session so that the 0° position of the laser matched the participant’s midsagittal line using the middle point of the chinrest as reference. To ensure full darkness of the room during the dark condition, all other sources of light were excluded from the room. The experiment was remotely controlled from the outside of the room.

Participants were presented with 40 trials separated in 2 blocks: 20 trials were performed with the room lighting switched on (light condition) and the other 20 trials with the light switched off (dark condition). The order of the blocks was counterbalanced. A trial began with the appearance of the red dot on the wall at a position randomly chosen from 20 possible positions between  $-30^\circ$  and  $-20^\circ$  and between  $20^\circ$  and  $30^\circ$  (one position per degree; negative values corresponded to left-sided positions, positive values to right-sided positions, relative to a calibrated  $0^\circ$ ). Participants were asked to press the button of the manual switch to initiate the dot displacement. If the starting position of the dot was on the left side, it moved rightward; if its position was right-sided, it moved leftward. Participants were instructed to press the switch button a second time to stop the dot as soon as it reached the position they estimated to correspond to the line prolonging their body midline, ie, the prolongation of the midsagittal plane of their body. The second press marked the end of the trial. The final position of the dot was then recorded by the Arduino and stored for offline analyses. After 2 seconds, the dot disappeared and the laser rotated to reach the starting position of the next trial. Participants were asked to respond as accurately as possible. The task took approximately 20 minutes and was preceded by a training session of 5 trials performed in the light with the experimenter in the room.

### 2.2.2. Proprioceptive straight-ahead task

Participants sat in front of a 53 cm long and 52 cm wide plastic-covered sheet displaying lines radiating from  $-90^\circ$  to  $90^\circ$ , one line per degree<sup>49</sup> (**Fig. 2**). Participants were asked to position their head on a chinrest spatially locked to the bottom edge of the graduated sheet



**Figure 3.** Visuoproprioceptive pointing task (VP-PT). The task was conducted using a box placed between the participant and the experimenter. The box was open on the participants’ side so that they could insert an upper limb into it (A). The top of the box was made of a wooden board so that the participants could not see their limb inside. On the other side, the experimenter raised an object up to the sight of the participants. The participants had to indicate the position of the object by pointing their index finger against the acrylic glass closing the box on the side of the experimenter. The latter could measure the position pointed by the participant using the graduations on the acrylic glass (B). Note that the box was precisely aligned with the participant’s midsagittal plane by means of the sheet used for P-SAT.

and aligned to a red dot marking the 0° of the sheet, so that participant's midsagittal plane was aligned with the 0° line of the graduated sheet.

During the experiment, participants were blindfolded. At the beginning of each trial, they were asked to position the index finger of the hand used to perform the task on the middle of their sternum. During each trial, they made a straight-ahead pointing movement with their index finger towards a position on the sheet that they considered as corresponding to the prolongation of their body midline. Participants were asked to move at their own speed, not too fast or too slow. The experimenter took note of the angle of the pointed line, and participants were asked to move back their index finger on their sternum. The task consisted of 40 trials of back and forth pointing movements, divided into 2 equal blocks. During one block, movements were made with the left hand, and during the other block with the right hand. The order of the blocks was counterbalanced. During a block, the unused hand rested on the participant's thigh in a comfortable position. The task took approximately 5 minutes and no training was completed before.

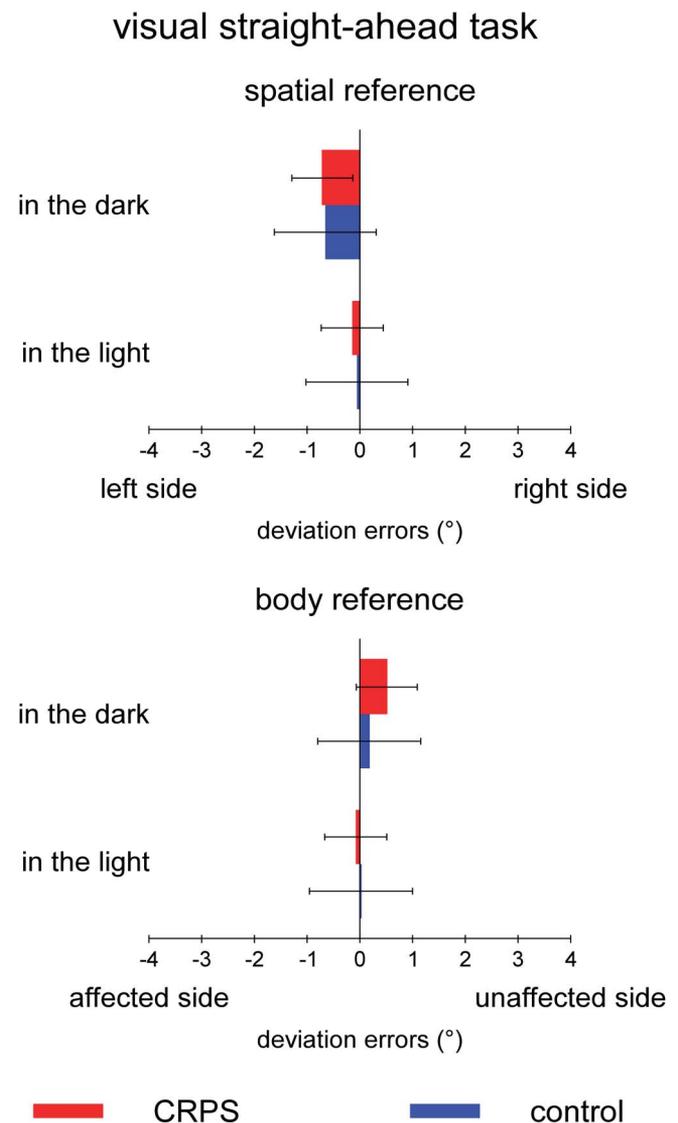
### 2.2.3. Visuoproprioceptive pointing task

Participants sat in front of a table with their head on a chinrest, the experimenter facing them on the other side of the table. In between, a 33 cm high, 75 cm wide, and 35.5 cm deep wooden box was placed on the table (Fig. 3; based on Refs. 16, 49). The top and bottom were pentagonal shaped panels with one 75 cm large side, two 19 cm sides, and two 41 cm sides. The side of the box corresponding to the 75 cm edge was open, whereas the sides corresponding to the 41 cm edges were closed by 2 translucent acrylic glass boards. The acrylic glass boards were graduated by means of vertical lines drawn every centimetre from 0 to 40 cm, with 0 cm corresponding to the intersection point between the 2 acrylic glass boards. The box was placed on the table, with the open part placed directly in front of the seated participant. The 75 cm edge was positioned at 17 cm from the table edge, so that participants could move their arms inside the box. The position of the box was calibrated so that the 75 cm edge was perpendicular to the participant's midsagittal planes and the intersection between the 2 acrylic glass boards prolonged their midsagittal planes. A black cloth was attached from the chinrest to the distal side of the box to prevent participants from seeing their arms.

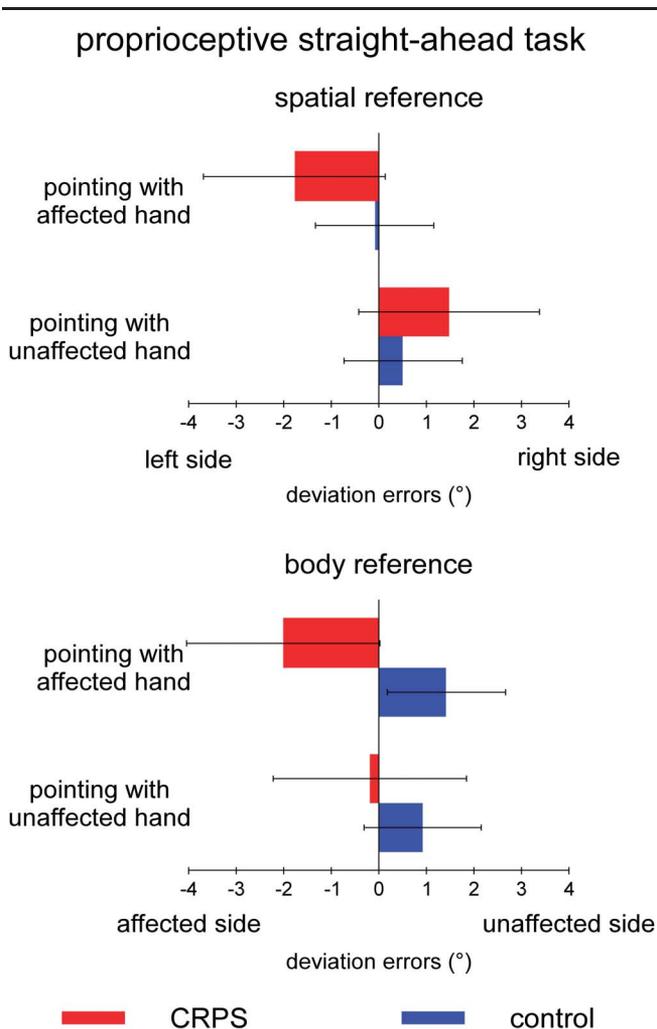
At the beginning of the task, and before each trial, participants were asked to place the hand used to perform the pointing task (ie, the pointing hand) on the middle of their sternum, and the unused hand on the thigh in a comfortable position. For each trial, the experimenter raised a target pen at 3 possible and randomly chosen positions on the acrylic glass boards, ie, at 0 cm, 21 cm leftward, or 21 cm rightward. About half of the pen was visible by the participants above the top panel of the box. Participants were asked to move the index finger of their active hand in the box and point towards the position of the pen according to the horizontal plane onto the acrylic glass. They were asked to move their hand at their own speed, not too fast or slow. The position of the index finger on the acrylic glass was noted by means of the graduation lines, and participants were asked to move back the active hand to their sternum before the next trial. Participants performed 2 blocks of back and forth pointing movements, one block with each hand, in a counterbalanced order. Each block was made of 60 trials during which each possible pen position was repeated 20 times. The task took approximately 20 minutes and no training was completed before.

### 2.3. Measures

In each task, performance was measured as a deviation error calculated for each trial, corresponding to the difference between the objective position of the target and the position subjectively estimated by the participants. For the V-SAT, the difference was measured in degree between the position where the dot was stopped and the laser position at 0° (ie, their actual body midline). For the P-SAT, the difference was measured in degree between the pointed line and the line at 0°. For the VP-PT, the difference was measured in centimetre between the pointed line on the acrylic glass and the true position of the pen. Visuoproprioceptive pointing task deviation errors were afterwards converted in



**Figure 4.** Deviation errors in the visual straight-ahead task. The figure illustrates the means of the deviation errors of the V-SAT for the CRPS (in red) and the control participants (in blue), according to whether the task was performed in the dark or in the light. The upper part of the figure illustrates the data of the spatial reference set, ie, the direction of the deviation coded according to the side of space (negative values = leftward deviations; positive values = rightward deviations). The lower part illustrates the data of the body reference set, ie, coded according to the direction of the deviation relative to the affected part of the body (negative values = deviations toward the side corresponding to the affected hemibody; positive values = deviations toward the side corresponding to the unaffected hemibody). Error bars indicate the 95% confidence intervals adapted according to the method of Cousineau.<sup>8</sup>



**Figure 5.** Deviation errors in the proprioceptive straight-ahead task. The figure illustrates the means of the deviation errors of the P-SAT for the CRPS (in red) and the control participants (in blue), according to whether the affected hand or the unaffected hand was used for pointing straight ahead. The upper part of the figure illustrates the data of the spatial reference set, ie, the direction of the deviation coded according to the side of space (negative values = leftward deviations; positive values = rightward deviations). The lower part illustrates the data of the body reference set, ie, coded according to the direction of the deviation relative to the affected part of the body (negative values = deviations toward the side corresponding to the affected hemibody; positive values = deviations toward the side corresponding to the unaffected hemibody). Error bars indicate the 95% confidence intervals adapted according to the method of Cousineau.<sup>8</sup>

degree using the angle between the objective and subjectively estimated positions of the pen on the top panel of the box with the middle of the chinrest at the height of the top panel as vertex of the angle. Note that in VP-PT, the 2 lateral positions of the pen were coded relatively to the affected side of CRPS participants' body (or to the matched side for the control participants), that is, whether it was presented ipsilaterally or contralaterally to the affected limb.

For the 3 tasks, data were coded according to 2 procedures in separate sets of analyses. In the first set, data from deviation errors were coded according to the side of space, ie, whether they were leftward vs rightward relative to participants' body, irrespective of which part of the body was affected by CRPS, and irrespective of which hand was used to perform the task in the P-SAT and VP-PT (spatial reference set). A positive value indicated a rightward deviation in pointing, and a negative value indicated a

leftward deviation. In the second set of analyses, data were recoded according to patients' affected hemibody, ie, according to whether the deviation errors were ipsilateral vs contralateral to the affected hand (body reference set). Indeed, some studies pointed out that cognitive biases in CRPS patients might be spatially locked to the side of space corresponding to the position of the affected limb.<sup>4,48,60–62</sup> To match the performances of all CRPS participants according to the affected limb, data of the participants with CRPS affecting their right limb and those of their matched controls were inverted (ie, multiplied by  $-1$  to obtain the additive inverse values). Consequently, negative values of the deviation errors corresponded to deviations towards the side ipsilateral to the affected hemibody, and positive values to deviations towards the contralateral, unaffected, side.

Values were then averaged for each participant according to each task condition, that is, lighting conditions (in the dark vs in the light) for the V-SAT, pointing hand (affected vs unaffected) for the P-SAT, and the target location (straight ahead vs in the ipsilateral side vs in the contralateral side) and pointing hand (affected vs unaffected) for the VP-PT.

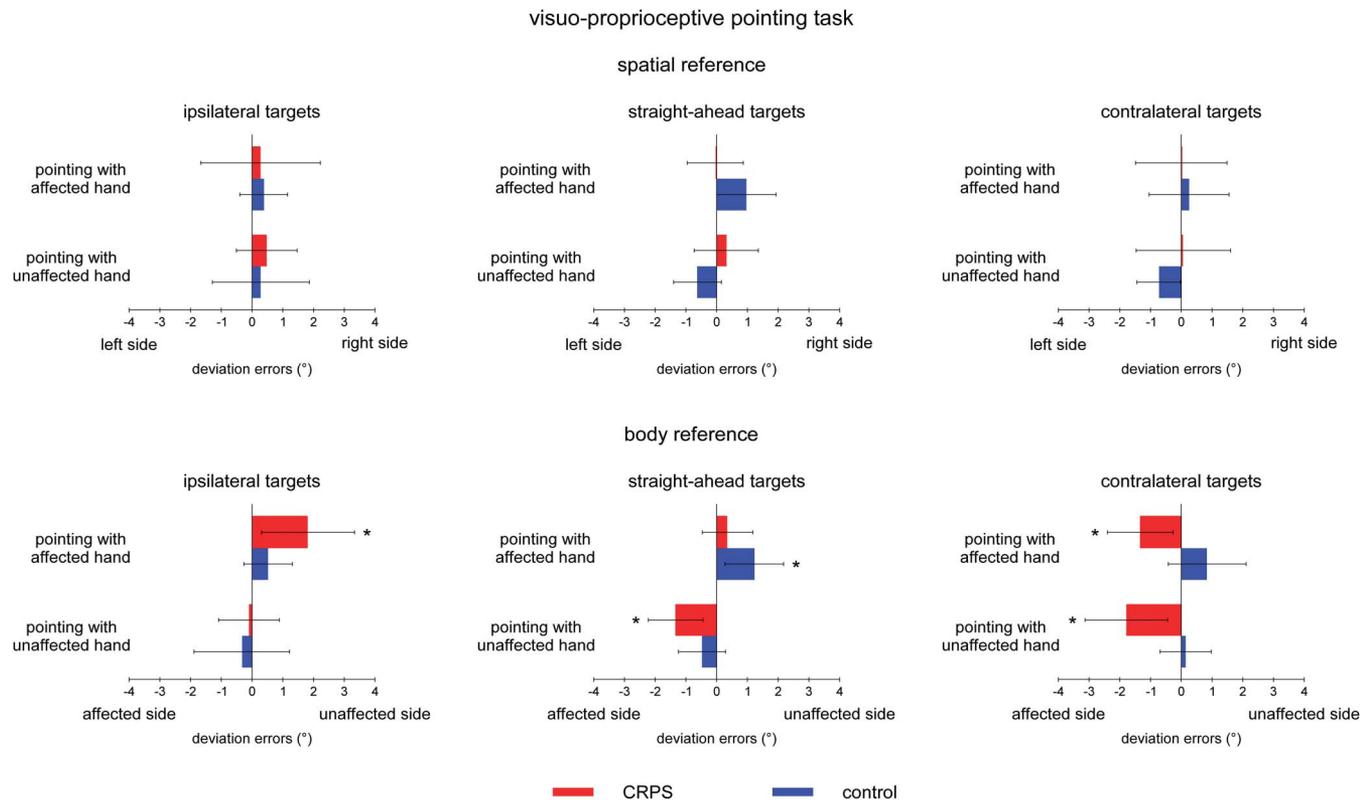
### 2.4. Data analyses

Analyses were done in the same way for the 2 sets of data. We first tested whether pointing performances were significantly deviated, by comparing deviation errors to 0 using one-sample t-tests for each condition of the 3 tasks and for each group. Next, performances between CRPS and control participants were compared for the different task conditions by means of analyses of variance (ANOVAs) with group (CRPS vs control) as the between-participant factor for the 3 tasks and the following within-participant factors: lighting (light vs dark) for the V-SAT, pointing hand (affected vs unaffected) for the P-SAT, and pointing hand (affected vs unaffected) and target location (straight ahead vs ipsilateral vs contralateral target) for the VP-PT. Effect sizes were measured using Cohen's *d* for t-tests and partial eta squared for ANOVAs. Greenhouse–Geisser corrections of the degrees of freedom were performed when the sphericity was not assumed. Contrast analyses were performed when needed (*P*-values are not corrected). Significance level was set at  $P \leq 0.05$ . Finally, classic frequentist statistical analyses were completed by Bayesian statistics using Bayesian repeated-measures ANOVA with JASP 0.12.2 (University of Amsterdam, the Netherlands). To this aim, we computed a Bayes factor ( $BF_{10}$ ) to quantify the alternative hypothesis (HA) relative to the null hypothesis (H0). Interpretations are based on the classification scheme established by Lee and Wagenmakers.<sup>33,70</sup>

It would have been interesting to include the hand dominance as a group factor to test whether the results could be impacted by the fact that CRPS affects the dominant vs nondominant hand. However, this would have decreased and unbalanced the size of the groups (**Table 1**) and, consequently, would have contributed to decreased statistical power. This variable was therefore discarded.

### 3. Results

Group-level results are illustrated in **Figures 4–6**, and individual performance of the CRPS participants are shown in **Figure 7**.



**Figure 6.** Deviation errors in the visuo-proprioceptive pointing task. The figure illustrates the means of the deviation errors of the VP-PT for the CRPS (in red) and the control participants (in blue), according to whether the affected hand or the unaffected hand was used for pointing to the target ipsilateral to the affected hand (left graphs), the target straight ahead (central graphs), and the contralateral target (right graphs). The upper part of the figure illustrates the data of the spatial reference set, ie, the direction of the deviation coded according to the side of space (negative values = leftward deviations; positive values = rightward deviations). The lower part illustrates the data of the body reference set, ie, coded according to the direction of the deviation relative to the affected part of the body (negative values = deviations toward the side corresponding to the affected hemibody; positive values = deviations toward the side corresponding to the unaffected hemibody). Error bars indicate the 95% confidence intervals adapted according to the method of Cousineau.<sup>8</sup> The stars (\*) indicate the conditions for which data were significantly different from 0 according to the *t*-tests.

### 3.1. Visual straight-ahead task

Regarding the first set of data measuring the direction of the biases according to the side of space (ie, spatial reference set: leftward vs rightward deviations; upper part of **Fig. 4**), none of the *t*-tests performed on V-SAT data were significantly different from 0 (CRPS: all  $|t(15)| \leq 1.15$ ,  $P \geq 0.267$ ,  $d \leq 0.30$ ; Controls: all  $|t(15)| \leq 0.69$ ,  $P \geq 0.501$ ,  $d \leq 0.18$ ; **Fig. 4**). The ANOVA did not reveal any significant main effect, neither for the *lighting* ( $F(1, 30) = 1.21$ ,  $P = 0.281$ ,  $\eta_p^2 = 0.04$ ) nor the *group* factors ( $F(1, 30) = 0.08$ ,  $P = 0.910$ ,  $\eta_p^2 < 0.01$ ), or significant interaction between the 2 factors ( $F(1, 32) = 0.00$ ,  $P = 0.977$ ,  $\eta_p^2 < 0.01$ ). Bayesian analyses revealed moderate evidence in favor of the null hypothesis for the *group* factor ( $BF_{10} = 0.320$ ), and anecdotal evidence for H0 the *lighting* factor ( $BF_{10} = 0.454$ ) and the interaction between the 2 factors ( $BF_{10} = 0.354$ ).

Similar results were observed for the second set of data measuring the direction of the biases according to the side of CRPS (ie, body reference set: ipsilateral vs contralateral to the affected limb; lower part of **Fig. 4**). Indeed, none of the *t*-tests were significantly different from 0 (CRPS: all  $|t(15)| \leq 0.81$ ,  $P \geq 0.430$ ,  $d \leq 0.21$ ; Controls: all  $|t(15)| \leq 0.19$ ,  $P \geq 0.852$ ,  $d \leq 0.05$ ; **Fig. 4**). The ANOVA did not reveal any significant effect, neither for the *lighting* ( $F(1, 30) = 0.49$ ,  $P = 0.487$ ,  $\eta_p^2 = 0.01$ ) nor the *group* factors ( $F(1, 30) = 0.03$ ,  $P = 0.867$ ,  $\eta_p^2 < 0.01$ ), or significant interaction between the 2 factors ( $F(1, 32) = 0.17$ ,  $P = 0.682$ ,  $\eta_p^2 < 0.01$ ). Bayesian analyses revealed moderate evidence in favor

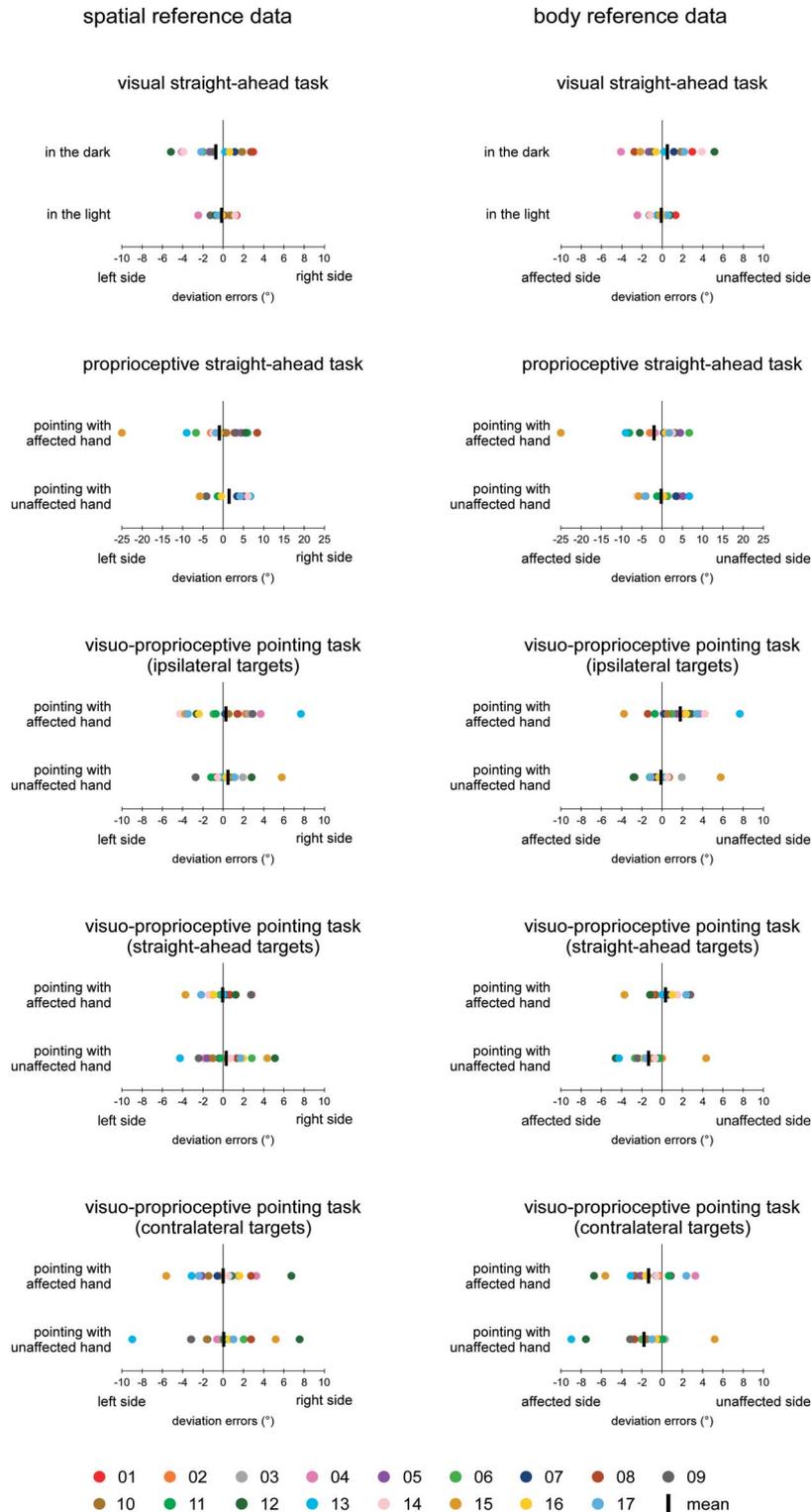
of H0 for the *lighting* ( $BF_{10} = 0.319$ ) and the *group* factors ( $BF_{10} = 0.324$ ) and anecdotal evidence for H0 regarding their interaction ( $BF_{10} = 0.413$ ).

This suggests that no significant deviation error and no significant difference between CRPS and control participants' performances were evidenced in the V-SAT.

### 3.2. Proprioceptive straight-ahead task

The *t*-tests performed on P-SAT data coded according to the side of space (upper part of **Fig. 5**) did not reveal any significant difference from 0 (CRPS: all  $|t(16)| \leq 1.52$ ,  $P \geq 0.147$ ,  $d \leq 0.38$ ; Controls: all  $|t(16)| \leq 0.39$ ,  $P \geq 0.701$ ,  $d \leq 0.10$ ; **Fig. 5**). The ANOVA did not show any significant effect of the *pointing hand* ( $F(1, 32) = 3.22$ ,  $P = 0.082$ ,  $\eta_p^2 = 0.09$ ), the *group* factor ( $F(1, 32) = 0.051$ ,  $P = 0.822$ ,  $\eta_p^2 < 0.01$ ), or significant interaction between the 2 factors ( $F(1, 32) = 1.55$ ,  $P = 0.222$ ,  $\eta_p^2 = 0.03$ ). Bayesian analyses revealed anecdotal evidence in favor of H0 for the *group* ( $BF_{10} = 0.341$ ) and the *pointing hand* factors ( $BF_{10} = 0.969$ ), as well as for their interaction ( $BF_{10} = 0.601$ ).

Similarly, the *t*-tests performed on data coded according to the side of CRPS (lower part of **Fig. 5**) were not significant (CRPS: all  $|t(16)| \leq 1.08$ ,  $P \geq 0.295$ ,  $d \leq 0.26$ ; Controls: all  $|t(16)| \leq 1.45$ ,  $P \geq 0.165$ ,  $d \leq 0.35$ ; **Fig. 5**), and the ANOVA did not show any significant effect of the *pointing hand* ( $F(1, 32) = 0.34$ ,  $P = 0.562$ ,  $\eta_p^2 = 0.01$ ), the *group* factor ( $F(1, 32) = 2.26$ ,  $P = 0.142$ ,  $\eta_p^2 =$



**Figure 7.** Individual scores of CRPS participants in the 3 tasks. The figure illustrates the deviation errors of each participant of the CRPS group for each condition of the 3 tasks, with the data coded according to the spatial reference (left part; negative values = leftward deviations; positive values = rightward deviations) and to the body reference (right part; negative values = deviations toward the side corresponding to the affected hemibody; positive values = deviations toward the side corresponding to the unaffected hemibody). Identification codes of the participants correspond to those of the Table 1. Note that because of the larger variability and the presence of outlier data, scale limits of the proprioceptive straight-ahead task are greater than for the other tasks.

0.07), or significant interaction between the 2 factors ( $F(1, 32) = 1.05, P = 0.313, \eta_p^2 = 0.03$ ). Bayesian analyses revealed moderate evidence in favor of H0 for *pointing hand* ( $BF_{10} =$

0.284), but anecdotal evidence for H0 for the *group* factor ( $BF_{10} = 0.736$ ) and the interaction with *group* ( $BF_{10} = 0.500$ ).

**Table 2**  
**Details of the ANOVAs performed on VP-PT data from the spatial reference set (left) and the body reference set (right), respectively.**

	Space reference set				Body reference set			
	<i>F</i>	<i>df</i>	<i>P</i>	$\eta_p^2$	<i>F</i>	<i>Df</i>	<i>P</i>	$\eta_p^2$
Group	0.06	1, 30	0.800	<0.01	4.35	1, 30	0.046	0.12
Pointing hand	0.31	1, 30	0.581	0.01	4.31	1, 30	0.047	0.13
Target location	0.66	1.09, 32.79	0.436	0.02	4.45	1.14, 34.24	0.038	0.13
Group × pointing hand	0.79	1, 30	0.380	0.03	0.49	1, 30	0.826	<0.01
Group × target location	0.08	1.09, 32.79	0.924	<0.01	8.68	1.14, 34.24	0.004	0.22
Pointing hand × target location	2.12	2, 60	0.129	0.07	6.24	2, 60	0.003	0.17
Group × pointing hand × target location	2.90	2, 60	0.063	0.09	2.31	2, 60	0.108	0.07

As for the V-SAT, analyses of the P-SAT did neither reveal any significant deviation errors in the 2 groups of participants, nor significant differences between them.

### 3.3. Visuoproprioceptive pointing task

None of the t-tests revealed deviation errors significantly different from 0 when VP-PT data were coded according to the side of space (upper part of **Fig. 6**; CRPS: all  $|t(15)| \leq 1.01$ ,  $P \geq 0.329$ ,  $d \leq 0.26$ ; Controls: all  $|t(15)| \leq 1.85$ ,  $P \geq 0.084$ ,  $d \leq 0.48$ ). The ANOVA did not reveal any significant effect of the *pointing hand* ( $F(1, 30) = 0.31$ ,  $P = 0.581$ ,  $\eta_p^2 = 0.01$ ), the *target location* ( $F(1.09, 32.79) = 0.66$ ,  $P = 0.436$ ,  $\eta_p^2 = 0.02$ ), the *group* factor ( $F(1, 30) = 0.06$ ,  $P = 0.800$ ,  $\eta_p^2 = 0.00$ ), or any significant interaction between these factors (all  $F(2, 60) \leq 2.90$ ,  $P \geq 0.063$ ,  $\eta_p^2 \leq 0.09$ ) (**Table 2**). Bayesian analyses revealed moderate to strong evidences in favor of H0 for all factors and interactions (all  $BF_{10} \leq 0.276$ ).

On the contrary, several t-tests were significant when data were coded according to side of CRPS (lower part of **Fig. 6**). In the control group, the only deviation errors significantly different from 0 were found when they pointed towards the target presented straight ahead with the hand matched to the affected hand of the CRPS participants to whom they were paired ( $t(15) = 2.52$ ,  $P = 0.043$ ,  $d = 0.65$ ). All the other values were not significantly different from 0 (all  $|t(15)| \leq 1.30$ ,  $P \geq 0.212$ ,  $d \leq 0.34$ ). By contrast, more significant deviation errors were found in the CRPS group, but their direction depended on where the target was presented relative to their affected limb, and which limb they used to point to it. When their unaffected hand was used, performances were significantly deviated towards the side of space corresponding to the affected hand when pointing towards the target located straight ahead ( $t(15) = -2.68$ ,  $P = 0.017$ ,  $d = 0.69$ ) and in the side contralateral to their affected limb ( $t(15) = -2.24$ ,  $P = 0.041$ ,  $d = 0.58$ ). Pointing to the pen in the ipsilateral side with the unaffected hand was not significantly deviated ( $t(15) = -0.194$ ,  $P = 0.849$ ,  $d = 0.05$ ). When their affected hand was used for pointing, performances were almost significantly deviated towards the affected side when pointing to the target located in the side contralateral to the affected part of the body ( $t(15) = -2.07$ ,  $P = 0.056$ ,  $d = 0.53$ ) and significantly deviated towards the unaffected side when pointing to the target located ipsilaterally to the affected part of their body ( $t(15) = 2.77$ ,  $P = 0.014$ ,  $d = 0.71$ ). Pointing to the target located straight ahead with their affected hand was not significantly deviated ( $t(15) = 0.85$ ,  $P = 0.408$ ,  $d = 0.22$ ).

The ANOVA performed on the VP-PT data of the body reference set revealed a significant main effect of *group* ( $F(1,30) = 4.35$ ,  $P = 0.046$ ,  $\eta_p^2 = 0.12$ ) that significantly interacted with the *target location* factor ( $F(1.14,34.25) = 8.68$ ,  $P = 0.004$ ,  $\eta_p^2 = 0.22$ ). Contrasts analyses showed that deviation errors were significantly different between CRPS and control participants when pointing to the target located straight ahead ( $F(1,30) = 7.87$ ,  $P = 0.009$ ,  $\eta_p^2 = 0.21$ ) and in the side of space contralateral to the affected limb ( $F(1,30) = 8.82$ ,  $P = 0.006$ ,  $\eta_p^2 = 0.23$ ), irrespective of which hand was used (the *group\*target location\*pointing hand* interaction was not significant:  $F(2,60) = 2.31$ ,  $P = 0.108$ ,  $\eta_p^2 = 0.07$ ). Deviations were not significantly different between the groups when pointing to the target ipsilateral to the affected limb ( $F(1, 30) = 2.41$ ,  $P = 0.131$ ,  $\eta_p^2 = 0.07$ ). The ANOVA also revealed significant main effects of the *pointing hand* ( $F(1,30) = 4.31$ ,  $P = 0.047$ ,  $\eta_p^2 = 0.12$ ) and the *target location* factors ( $F(1.14,34.24) = 4.45$ ,  $P = 0.02$ ,  $\eta_p^2 = 0.13$ ) with a significant interaction between the 2 factors ( $F(2,60) = 6.24$ ,  $P = 0.003$ ,  $\eta_p^2 = 0.17$ ), irrespective of the group of participants. This interaction is explained by the fact that deviation errors were significantly different when pointing with the affected hand (or the hand matched to the CRPS affected hand for control participants) towards the target located straight ahead vs contralateral to the affected hand ( $F(1,30) = 8.03$ ,  $P = 0.008$ ,  $\eta_p^2 = 0.21$ ), and towards the ipsilateral vs contralateral target ( $F(1,30) = 8.03$ ,  $P = 0.008$ ,  $\eta_p^2 = 0.21$ ). The other results were not significant (**Table 2**). Frequentist analyses are corroborated by Bayesian analyses as they revealed extreme evidence in favor of the alternative hypotheses supporting the contribution of the main effects of the *group*, *pointing hand*, and *target location* factors and the interaction between *group* and *target location* ( $BF_{10} = 1165.461$ ). Adding the *pointing hand\*target location* interaction also revealed strong evidence in favor of these HA ( $BF_{10} = 302.288$ ).

## 4. Discussion

This study was aimed to evaluate spatial cognition abilities of CRPS patients, more precisely their ability to use the egocentric reference frame to locate external objects and their own body limbs. Patients with upper-limb CRPS and matched control participants were asked to locate a visual stimulus relative to their own body midline (V-SAT), to manually point to a spatial position corresponding to their body midline (P-SAT) and to reach and point with their hands to the position of a visually presented target in their surrounding space (VP-PT).

Although V-SAT and the P-SAT did not show significant deviations in CRPS patients, they made more and significantly larger errors in the VP-PT as compared to control participants. Our V-SAT results are in line with those reported in previous studies,<sup>6,29,72</sup> and failed to replicate the systematic deviation biases observed in other studies.<sup>49,59–61,65</sup> Similarly, we could not evidence any significant deviation in the P-SAT as observed by Christophe et al.<sup>6</sup> (see however, 7, 25).

To the best of our knowledge, the VP-PT has never been used to characterize spatial perception deficits in CRPS participants, except for one study that used it to evaluate the efficiency of prismatic adaptation rehabilitation<sup>6</sup> (see below). The deviation errors we observed in CRPS participants were not systematically directed towards one specific side of space or towards one particular part of the body. On the contrary, they were mostly related to the location of the target and the limb used to reach it. It is noteworthy that deviation errors were observed whether pointing movements were performed with the CRPS participants' affected or unaffected hand.<sup>69</sup> In other words, although CRPS participants were able to correctly use their egocentric reference frame to locate visual stimuli in external space or to position their limbs, they seemed less able to coordinate proprioceptive information about limb position and visual information about the to-be-reached target in the absence of visual feedback about the position of their limb and its trajectory. Similarly, Brun et al.<sup>3</sup> showed that CRPS participants have difficulties to estimate upper-limb movement when visual information about its actual position is lacking. Planning and controlling goal-directed movements depend on the ability to take into account and integrate multiple signals about body posture and the relative position of the body parts. Studies have highlighted distinctive roles for proprioceptive vs visual cues about limb position. For instance, it has been suggested that vision would be mainly used to generate a kinematic schema of the movement, whereas proprioception would be mostly used to translate such a schema into motor commands.<sup>54</sup> Movements are more accurate when both proprioceptive and visual cues about limb position are available.<sup>68</sup> However, several studies have also emphasized the importance of vision in controlling movement.<sup>51,53,63,71</sup> Yet, at the perceptual level, vision of the limb has been shown to facilitate multisensory interaction between somatic and extrasomatic inputs.<sup>19,32,38,41</sup> Regarding motor control, preventing or distorting vision of the limb has been shown to induce trajectory deviation and endpoint errors.<sup>9,24,51,64</sup> Accordingly, the present results would suggest that CRPS participants were less able than control participants to compensate the absence of vision to adequately use proprioceptive information to estimate limb position and controlling limb movement. Despite the fact that previous data suggested deficits in processing proprioceptive inputs in CRPS,<sup>1,36</sup> this may not be considered as the primary explanation for the poorer pointing performance of our CRPS participants since we did not observe significant deviation errors in the P-SAT (see also<sup>6</sup>). Studies have suggested that during motor movements that require the combination of several sensory inputs, such as visual vs proprioceptive cues about limb position, the contribution of each sensory input would be weighted based on probabilistic estimation of its reliability.<sup>30,31</sup> The contribution of each sensory input would be adapted based on the stage of the motor plan or control at which it would be needed,<sup>57</sup> as well as on internal factors such as handedness<sup>20</sup> or attention,<sup>37</sup> or external factors such as the properties of the task and the to-be-reached target.<sup>58</sup> Following such a theoretical framework, the present data could possibly indicate that CRPS-related cognitive deficits are not specifically resulting from

unbalanced perception and representation between the affected vs unaffected hemibodies and their respective surroundings, but would instead result from difficulties in correctly integrating and adapting the relative contribution of sensory information during motor planning and control. We hypothesize indeed that CRPS participants seemed to have more difficulties to compensate the loss of visual cues to estimate the limb position and to adapt the contribution of proprioceptive information to spatially guide movement of the limb towards the visual target. Alternatively, we might also hypothesize that controlling movement only based on proprioceptive inputs without any visual feedback about limb position might be more effortful. Because chronic pain can impair cognitive functions such as attention,<sup>39</sup> we then suggest that compensating the lack of visual information with only proprioceptive feedback could have overloaded CRPS patient's attentional abilities.

The present data can give insights to better understand and adapt cognitive rehabilitation used to treat CRPS. For instance, prismatic adaptation (PA) was shown to efficiently alleviate pain and other CRPS symptoms<sup>4,6,21,60</sup> (see Ref. 62 for review). Prismatic adaptation, usually used to rehabilitate HSN symptoms, is a procedure that is aimed at inducing a sensory-motor adaptation, triggered by the participants engaging in a perceptual motor task while wearing goggles that induce an optical shift towards one side of their visual field. Typically, HSN patients exposed to PA exhibit a compensation of their visuospatial deficits and spatial cognition disorders.<sup>26,46,52</sup> Regarding CRPS, based on V-SAT results having shown deviation biases to the detriment of the side of space contralateral to the participants' affected hemibody, Sumitani et al.<sup>60</sup> used prisms inducing an optical shift to that specific side, ie, away from the affected body part. Significant pain relief was observed in all 5 patients after 2 weeks of PA performed with the affected limb. Interestingly, the follow-up of one of the patients showed that PA with an optical shift in the opposite direction, that is, toward the affected hemibody, tended to worsen pain. Similarly, Bultitude and Rafal<sup>4</sup> showed in a single case significant reduction of pain and improvement of the range of motion of the affected hand when the adaptation was done with the affected hand, but not with the unaffected one. These results were recently replicated by Christophe et al.<sup>6</sup> who showed significant reduction of CRPS symptoms after PA with an optical shift towards the side of the unaffected limb, despite the absence of significant deviation during V-SAT and other perceptual visuospatial and visuomotor tasks. In line with the present data, these latter results are puzzling as they address the crucial question of the direction of the optical shift during PA. First of all, Sumitani et al.<sup>60</sup> used a shift towards the side of the unaffected hand, which corresponded to the biased side of space as measured with the V-SAT. However, the rationale for using PA in HSN mostly relied on shifts of the P-SAT.<sup>26,46</sup> Hemispatial neglect patients show shifts in straight-ahead judgements and pointing towards the side ipsilateral to their lesion, and PA uses optical shift towards the ipsilesional (ie, nonneglected) side. Crucially, PA induces opposite shifts for V-SAT and P-SAT<sup>26,50</sup>: it induces a visual shift in the direction of the optical deviation while a compensatory shift is observed in the opposite direction during manual straight-ahead pointing. This implies that the direction of the optical shift must be chosen carefully. The lack of replication of the V-SAT deviation suggests that an efficient PA should probably not be based on an optical shift determined by visuospatial abilities in CRPS. Importantly, a recent study showed reduction of CRPS symptoms after prism exposure, but without significant difference between patients who wore prisms inducing an optical shift towards the side of the

unaffected limb and those who wore neutral prisms, ie, that distorted acuity and clarity of vision without laterally shifting the visual field.<sup>21</sup> Christophe et al.<sup>6</sup> proposed that PA could possibly alleviate CRPS symptoms by realigning proprioceptive and visuospatial reference frames. Their interpretation is partially based on the idea that CRPS patients can show opposite perceptual deviations when processing somatic vs extrasomatic inputs (see Ref. 47). However, the present results suggest that the direction of cognitive bias might not be the essential feature in the cognitive symptomatology in CRPS. Based on the VP-PT data, we rather hypothesize that the visuomotor tasks performed during PA could force CRPS patients to readapt multisensory integration between the different sensory signals informing them about the state of their limbs during goal-directed movements.

We conclude that cognitive impairments in CRPS are not specifically characterized by a direction-specific perceptual and representational imbalance between the 2 parts of the body and their respective surroundings in extrapersonal space. Instead, CRPS patients might be impaired in integrating various sensory signals used to control goal-directed movements of their limbs.

### Conflict of interest statement

The authors have no conflicts of interest to declare.

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