An investigation of perceptual biases in complex regional pain syndrome

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Patients with complex regional pain syndrome (CRPS) report cognitive difficulties, affecting the ability to represent, perceive and use their affected limb. Moseley et al. (https://doi.org/10.1093/brain/awp224) observed that CRPS patients tend to bias the perception of tactile stimulation away from the pathological limb. Interestingly, this bias was reversed when CRPS patients were asked to cross their arms, implying that this bias is embedded in a complex representation of the body that takes into account the position of body-parts. Other studies have failed to replicate this finding (doi:10.1038/s41598-017-10077-8) or have even found a bias in the opposite direction (e.g. doi:10.1212/01.wnl.0000250242.99683.57). Moreover, perceptual biases in CRPS patients have not often been compared to these of other chronic pain patients. Chronic pain patients are often characterized by an excessive focus of attention for bodily sensations. We might therefore expect that non-CRPS pain patients would show a bias *towards* instead of away from their affected limb. The aim of this study was to replicate the study of Moseley et al. (https://doi.org/10.1093/brain/awp224) and to extend it by comparing perceptual biases in a CRPS group with two non-CRPS pain control groups (i.e. chronic unilateral wrist and shoulder pain patients). In a temporal order judgment (TOJ) task, participants reported which of two tactile stimuli, one applied to either hand at various intervals, was perceived as occurring first. TOJs were made, either with the arms in a normal (uncrossed) position, or with the arms crossed over the body midline. We found no consistent perceptual biases in either of the patient groups and in either of the conditions (crossed/uncrossed). Individual differences were large and might, at least partly, be explained by other variables, such as pain duration and temperature differences between the pathological and non-pathological hand. Additional studies need to take these variables into account by, for example, comparing biases in CRPS (and non-CRPS) patients

in an acute versus a chronic pain state.

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31 **Abstract**

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33 ability to represent, perceive and use their affected limb. Moseley et al.

34 (https://doi.org/10.1093/brain/awp224) observed that CRPS patients tend to bias the

35 perception of tactile stimulation away from the pathological limb. Interestingly, this bias was

36 reversed when CRPS patients were asked to cross their arms, implying that this bias is

37 embedded in a complex representation of the body that takes into account the position of body

38 parts. Other studies have failed to replicate this finding (doi:10.1038/s41598-017-10077-8) or

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41 not often been compared to these of other chronic pain patients. Chronic pain patients are

42 often characterized by an excessive focus of attention for bodily sensations. We might

43 therefore expect that non-CRPS pain patients would show a bias *towards* instead of away from

44 their affected limb. The aim of this study was to replicate the study of Moseley et al. (

45 https://doi.org/10.1093/brain/awp224) and to extend it by comparing perceptual biases in a

46 CRPS group with two non-CRPS pain control groups (i.e. chronic unilateral wrist and shoulder

47 pain patients). In a temporal order judgment (TOJ) task, participants reported which of two

48 tactile stimuli, one applied to either hand at various intervals, was perceived as occurring first.

49 TOJs were made, either with the arms in a normal (uncrossed) position, or with the arms

50 crossed over the body midline. We found no consistent perceptual biases in either of the

51 patient groups and in either of the conditions (crossed/uncrossed). Individual differences were

52 large and might, at least partly, be explained by other variables, such as pain duration and

53 temperature differences between the pathological and non-pathological hand. Additional

54 studies need to take these variables into account by, for example, comparing biases in CRPS

55 (and non-CRPS) patients in an acute versus a chronic pain state.

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1. Introduction

61   Complex regional pain syndrome (CRPS) is a chronic disorder associated with sensory, motor,

62   autonomic and trophic symptoms such as pain, temperature change, skin color change,

63   swelling, and limited movement in usually one limb. CRPS often follows a minor or mild trauma

64   to a limb [1]. The pathophysiology of CRPS is complex and still poorly understood,

65   encompassing both structural and functional changes of the central nervous system [2–9]. It

66   has been shown that CRPS is associated with cognitive dysfunctions affecting the mental

67   representation [10], the perception and the use of the affected part of the body [11]. Patients

68   report that moving the affected limb is slow, requires effort and involves conscious control

69   [12,13]. Studies have revealed that patients have difficulties with the perception of the shape

70   and the position of the affected limb [14–19]. Moreover, it has been shown that CRPS is

71   associated with a spatially-defined disruption of motor performance [20,21]. The limb may even

72   feel disconnected from the body [12,13]. Some authors have argued that CRPS has similarities

73   to hemispatial neglect [11,13], a syndrome consecutive to a brain lesion and characterized by a

74   deficit in perceiving and exploring stimuli at the side of space contralateral to the damaged

75   cortical hemisphere [22,23]. However, the idea that the cognitive symptomatology in CRPS is

76   akin to hemispatial neglect is contested [11,24–29].

77   Studies have shown that CRPS patients also tend to have more difficulties to perceive

78   somatosensory stimuli applied to the affected part of the body [30,31]. For instance, Moseley

79   et al. [32] used a temporal order judgment (TOJ) task, in which participants have to judge which

80   of two tactile stimuli applied to either hand in rapid time succession was perceived as being

81   delivered first. They showed that CRPS patients gave priority to the processing of the tactile

82   stimulus applied to the healthy hand at the detriment of the processing of the stimulus applied

83   to the affected hand. Intriguingly, this pattern was reversed when the hands were crossed over

84   the body midline, that is, the line separating the body in two equal parts according to its sagittal

85   plane. Priority was given to the processing of the stimulus applied on the affected hand to the

86 detriment of the processing of the stimulus applied to the healthy hand. This pattern of result

87 seems to indicate that CRPS patients have difficulties to perceive stimuli arising at the side of

88 space corresponding to the pathological part of the body, rather than at their affected limb

89 itself whatever its position. Furthermore, it indicates that the observed perceptual deficits

90 cannot be accounted for by deficits at the peripheral coding and the spinal transmission of

91 somatosensory inputs [33], but involve higher order cortical mechanisms [34]. Conversely,

92 Filbrich et al. [35] used a similar TOJ tasks with either visual or vibrotactile stimuli and found

93 that a bias towards the unaffected side of space was present only for the visual stimuli.

94 Visuospatial biases in CRPS were also found in a study of Bultitude et al. [36] who have shown

95 in addition that patients' judgements about lateralized visual stimuli can be impacted by the

96 posture of the limb, that is, if the hands are crossed or uncrossed. These latter results suggest

97 that lateral cognitive difficulties in CRPS are not only determined by which side of the body is

98 affected, but also depend on the actual position of the pathological limb (see [37]). Moreover,

99 Bultitude et al. [36] found that the strength of the attentional bias was predicted by scores on a

100 self-report measure of body perception distortion, but not by pain intensity, time since

101 diagnosis or affected body site.

102 Apart from the lack of clarity regarding the precise nature of the cognitive deficits in CRPS

103 patients, the specificity of these deficits for CRPS still has to be demonstrated. CRPS patients'

104 performance are rarely compared to those of patients suffering of other types of chronic pain

105 conditions. For example, Frettlöh et al. [38] observed that patients with CRPS reported

106 significantly more disownership feelings and underuse of their painful limb as compared to

107 patients with chronic pain syndromes of other origins. However nothing is described about the

108 exact nature of these non-CRPS conditions, and most importantly, whether the body is affected

109 unilaterally or bilaterally. Similarly, despite the fact that Kolb et al. [26] did not notice any

110 difference between patients suffering from CRPS and non-CRPS chronic pain conditions

111 affecting upper limbs, it is worth noting that for an important number of patients (8/20) of the

112 non-CRPS chronic pain group both limbs were affected. Uematsu et al. [39] compared

113 performances of CRPS patients to those of patients with post-herpetic neuropathic pain and

114 observed shifts of visual subjective body midline judgments only for CRPS patients. Moseley et

115 al. [40] found that imagined movements increased pain and swelling to the same extent in

116 patients with CRPS as compared to non-CRPS pain patients. However, CRPS patients were on

117 average slower to recognize their affected hand compared to their unaffected hand. This could

118 be in accordance with studies suggesting that non-CRPS chronic pain patients have a

119 *heightened* attention for bodily sensations [41,42]. We could therefore expect that these

120 patients, in contrast to CRPS patients, would show a perceptual bias towards their affected

121 limb, instead of away from their affected limb. One study of Moseley et al. [43] contradicts this

122 hypothesis. In this study unilateral back pain patients performed a TOJ task with tactile stimuli

123 delivered to either side of their lower back. Similar to the results found in CRPS patients, stimuli

124 presented on the unaffected side were prioritized in favor of those presented to the affected

125 side. However, no CRPS patients were included in this study, so no direct comparison between

126 CRPS and non-CRPS patients was made.

127  The aim of the study was to replicate the findings of Moseley et al. [32] on space-based

128 perceptual biases in patients with CRPS to clarify the exact nature of the cognitive deficits

129 observed in this patient group, and to extend these results by comparing a CRPS group with two

130 non-CRPS pain control groups to verify whether these space-based biases are specific to CRPS

131 patients. To this end, CRPS patients performed temporal order judgment tasks using pairs of

132 tactile stimuli applied to either hand, and their performances were compared to those of two

133 groups of patients with lateralized chronic pain but not from CRPS origin: a group patients with

134 unilateral wrist pain and a group of patients with unilateral shoulder pain. The TOJ task was

135 performed either with the arms in a normal uncrossed posture or with the arms crossed over

136 the body midline so that each arm laid in the opposite side of space. If lateralized cognitive

137 deficits are not specific for CRPS patients, we expected to observe biased TOJs also in the other

138 patient groups. In addition, given that somatosensory inputs can be spatially coded according to

139 different reference frames, different hypotheses can be proposed. If the direction of the biases

140 depends on an *anatomical* reference frame, they should affect the perception of the stimuli

141 applied on the pathological limb whatever its position in external space. On the contrary, if the

142 direction of the biases depends on an *external space* reference frame, they would not depend

143   on the limb posture and participants' judgments should be biased towards the side of space in

144   which their affected limb normally resides [32].

2. Methods

2.1.   Participants

147   Participants aged between 18 and 70 years were recruited from January 2014 until May

148   2015 at Ghent university hospital and the Ghent Maria Middelares hospital. Three groups of

149   participants were recruited (see criteria below): (1) patients with Complex Regional Pain

150   Syndrome type I (CRPS) of one of the upper limbs, (2) patients with unilateral wrist pain and (3)

151   patients with unilateral shoulder pain. Participants from all groups were included when they

152   were native Dutch speaking and had experienced unilateral upper limb pain for longer than 3

153   months. They were excluded when they also reported pain at the opposite side of the body

154   with respect to their affected limb, nerve injury (e.g. CRPS type II), ongoing limb trauma or

155   recent (< 3 weeks) surgery of the painful limb. At entry, all participants were tested with the

156   same battery of tests to either confirm (in case of CRPS patients), or rule out (in case of wrist

157   and shoulder pain patients) the diagnosis of CRPS according to the Budapest criteria (see

158   Appendix). All patients had normal or corrected to normal vision. We aimed at recruiting 20

159   patients in every group. The study was approved by the Ethics Committee of University Hospital

160   Ghent (registration number: 2013/706) in agreement with the Declaration of Helsinki. All

161   participants gave their written informed consent and received a compensation.

2.2.   Self-report measures

163   Participants completed an ad hoc questionnaire assessing socio-demographic characteristics,

164   the Pain Grading Scale (PGS; [44]), and a Hand Dominance Questionnaire [45].

165   After each experimental block, a series of self-report items assessed i) the intensity of the

166   vibrotactile stimuli on each hand (Likert scale from 0 "not intense at all" to 10 "very intense");

167   ii) to what extent they were able to concentrate during the task (Likert scale from 0 "not at all"

168   to 10 "very well"); iii) to what extent they experienced the task as fatiguing (Likert scale from 0

169   "not at all" to 10 "very much"). At the end of the experiment, additional items assessed to what

170   extent participants iv) directed their attention to the vibrotactile stimuli; v) made an effort to

171   complete the task; vi) experienced fear/tension during the task and vii) found the task

172   meaningful (all measured on a Likert scale from 0 "not at all" to 10 "very much"). Participants

173   also completed a set of self-report questionnaires (see full methods and recruitment flow

174   charts presented here: http://hdl.handle.net/1854/LU-7179946), but these results were not

175   used for the purpose of this study and are therefore not further discussed.

176   **2.3 Stimuli and apparatus**

177   Participants were seated in a dimly lit room with their hands, palms down, resting on a table

178   (see Figure 1). The distance between the edge of the table, near the trunk, and the index

179   fingers was 35 cm and the distance between both index fingers was 40 cm. 35 cm in front of the

180   imaginary line connecting both index fingers, a red fixation LED was positioned in the middle of

181   this line. The participant's head was maintained static using a chin rest. To protect them from

182   any auditory distraction, all participants wore headphones through which continuous white

183   noise (46 dB) resounded. The experimenter was sitting opposite to and facing the participant.

184   [enter Figure 1 here]

185   Vibrotactile stimuli were delivered using two magnet linear actuators (C-2 TACTOR,

186   Engineering Acoustics, Inc., Florida), attached to the sensory territory of the superficial radial

187   nerve of each hand (10 ms duration, 200 Hz). The actuators were driven by self-developed

188   software and a controlling device that converted electrical signals (Watt) into oscillating

189   movements of the actuators against the skin. The intensity of the vibrotactile stimuli were

190   determined individually and matched between both hands by means of a double random

191   staircase procedure, based on the staircase procedure of Levitt [46]. In the first part of the

192   procedure, 16 stimuli presented on the left hand were judged relative to a reference stimulus

193   with maximum intensity (power = 0.21 Watt) on a 5-point Likert scale ranging from 1 ("almost

194   no sensation") to 5 ("maximum intensity"). The intensity that corresponded to an average

195   rating of 3 was selected as the stimulus intensity for the left hand and served as the reference

196   stimulus for the second part of the staircase procedure. In the second part, another 16 stimuli

197   were presented, now to the right hand, and were compared to the selected reference stimulus

198   on the left hand on a 5-point Likert scale (1 = "more than less strong", 2 = "less strong", 3 =

199 "equally strong", 4 = "stronger", 5 = "much stronger"). The intensity that resulted in an

200 averaged rating of 3 was selected as the intensity for stimuli on the right hand.

2.4 Procedure

202 In the first phase of the study, participants completed the socio-demographic questionnaire,

203 the Pain Grading Scale and the Hand Dominance Questionnaire (~10 minutes). In the second

204 phase, participants were seated and the diagnostic screening (interview + testing) for CRPS took

205 place (~20 minutes). In the third phase of the study (~90 minutes) during which the TOJ task

206 was performed, the experimenter attached the actuators to the hands and gave the

207 participants instructions about the staircase procedure. Following this, the headphones were

208 turned on and the staircase procedure was initiated. Responses were inserted manually on a

209 keyboard by the experimenter. As soon as the staircase procedure was finished, headphones

210 were temporarily removed.

211 During the TOJ task, participants were instructed to fixate their gaze on a red LED in front of

212 them, to place their chin in the chin wrest and to keep their hands still on the table throughout

213 the task. After receiving these instructions, headphones were turned back on. The TOJ task

214 started with three practice blocks of increasing difficulty. In the first practice block (8 trials),

215 participants were administered only one tactile stimulus in each trial (4 left and 4 right, in

216 random order) and were asked to locate the stimulus ("*left*" versus "*right*") in order to practice

217 response mapping. In the second practice block (12 trials), pairs of tactile stimuli were

218 administered one to either hand and separated by the three largest stimulus onset

219 asynchronies (SOA's) used during the experiment, i.e., ±200, ±90 or ±55ms (negative values

220 indicating that the stimulus to the left hand was applied first, positive values that the stimulus

221 to the right hand was applied first) [47]. Participants had to report verbally which of the stimuli

222 they perceived as first delivered ("*left first*" versus "*right first*"). The third practice block (18

223 trials) was identical to the second but was made up of 18 trials and participants were asked to

224 cross their hands over the body midline (which arm was on top was counterbalanced). When

225 instructions were not completely understood, or if performance was suboptimal, practice

226 blocks were repeated until performance was satisfactory. In addition, participants could only

227 proceed from the third practice block to the first experimental block when a minimal

228 performance of 75% was achieved on trials with the highest SOA (±200ms).

229 During the experiment proper, 4 blocks of 60 trials each were presented to the participants.

230 Each trial was made up of a pair of tactile stimuli one administered to the left and one on the

231 right hand, according to 5 possible SOAs ranging from 10 to 200ms [48,49]. The ten different

232 trial types (±200, ±90, ±55, ±30, ±10ms) were delivered six times each in the four blocks in

233 random order [47]. The position of the arms was either uncrossed or crossed. This position was

234 alternated between blocks and the order was counterbalanced across participants. Each trial

235 started with the illumination of the red fixation LED for 1s, followed by the first tactile stimuli of

236 the pair. Participants reported verbally on which hand they perceived the stimulus as first

237 delivered ("*left hand*" versus "*right hand*"), regardless of arm position. The experimenter

238 inserted these responses manually on a keyboard (a = "left *hand*", p = "right *hand*").

239 Participants were asked to maintain a steady pace in responding and to be as accurately as

240 possible. After each experimental block, participants filled in the post-block items and

241 temperature was reassessed on the back of both hands.

242 **2.5 TOJ measures**

243 Based on the procedure of Spence, Shore and Klein [50], the proportion of trials on which

244 participants reported the tactile stimulus on their painful limb first was calculated for each

245 participant, for each SOA and for each posture (crossed vs. uncrossed arm position). A sigmoid

246 function was then fitted to these proportions and a standardized cumulative normal

247 distribution (probits) was used to convert the proportion of left hand/right hand first responses

248 (left hand first when the left hand/wrist/shoulder was painful, right hand first when the right

249 hand/wrist/shoulder was painful) into a z-score. The best-fitting straight line was computed for

250 each participant and for both postures (crossed vs. uncrossed arm position) and the derived

251 slope and intercept were used to calculate the point of subjective simultaneity (PSS) and the

252 just noticeable difference (JND).

253 The PSS refers to the point at which a participant reports the two tactile stimuli (on the left

254 and right hand) as occurring first equally often. This point can be interpreted as the SOA value

255   that corresponds to a 0.5 proportion of left hand/right hand first responses [50]. The PSS is

256   calculated by taking the opposite of the intercept and dividing this by the slope, both derived

257   from the best- fitting straight line. To simplify the interpretation, the sign of the PSS was

258   inversed for participants with pain on the right hand/wrist/shoulder. As such, the PSS indicates

259   how much time the stimulus on the unaffected limb had to presented before/after the stimulus

260   on the affected limb, in order to be perceived as simultaneous. A positive PSS thus reflects

261   biased TOJ at the advantage of stimuli applied on the affected limb and to the detriment of

262   those applied on the unaffected hand, regardless of arm position (crossed vs. uncrossed).

263   Similarly, negative PSS reflects biased TOJ at the advantage of stimuli of the unaffected hand

264   and to the detriment of stimuli of the affected hand.

265   The JND indicates the interval between both tactile stimuli (on the left and right hand)

266   needed to achieve a 75% correct performance and, as such, provides a standardized measure of

267   the sensitivity of participants' temporal perception. It is calculated by dividing 0.675 by the

268   slope of the best-fitting straight line [50] and corresponds to the value obtained by subtracting

269   the SOA at which the best fitting straight line crosses the 0.75 point from the SOA at which the

270   same line crosses the 0.25 point, and dividing it by 2.

271   **2.6 Analyses**

272   PSS values and their corresponding JND values were excluded from the analyses, if one of

273   following criteria was not met: (1) the absolute value of the PSS values had to be smaller than

274   twice the largest SOA (i.e. 400 ms); (2) the performance (% correct answers) of the participants

275   for the largest SOA (i.e. 200 ms) had to be above 60% (i.e. well above chance level) in both

276   postures (hands uncrossed versus crossed). Extremely large PSS values and low performance

277   indicate that participants were not able to perform the task correctly even at large SOAs, where

278   the task performance is expected to be nearly perfect. The difference in missing values

279   between the uncrossed and the crossed position was compared using a chi-squared test for

280   equality of proportions.

281   To investigate the equivalence of the average self-reported intensity for the left compared to

282   the right hand, a repeated measures ANOVA was conducted with *Hand* (left versus right hand)

none
none

283   as within-subjects' factor and *Group* (CRPS, shoulder pain, wrist pain) as between-subjects'

284   factor[1]. The same analysis was used to compare the average intensity of the tactile stimulation,

285   as delivered by the apparatus, in Watt (W). The mean scores on the other self-report measures

286   (see section 2.2) were compared between the three patient groups with a one-way ANOVA.

287   To investigate whether there was a prioritization of stimuli on either the affected limb or the

288   unaffected limb, one-sample *t*-tests were performed. For each patient group we tested if the

289   PSS values in the crossed and uncrossed posture differed significantly from 0 ms. Next, in order

290   to compare the PSS values across the different postures, results were analyzed using linear

291   mixed effect models in R (lmerTest, [51]). Linear mixed effects models account for the

292   correlations in within-subjects data by estimating subject-specific deviations (or random

293   effects) from each population-level effect (or fixed effect) of interest (see [52] for an

294   elaboration). We chose to analyze the data with linear mixed models because it is a more

295   subject-specific model and it allows unbalanced data, unlike the classical general linear models

296   which requires a completely balanced array of data [52]. All models included a random

297   intercept conditional on *subject*. First, a model was fitted to investigate the influence of *posture*

298   (uncrossed versus crossed hands) across patient *groups* (CRPS, shoulder or wrist pain) on the

299   PSS values. *Posture* and *group* as well as their interaction effect were entered to the model as

300   fixed factors and a random subject-based intercept was added to the model. This model was

301   not simplified as it included only the main variables of interest. Second, a model was fitted for

302   each patient group separately to explore the potential influence of individual difference

303   variables: *pain intensity* at the moment of testing (0-10), *pain duration* (in months), *affected*

304   *side* (left or right) and *temperature difference* (see Appendix) between the affected and

305   unaffected limb measured immediately after each block. For five participants (two CRPS

306   patients, three wrist pain patients) the measurements of the temperature of the limbs after

307   each block was missing. For these participants the temperature difference was imputed by the

308   median difference of their group. Two-way interactions between the four variables (*pain*

309   *intensity*, *pain duration*, *affected side* and *temperature difference*) and *posture* were included in

310   the model. We attempted to simplify the model to obtain the most parsimonious model that

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[1] Note that data on the self-reported intensity of the tactile stimulation was missing for one shoulder pain patient.

311   fitted the data. To achieve this, we systematically restricted the full model based on Akaike's

312   Information Criterion (AIC) [53]. A variable was only included in the model when it decreased

313   the AIC value with more than 2 units. Finally, a model was fitted to investigate the influence of

314   *posture* (uncrossed versus crossed hands) across patient *groups* (CRPS, shoulder or wrist pain)

315   on the JND values.

316   We did not a priori include or exclude participants based on their JND value. However,

317   sensitivity analyses were performed for both the PSS and JND to check whether excluding

318   participants with JND values larger than the largest SOA (i.e. < -200) changed the results

319   profoundly. Moreover, sensitivity analyses were performed excluding three patients who did

320   not fulfill the research criteria of CRPS (see section 2.1.1 and appendix).

321   The final models were fitted with REML estimation. The ANOVA table was inspected to test

322   hypotheses about main and interaction effects. Kenward-Roger approximations to the degrees

323   of freedom were used to adjust for small sample sizes [54]. The significance level was set at $p <$

324   0.05. The regression coefficients (β) and their associated confidence intervals were reported as

325   a measure of the effect size. Raw data and R scripts are available at

326   https://osf.io/x82wk/?view_only=ecd3a2c52fce489c986ef08b241e8204.

327

328   3   Results

329   3.1   Participants

330   An overview of patient characteristics is presented in Table 1 and results from the diagnostic

331   screening can be found in the Appendix (table A1). Although screening results were missing for

332   4 shoulder pain patients, it is very unlikely that these participants would have met the criteria

333   for the diagnosis of CRPS as they never received the diagnosis of CRPS and also did not report

334   pain on the upper extremities.

335   3.1.1   Complex regional pain syndrome

336   CRPS patients were initially diagnosed by their medical doctor. At the beginning of

337   the research session the Budapest criteria were assessed by the researcher (see

338   Appendix). The presence of nerve injury (CRPS type 2) was considered as an exclusion

339   criterion. Sixteen CRPS patients (age: M = 51.31, SD = 11.72, range = 23-68 years; 3 men,

340   2 ambidextrous at the moment of testing; average pain duration: M = 10.29 months, SD

341   = 9.93) took part in this study (out of the 39 participants that were contacted, 41%). The

342   experiment was discontinued for one participant who was unable to perform the task

343   adequately, and another had to be excluded due to contralateral upper limb pain at the

344   time of the experiment. Three more participants did not meet the research criteria for

345   the diagnosis of CRPS at the time of the experiment. Analyses were first performed

346   including these participants. Next, a sensitivity analysis was performed, excluding these

347   participants (11 participants; age: M = 48.27, SD = 11.99, range = 23-66 years; 1 male; 2

348   ambidextrous; 3 left side painful; average pain duration: M = 7.45 months, SD = 7.34).

349   See http://hdl.handle.net/1854/LU-7179946 for a more detailed overview of

350   recruitment and inclusion.

3.1.2   Unilateral wrist pain

352   Patients with unilateral ulnar wrist pain [55,56] were invited to take part in this study.

353   Sixteen unilateral wrist pain patients (age: M = 39.69, SD = 12.38, range = 24-59 years; 4

354   male; 5 left handed, 2 ambidextrous; 9 left side painful; average pain duration: M =

355   24.38 months, SD = 28.25) participated (out of the 46 participants that were contacted,

356   35%). Participants could still be excluded after the study when they reported

357   contralateral upper body pain at the time of the experiment or when the diagnostic

358   screening resulted in a diagnosis of CRPS. However, none of the participants had to be

359   excluded (see http://hdl.handle.net/1854/LU-7179946).

3.1.3   Unilateral shoulder pain

361   Patients with unilateral shoulder pain, due to frozen shoulder syndrome [57,58] or

362   rotator cuff syndrome [59–61], were invited to participate in this study. Twenty

363   unilateral shoulder pain patients (age: M = 52.15, SD = 7.58, range = 40-64 years; 9 male,

364   1 left handed, 5 ambidextrous; average pain duration: M = 21.39, SD = 16.50) took part

365   (out of the 38 participants that were contacted, 53%). Two participants who were

366   unable to perform the task adequately, were excluded. Three additional participants

367   were excluded due to contralateral upper body pain at the time of the experiment. In

368   sum, 15 participants (age: M = 51.00, SD = 8.94, range = 35-64 years; 7 men; 1 left

369   handed, 5 ambidextrous; 6 left side painful; average pain duration: M = 23.80, SD =

370   17.02) were included for further analysis (see http://hdl.handle.net/1854/LU-7179946)

371

372   [enter Table 1 here]

373   **3.2   Self-report measures**

374   The results of the PGS are illustrated in Table 1. The mean self-reported intensity of the

375   vibrotactile stimuli was low (left hand: M = 2.61, SD = 2.64; right hand: M = 3.00, SD = 2.45) and

376   did not differ significantly between both hands ($F_{(1,42)}$ = 3.23, p = 0.08) across all patient

377   groups (interaction *Hand x Group:* $F_{(2,42)}$ = 1.88, p = 0.17). Participants reported directing their

378   attention to a large extent to the vibrotactile stimuli (M = 7.68, SD = 2.52). They reported that

379   they were able to concentrate well during the task (M = 7.21, SD = 1.72) and that they found

380   the task only mildly fatiguing (M = 2.80, SD = 2.42). Participants made a large effort to complete

381   the task (M = 7.95, SD = 1.83), reported finding the task meaningful (M = 8.02, SD = 1.42) and

382   reported little fear/tension during the task (M = 1.91, SD = 2.11). There were no significant

383   differences between the three patient groups.

384   **3.3 Tactile intensities**

385   The mean intensity (in Watt) of the tactile stimuli, derived from the staircase procedure, was

386   not significantly different between the left and the right hand (left: M = 0.094, SD = 0.023; right:

387   M = 0.093, SD = 0.045; $F_{(1,39)}$ = 0.02, p = 0.905) for none of the three patient groups

388   (interaction hand * group: $F_{(2,39)}$ = 1.51, p = 0.233). There were also no differences in intensity

389   of the tactile stimuli between the affected and the unaffected hand (affected: M = 0.096, SD =

390   0.043; unaffected: M = 0.091, SD = 0.027; $F_{(1,39)}$ = 0.62, p = 0.435) for none of the three

391   patient groups (interaction hand * group: $F_{(2,39)}$ = 0.37, p = 0.691).

3.4 PSS values

3.4.1 Missing values

In the crossed hands posture, 10 PSS values (22%) were excluded from the analyses: two values because they did not meet criterion 1, four values did not meet criterion 2, and finally three values were excluded because they did not meet both criteria. These values belonged to three CRPS patients (21%), three shoulder pain patients (20%) and four wrist pain patients (25%). No values were excluded in the uncrossed hands posture. A chi-squared test indicated that the proportion missing values was significantly larger for the crossed than for the uncrossed posture ($\chi^2 = 11.25$, $p < 0.001$).

3.4.2 Results for all groups

PSS values for each patient group and each posture are displayed in Figure 2. The one-sample t-tests revealed that PSS values were not significantly different from 0 for each of the three groups both in the uncrossed (CRPS: M = -0.60, 95% CI [-31.80 to 30.60], t(13) = -0.04, p = 0.97; Shoulder: M = -10.33, 95% CI [-31.42 to 10.76], t(14) = -1.05, p = 0.31; Wrist: M = -1.45, 95% CI [-21.06 to 18.15], t(15) = -0.16, p = 0.88) and the crossed (CRPS: M = -32.92, 95% CI [-78.89 to 13.06], t(10) = -1.60, p = 0.14; Shoulder: M = -7.05, 95% CI [-49.79 to 35.69], t(11) = -0.36, p = 0.72; Wrist: M = -33.23, 95% CI [-74.57 to 8.11], t(11) = -1.77, p = 0.10) posture.

[enter Figure 2 here]

The model investigating the main and interaction effect of *group* and *posture* revealed no significant effects (*group:* F(2,73.76) = 0.14, p = 0.87; *posture:* F(1,38.65) = 2.22, p = 0.14; *group x posture:* F(2,38.83) = 0.92, p = 0.41), indicating that the PSS values did not differ significantly between the three groups and between the two postures.

3.4.3 Individual difference variables

CRPS patients. None of the variables (posture, pain intensity, pain duration, affected side and temperature difference) improved the fit of the model. None of the variables had a significant effect on the PSS values (all F < 1.59, all p > 0.24).

418   **Shoulder pain patients.** The final model included the main effect of *posture*, *temperature*

419   *difference* and *pain duration* and the interaction effect between *posture* and *temperature*

420   *difference* and *posture* and *pain duration.* The interaction effect between *temperature*

421   *difference* and *posture* (F(1,18.44) = 5.44, *p* = 0.03, β = -37.69, CI [-67.40 to -7.98]) was

422   significant. Higher temperatures for the affected versus the unaffected limb are associated with

423   more positive PSS values in the uncrossed posture, but more negative PSS values in the crossed

424   posture (Figure 3). Interestingly, a paired samples t-test showed that for this patient group the

425   affected hand had a significantly higher temperature than the unaffected hand (Δ = 0.06, 95%

426   CI [0.008 to 0.12], t(29) = 2.35, *p* = 0.03)[2]. None of the other main or interaction effects were

427   significant (all F < 3.18, all *p* > 0.09).

428   **Wrist pain patients**. The final model included the main effect of *temperature difference* and

429   *pain duration.* In this model the main effect of *temperature difference* was significant (F(1,

430   18.90) = 8.51, β = 12.25, CI [4.48 to 20.03]), indicating that higher temperatures for the affected

431   versus the unaffected limb are associated with more positive PSS values and thus a stronger

432   prioritization of the unaffected limb (Figure 3). The main effect of *pain duration* was not

433   significant (F(1,11.53) = 4.39, *p* = 0.06, β = -0.74, CI [-1.44 to -0.05]), but there was a trend

434   suggesting that longer symptom duration might be associated with more negative PSS values

435   (Figure 4).

436

437   [enter Figure 3 and 4 here]

438   **3.5 JND values**

439   JND values for each patient group and each posture are displayed in Figure 5. One CRPS

440   patient had an extremely large JND value (-933.01) in the crossed posture. This participant was

441   not a priori excluded from the analyses, but sensitivity analyses were performed to check

442   whether excluding this participant changed the results (see section 3.8). The model

443   investigating the main and interaction effect of *group* and *postur*e revealed a significant main

---

[2] Note that for the other two patient groups this difference was not significant (CRPS patients: Δ = 0.52, 95% CI [-
0.62, 1.66], t(27) = 0.93, *p* = 0.36; wrist pain patients: Δ = 0.53, 95% CI [-0.31, 1.38], t(31) = 1.28, *p* = 0.21).

444   effect of *posture* (F(1,35.72) = 11.48, *p* = 0.002, β = 156.17, CI [66.13 to 246.21]), indicating that

445   participants had more difficulty with the task when their hands were crossed. The main effect

446   of *group* (F(2,69) = 1.64, *p* = 0.20) and the interaction effect between *group* and *posture*

447   (F(2,36.38) = 0.74, *p* = 0.48) were not significant.

448   [enter Figure 5 here]

449   **3.6 Sensitivity analyses**

450   **3.6.1. Exclusion based on JND values**

451   Five patients had a JND < -200 (1 CRPS patient, 3 shoulder pain patients, 1 wrist pain patient)

452   and were excluded from the analyses. The JND of the other patients ranged from -198.07 to -

453   43.48.

454   For the PSS values, the model investigating the main and interaction effect of *group* and

455   *posture* still revealed no significant effects (*group:* F(2,63.73) = 0.28, *p* = 0.75; *posture:*

456   F(1,33.30) = 1.25, *p* = 0.27; *group x posture:* F(2,33.71) = 0.76, *p* = 0.48). For all patient groups,

457   the models controlling for individual difference variables were refitted. For the CRPS patients,

458   the final model included the main effect of *pain intensity*, *affected side, posture* and

459   *temperature difference* and the interaction effect between *posture* and *temperature difference*.

460   There was a significant effect of *affected side* (F(1,7.78) = 7.40, *p* = 0.03, β = -78.07, CI [-133.44

461   to -22.71]), indicating that patients with CRPS affecting the left side had significantly more

462   positive PSS values than patients with CRPS affecting the right side of their body. The

463   interaction effect between *posture* and *temperature difference* was marginally significant

464   (F(1,13.98) = 4.40, *p* = 0.05, β = 16.52, CI [2.06 to 30.98]). Higher temperatures for the affected

465   versus the unaffected hand were associated with more positive PSS values. This association was

466   stronger in the crossed versus the uncrossed posture. None of the other effects were significant

467   (all F < 4.60, *p* > 0.06). For the shoulder patients, the final model included the main effects of

468   *pain duration*, *posture* and *temperature difference* and the interaction effects between

469   *temperature difference* and *posture* and between *pain duration* and *posture.* The interaction

470   effect between *posture* and *temperature difference* was significant (F(1,12.74) = 5.38, *p* = 0.04,

471   β = -34.64, CI [-61.39 to -7.89]), indicating that lower temperatures for the affected versus the

472   unaffected limb are associated with more positive PSS values in the crossed posture and more

473   negative PSS values in the uncrossed posture. Finally, the interaction effect between *pain*

474   *duration* and *posture* was also significant ($F_{(1,7.68)}$ = 9.62, *p* = 0.02, β = 4.40, CI [1.68 to 7.12]),

475   indicating that longer pain duration was associated with more positive PSS values in the crossed

476   posture, while there was no clear association in the uncrossed posture. None of the other

477   effects were significant (all F < 3.31, *p* > 0.20). For the wrist pain patients, the final model

478   included the main effects of *temperature difference* and *pain duration*. The main effect of

479   *temperature difference* was significant ($F_{(1,21.81)}$ = 8.62, *p* = 0.008, β = 14.05, CI [5.32 to

480   22.79]), with lower temperature for the affected limb versus the unaffected limb associated

481   with more negative PSS values. The main effect of *pain duration* was not significant ($F_{(1,10.78)}$

482   = 4.13, *p* = 0.07, β = -0.76, CI [-1.49 to -0.03]), but there was a trend suggesting that longer pain

483   duration was associated with more negative PSS values.

484   For the JND values, the model investigating the main and interaction effect of *group* and

485   *posture* still revealed a significant main effect of *posture* ($F_{(1,32.75)}$ = 28.30, β = -65.66, CI [-

486   89.73 to -41.60]), indicating that JND values were more negative in the crossed than in the

487   uncrossed posture. The main effect of *group* ($F_{(2,62.78)}$ = 0.26, *p* = 0.77) and the interaction

488   effect of *group* and *posture* ($F_{(2,33.14)}$ = 0.09, *p* = 0.91) were not significant.

489   **3.6.2. Inclusion criteria CRPS**

490   Three CRPS patients did not fulfill the research criteria of CRPS (see section 2.1.1) during the

491   diagnostic screening procedure. Keep in mind that these were initially diagnosed by a clinician.

492   Analyses were performed again excluding these participants.

493   The final model included the fixed effect of *posture*, *pain duration*, *pain intensity*, and the

494   interaction between *posture* and *pain duration* and *posture* and *pain intensity*. None of the

495   main or interaction effects reached significance (all F < 4.41, *p* > 0.07).

4   Discussion

497   The goal of this study was to replicate and extend the findings of Moseley et al. [29], by

498   testing whether somatosensory impairments observed in previous studies [27,32,62] were

499   specific to CRPS or whether they can also characterize other types of lateralized chronic pain.

500   Temporal order judgment (TOJ) tasks were used to compare perceptual biases between tactile

501   stimuli applied to the affected or the unaffected limbs in patients with CRPS and patients with

502   lateralized pain in one limb from non-CRPS origins, i.e. patients with either wrist or shoulder

503   pain. Next, by asking patients to adopt different postures, i.e. the limbs uncrossed or crossed

504   over the body midline, we tested whether potential biases can be determined by either the side

505   of space corresponding to the affected hemibody or the actual position of the limbs during the

506   experiments. Finally, we assessed whether the difference between individuals in terms of

507   temperature difference between the affected versus the unaffected hand and the duration of

508   the pain, could influence temporal order judgments in the three patient groups.

509   In general, the results of this study did not support a bias to tactile stimuli in patients with

510   CRPS. First, the mean PSS values were not significantly different from zero, suggesting the

511   absence of a consistent bias at the advantage of one of the two stimulated body parts, neither

512   the affected nor the unaffected hand. This is in contrast with the results of previous studies

513   [27,32,62]. Also, for the two other groups of unilateral chronic pain patients we found no

514   evidence for a perceptual bias. Second, there was no difference between judgements of the

515   CRPS patients and those of the non-CRPS patients. Inspection of the individual data show that

516   there was a substantial variability between patients, maybe hampering us to find any

517   systematic bias towards one side of space at the group level. Whereas some patients showed

518   more negative PSS values in the uncrossed versus the crossed posture, others showed the

519   opposite pattern. Present data are in line with a study of Filbrich et al. [35] who also did not

520   find a systematic spatial bias in a tactile TOJ task with CRPS patients. Moreover, the reverse

521   pattern of biases was also found. For instance, using the visual version of the subjective body

522   midline judgment task, some studies found systematic deviations of the judgments towards the

523   side of space corresponding to the affected part of the body [39,63,64]. Those results were

524   however not replicated by other teams [26,65]. The inconsistency in the literature with respect

525   to CRPS-related cognitive deficits might reflect substantial inter-individual differences in the

526   cognitive symptomatology of CRPS. It has been suggested that cognitive deficits are caused by a

527   maladaptive cortical reorganization consecutive to behavioral strategies used, even implicitly,

528   by the patients to avoid the provocation of pain [1]. Distinct strategies across the patients might

529 therefore differentially influence cortical changes, and, as a consequence, impact patients'
530 behavior differently. Following this reasoning, we assessed for each patient group whether
531 individual difference variables (pain duration, temperature differences between the affected
532 and the unaffected hand, the side of CRPS symptoms and the intensity of the pain during
533 testing) affected the results of this study. We found some evidence that pain duration or
534 temperature differences between the affected and unaffected hand might play a role. It is
535 reasonable to think that the history of the pathology might influence the potential presence of
536 cognitive deficits. The longer duration of the pathology, the higher the probability to develop
537 cognitive deficits affecting the perception of the pathological limb. It could therefore be argued
538 that TOJ biases were masked in the present study by the data of the patients with more recent
539 CRPS.

540   It has to be noted that there are some differences in design or patient characteristics
541 between the present and previous studies [27,32,62] that may explain discrepancies in findings.
542 First, as mentioned above, the duration of the pathology might play a role in the presence of
543 cognitive deficits. Cognitive deficits might only be apparent after a longer duration of the
544 pathology. Previous studies [27,32,62] involved more chronic CRPS patients (average duration
545 of 30, 20 and 32 months respectively) compared to the present study (average duration of 10
546 months). Second, in previous studies [32,62] participants were cold type CRPS (the affected arm
547 is cooler than the unaffected arm), whereas in the present study there was a mix between cold
548 and warm type CRPS (5 patients with cold type CRPS). It has been suggested that early CRPS is
549 associated with an increased temperature of the affected limb (warm type), while CRPS of
550 longer duration is associated with a decreased temperature of the affected limb (cold type) [1].
551 The transition from hot to cold CRPS could be associated with a shift in spatially defined tactile
552 processing [32]. Third, the vibrotactile stimuli used in the present study were different from the
553 ones used in previous studies [27,32,62]. In previous studies, stimuli were presented by means
554 of bone conduction vibrators, which delivered vibrotactile stimuli to the finger pads. In the
555 present study the vibrotactile stimuli were delivered to the superficial radial nerve of each
556 hand. Nevertheless, it is important to point out that we have used these vibrotactile stimuli in
557 several other studies that succeeded to find biases in TOJs [41,66-67], using the same

558   procedure to determine the intensity as used in the present study. Moreover, from Figure 2 it is

559   clear that for most participants a bias was present, but just not consistently to one side within a

560   patient group. Fourth, verbal reports were used to report which hand was stimulated first as

561   opposed to a foot switch. We decided to use verbal reports instead of a foot switch to make the

562   task easier for the participants. We worked with both verbal reports as well as a foot switch in

563   the past and were able to find biased order judgments with both response modalities [49].

564   Fifth, the experimenter sat opposite to and facing the participant instead of behind the

565   participant. Moreover, she was unblinded to the aim of the study and the patient group.

566   However, the experimenter was blinded to the particular trial that was presented and could

567   therefore not have influenced the results intentionally.

568   Conversely to the PSS values, we did observe significant results on the JND index. The JND,

569   standing for Just Noticeable Difference, is a measure of the slope of the psychometric functions

570   fitting participants' performances. It reflects the sensitivity of the task and the ability of the

571   participants to perform it (see [68]). In the present study, it reflects the minimal time interval

572   the participants need to perform the task with 75% correct responses (see [68,69] for

573   alternative methods to measure the slope). The JND was significantly larger in the crossed hand

574   posture than in the uncrossed posture, meaning that the patients needed much more time to

575   discriminate the time order between the two tactile stimuli correctly when their arms were

576   crossed. Such an effect of posture on the participants' performance was present in the three

577   groups of patients and was already shown for CRPS patients in previous studies [32,62] (but see

578   [70] for an exception). Decreased performance during TOJ tasks with somatosensory stimuli

579   when crossing the hands on which the stimuli are applied is a very recurrent and strong effect

580   throughout the literature (e.g. [49,70-76]). Such an effect is supposed to be due to a conflict

581   between a somatotopic representation of somatosensory stimuli, i.e. the ability to represent

582   them according to which body parts are stimulated, and a spatiotopic representation, i.e. the

583   ability to represent somatosensory sensations according to where the stimulated body parts

584   are located in external space. In other words, the crossing hand effect during somatosensory

585   TOJ illustrates the ability of the brain to remap somatosensory inputs from an initial

586   somatotopic or anatomical representation into a spatiotopic representation for which external

587   space is used as reference frame (see [68]). The fact that CRPS patients do show an impaired

588   performance during tactile TOJ when their hands are crossed, just like healthy volunteers,

589   suggests that somatosensory remapping abilities are not affected in CRPS. Similarly, the data of

590   three CRPS patients were disregarded in the crossed hand posture, confirming that the task was

591   too difficult to perform for these patients in the crossed posture. In comparison, in a TOJ task

592   with somatosensory stimuli with healthy volunteers conducted in our lab, a larger range of

593   SOA's was used (largest SOA 600 ms). Nevertheless, two participants also had to be excluded

594   due to poor performance (less than 80% correct) [77]. Future studies including a control group

595   with healthy volunteers could directly compare the JND for healthy volunteers versus CRPS

596   patients, to confirm that the remapping abilities for CRPS patients are similar to those of

597   healthy volunteers.

598   This study has some limitations. First, a small sample of patients was tested in each group

599   and an a-priori sample size calculation based on the study of Moseley et al. [32] was not

600   performed. Results of section 3.4.3 (individual differences) should therefore be interpreted

601   with caution. Future studies should calculate the ideal sample size based on the effect sizes of

602   the present and previous studies [27,32,62] and should presumably use a more important

603   sample size. Nevertheless, our sample of CRPS patients (N = 14 for the uncrossed posture and N

604   = 11 for the crossed posture) was comparable to the sample used by Moseley et al. [32,62] (N =

605   10) and Reid et al. [27] (N = 13).

606   Second, for several patients the task was too difficult in the crossed posture as evidenced by

607   extremely large PSS values and consequently we were not able to use some of the data for the

608   crossed posture. This could have artificially reduced the effect of posture. Sensitivity analyses

609   showed that excluding these participants from the analyses did not drastically alter the results.

610   Future studies might choose to use data-adaptive methods (e.g. [76,78]) in which the tested

611   SOAs are adapted to each participant's own performance. This has the advantage that TOJ

612   parameters can be measured in a valid and reliable way without probing extensively all the

613   possible SOAs.

614   Finally, we did not submit an a-priori locked protocol for this study. Current guidelines within

615   the pain field recommend to preregister the research plan before data collection [79]. It should

616   be noted that this study was conducted before the publication of these recommendations.

617 **5   Conclusion**

618   The results of this study did not support the hypotheses about the existence of systematic

619   and specific cognitive biases affecting the ability of CRPS patients to process their affected

620   hand. However, variability of the patients' data was large, suggesting that other factors, such as

621   duration of symptoms and temperature differences between the affected and unaffected limb,

622   might play a role in the development of cognitive deficits in CRPS. This could also be the case in

623   non-CRPS chronic pain patients, as skin temperature seemed to influence tactile TOJ in these

624   patients. Additional studies are needed that take these variables into account by, for example,

625   comparing biases in CRPS (and non-CRPS) patients in an acute versus a chronic pain state.

626

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632

633 **Conflict of interest**

634 The authors declare that they have no conflict of interest.

635

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Figure 1

Experimental set-up of the TOJ task

(A) uncrossed arms condition. (B) crossed arms condition.

A

35cm

40cm

35cm

B

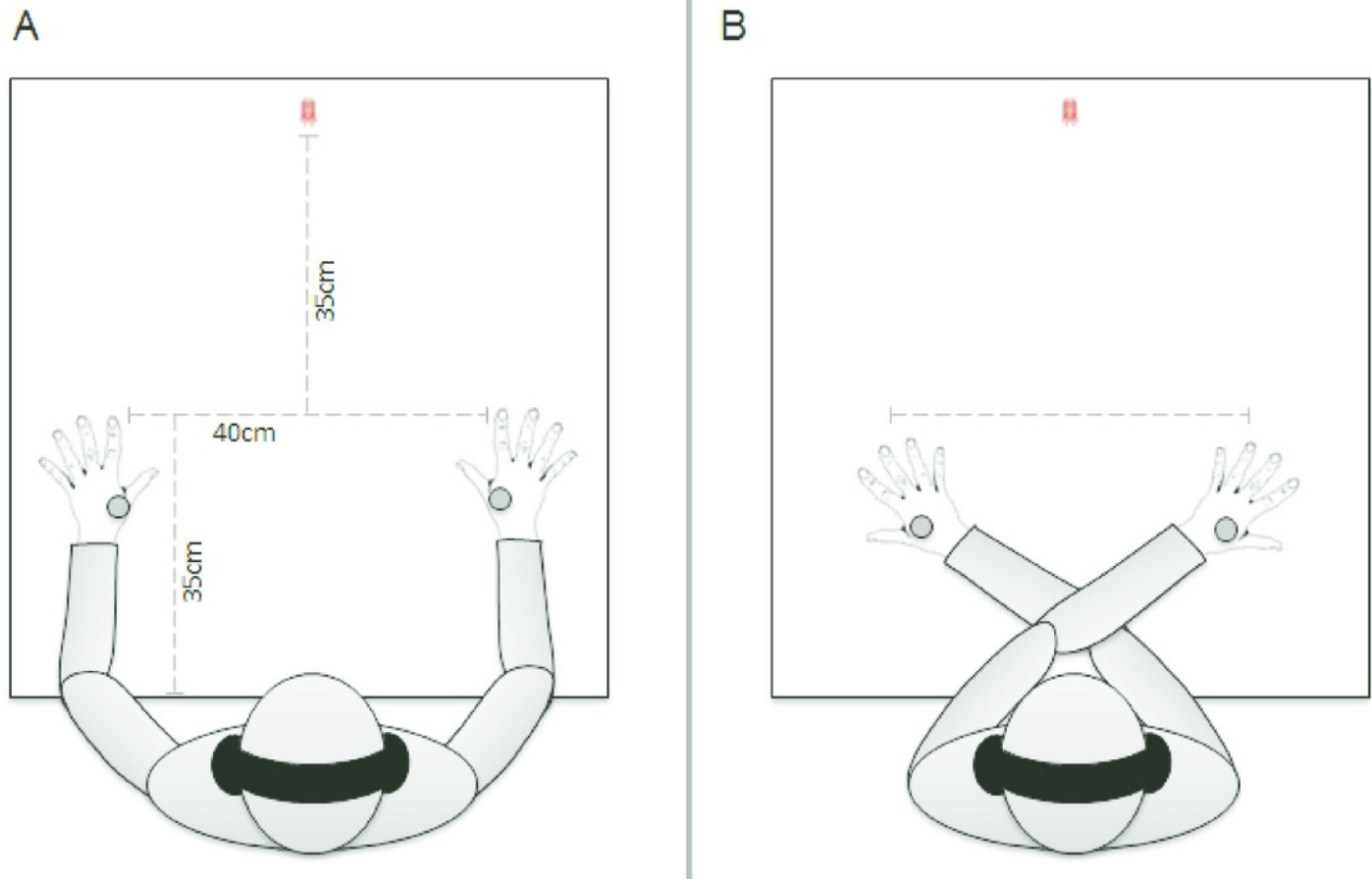



Figure 2

Individual and mean PSS values

Individual (black) and mean (grey) PSS values per group and per posture.

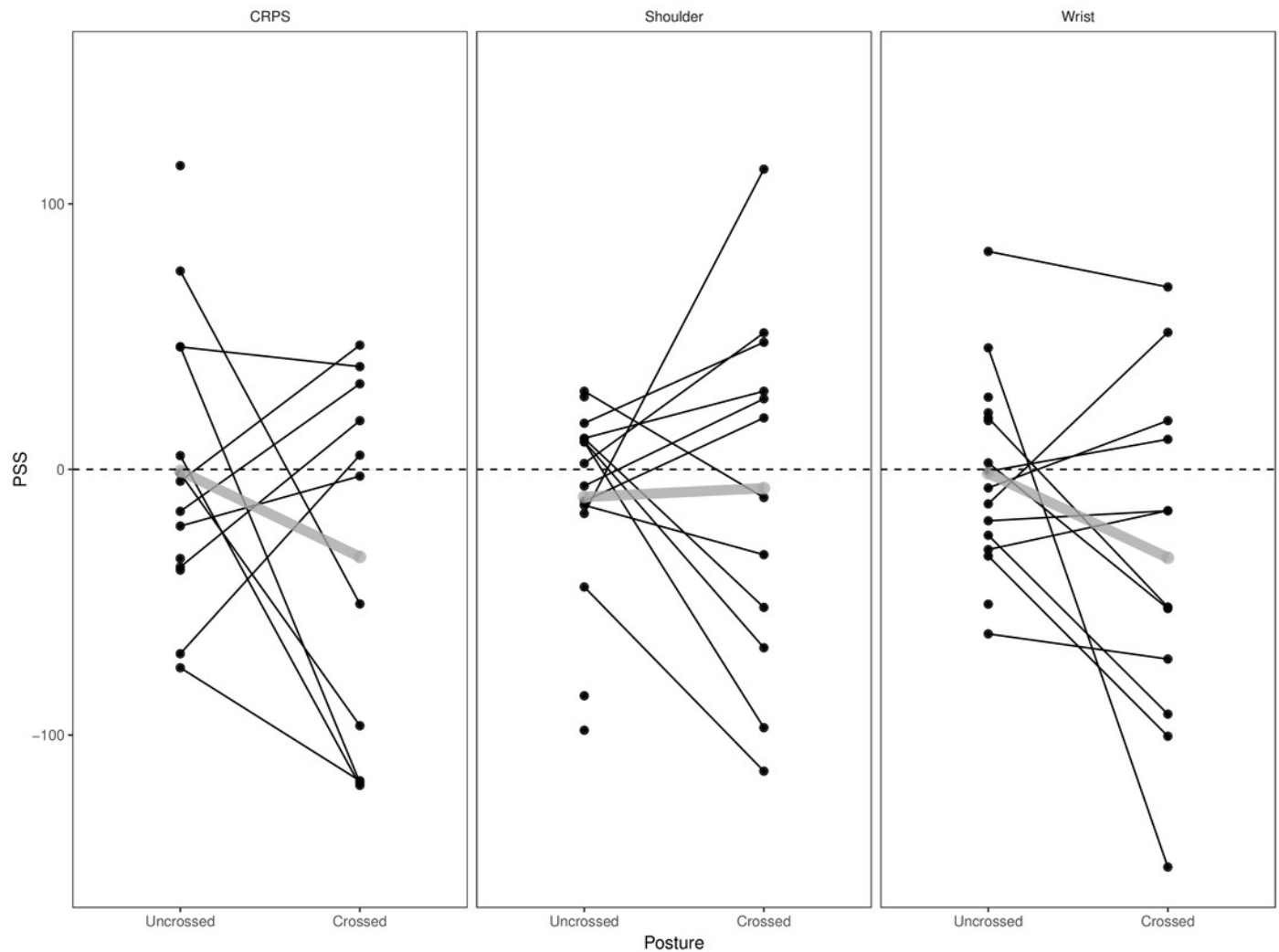



Figure 3

Observed PSS values in function of temperature difference and posture for the three patient groups.

The lines represent linear regression lines.

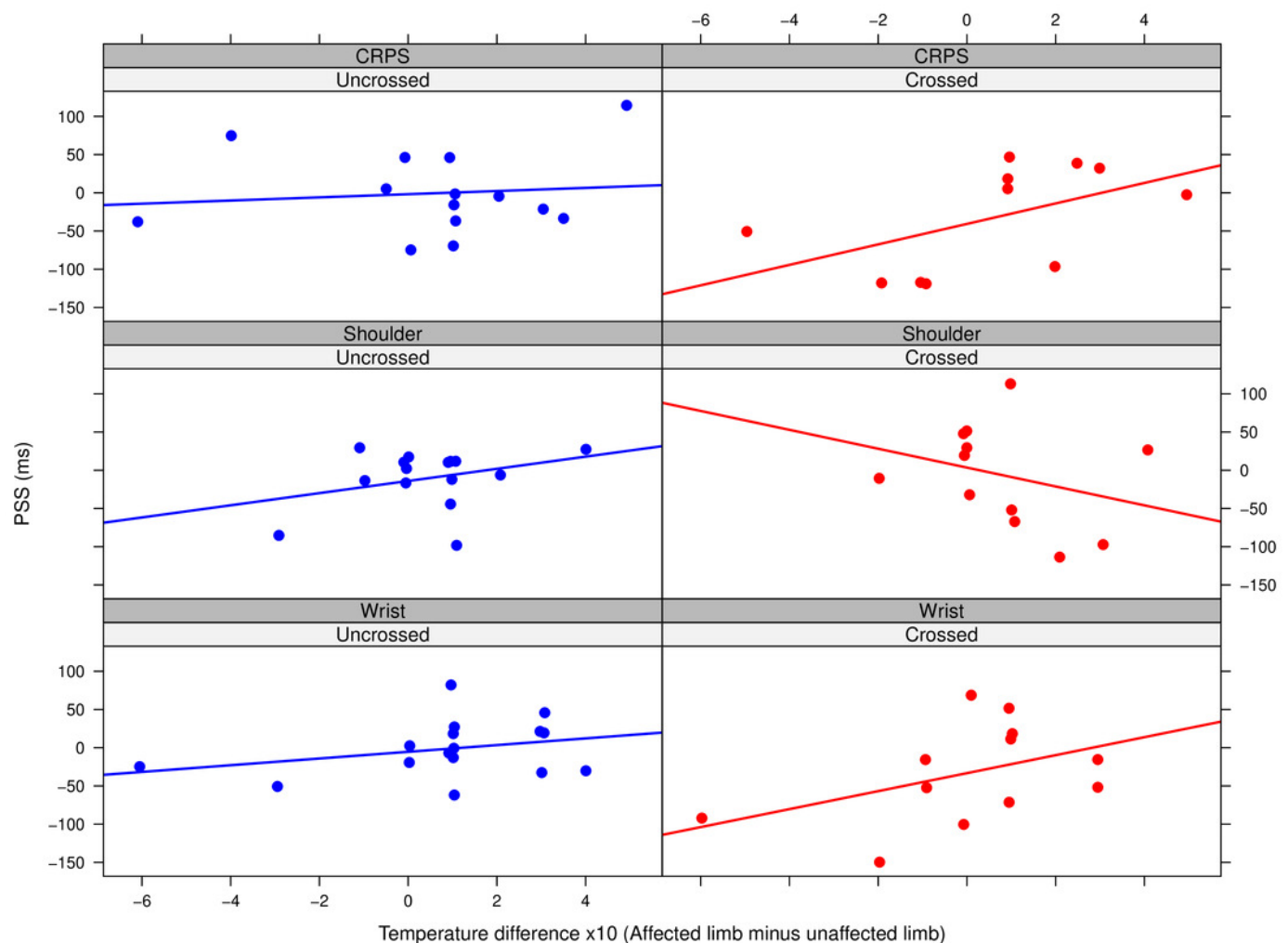



Figure 4

Observed PSS values in function of pain duration and posture for the three patient groups.

The lines represent linear regression lines

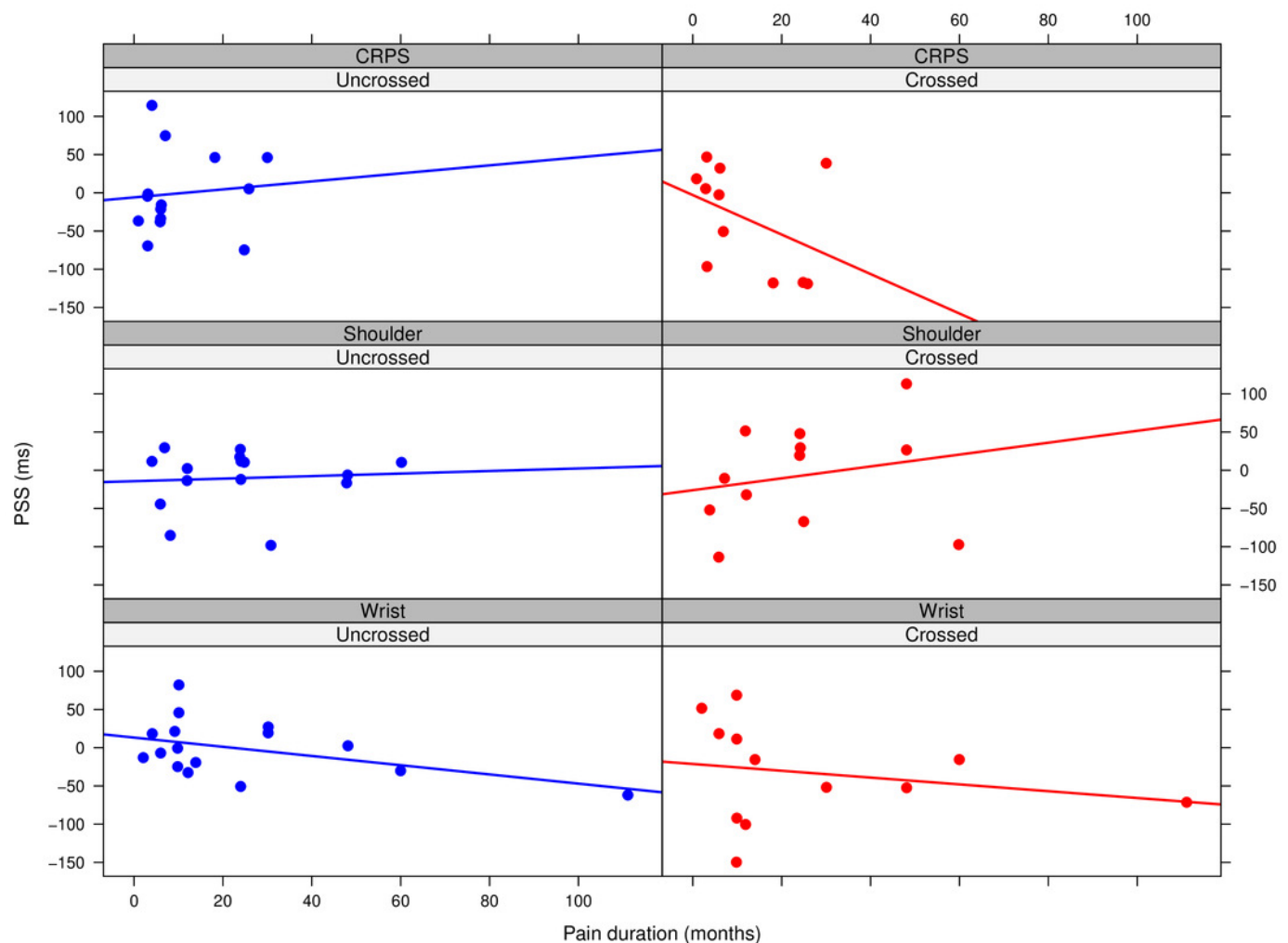
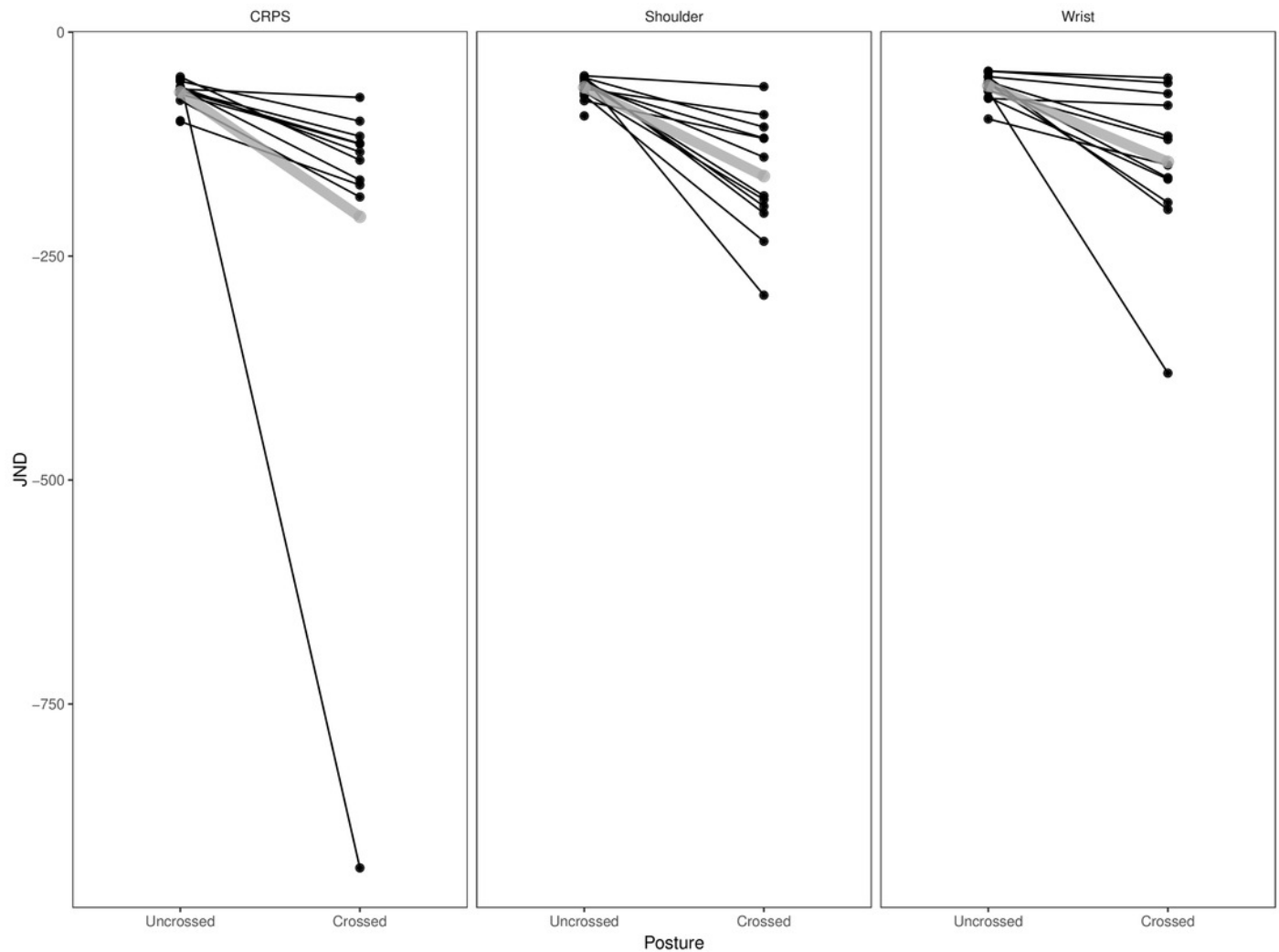



Figure 5

Individual and mean JND values.

Individual (black) and mean (grey) JND values per posture and per group.

Overview of patients characteristics for each patient group

Age in years; F = Female; M = Male; R = right; ambi = ambidextrous; L = left; NS = Not Specified. 'Hand dominance' based on Hand Dominance Questionnaire. 'PGS', Pain Grading Scale. PGS missing for 1 wrist pain patient. Remark: CRPS patient 4, 8 and 13 did not fulfill the research criteria for CRPS. Analysis were performed with and without including these patients.

	ID	Age/sex/handedness	Location of pain	Diagnosis	Pain duration (months)	PGS (grade score)	Other pain	Other
CRPS	1	62/F/R	R wrist and hand	CRPS	4	3	/	dystionia neck, familial tremor
	2	37/F/R	R elbow, wrist, hand, pink	CRPS	18	4	R shoulder	/
	3	66/F/R	R wrist and hand	CRPS	6	4	/	/
	4	68/F/R	R wrist, hand, lower arm	CRPS	6	3	/	fibromyalgia
	5	48/F/R	L wrist and hand	CRPS	3	4	L knee, L frozen shoulder	/
	6	45/F/R	L wrist and hand	CRPS	7	3	/	/
	7	49/F/R	L wrist and hand	CRPS	3	1	L frozen shoulder	/
	8	45/F/R	R hand, wrist,		18	4	R frozen shoulder	/

	9	23/F/R	R	CRPS	6	3	/	/
			elbow, shoulder					
	10	41/F/R	R wrist, hand, elbow	CRPS	25	3	/	/
	11	51/M/R	R Wrist, hand, elbow	CRPS	6	4	R shoulder	/
	12	57/M/R	R wrist and hand	CRPS	30	4	/	/
	13	53/F/R	R wrist	CRPS	3	3	fracture R elbow	/
	14	57/F/R	R wrist, hand, elbow	CRPS	1	4	/	/
Shoulder	1	54/M/R	R wrist and hand	NS	24	4	/	/
	2	51/M/R	R shoulder and elbow	rotator cuff	24	2	/	/
	3	61/M/ambi	R shoulder and elbow	rotator	60	2	/	/
			L					

			shoulder	cuff				
4	53/M/L	L shoulder	NS	12	2	/	/
5	41/F/R	R shoulder and neck	frozen shoulder	12	4	/	/
6	40/F/R	L shoulder	frozen shoulder	48	2	/	/
7	64/M/L	R shoulder	NS	4	4	/	/
8	52/M/R	R shoulder	NS	48	4	/	/
9	46/F/L	R shoulder	frozen shoulder	8	4	/	/
10	56/F/R	R shoulder and elbow	frozen shoulder	24	4	arthritis, convulsions hands	/
11	42/M/R	L shoulder	frozen shoulder	25	2	chronic low back pain	/
12	49/F/R	R shoulder		31	2	/	/
13	44/F/R	R shoulder and elbow	frozen shoulder	24	3		scoliosis back (no pain)
14	64/F/R	L shoulder and upper arm	frozen shoulder	6	4		hypothyroidie

	15	59/F/R	L shoulder and neck	frozen shoulder	7	2	/	/
Wrist	1	58/F/R	L wrist	malunion fracture wrist	12	1	/	/
	2	52/F/R	R wrist	NS	6	1	/	/
	3	40/F/L	R wrist	wrist distortion	10	4	/	
	4	30/F/L	L wrist	NS	24	3	/	/
	5	45/M/L	L wrist and hand	Fracture wrist	10	4	/	/
	6	28/F/R	R wrist, elbow, hand	NS	30	4	/	/
	7	26/F/	L wrist	wrist distortion	10		/	/
	8	28/M/R	L Wrist and lower arm	Fracture wrist	48	2	/	/
	9	32/F/R	R wrist, elbow, hand	wrist distortion	14	1	/	/
	10	53/F/R	L	tendonitis	2	2	/	/

		wrist, Lower arm					
11	24/F/R	L wrist	NS	9	1	low back pain	/
12	59/F/R	R wrist, elbow, hand	NS	60	4	/	/
13	26/M/R	L wrist	NS	4	3	/	/
14	45/F/L	R wrist and hand	tendonitis, ehlers danlos	111	4	L knee	/
15	40/M/L	R wrist	NS	10	4	/	/
16	51/F/R	L wrist	NS	30	4	/	/

1   *Table 1. **Overview of patient characteristics for each patient group.** Age in years; F = Female; M = Male; R = right; ambi = ambidextrous; L = left;*
2   *NS = Not Specified. 'Hand dominance' based on Hand Dominance Questionnaire. 'PGS', Pain Grading Scale. PGS missing for 1 wrist pain patient.*
3   *Remark: CRPS patient 4, 8 and 13 did not fulfill the research criteria for CRPS. Analysis were performed with and without including these patients.*