Prism adaptation effects in complex regional pain syndrome:

A therapo-physiological Single Case Experimental Design exploratory report

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) is an invalidating chronic condition that can occur after an acute peripheral lesion. Prism adaptation therapy is regarded as a promising tool to improve chronic pain in this syndrome but the mechanisms which lead to pain amelioration remain unknown. In this exploratory report we performed a retrospective analysis of longitudinal data collected from a single, atypical patient, who showed hyper-attention toward her affected (left) hand. Repeated assessments of pain and spatial neglect made during the course of the prism adaptation treatment revealed differential contributions of the two hands to adaptation-induced pain reduction. Treatment response appeared to be associated with a relative modification of the spatial behaviour of the two hands. This case study provides a new example of pain relief following prismatic deviation away from the pathological side.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a lateralized chronic pain condition that usually appears after a mild traumatic/noxious event. It is characterized by severe and disproportionate pain, reduced range of motion, and autonomic symptoms. The evolution of CRPS is usually long and unpredictable. Patients often endure permanent and intense pain, which can have dramatic consequences for their everyday functioning, and for which there is often no effective treatment. Beyond the chronic pain itself, motor disabilities jeopardize their employment and social roles, and patients frequently suffer from sleep disturbances and intense reactive depression, resulting in a marked handicap and heavy social costs (Birklein & Schlereth, 2015).

Although the precise mechanisms underlying CRPS may vary from individual to individual, including biological pathways involved in aberrant inflammation or vasomotor dysfunction, it is generally accepted that maladaptive plastic processes in the central nervous system accompany the peripheral pathology (Marinus et al., 2011; Birklein & Schlereth, 2015), and sensory dysfunction and pain have been connected with cortical reorganization in the primary and secondary somatosensory cortices (Pleger et al., 2006). Tactile sensory abnormalities such as hypersensitivity, hypoaesthesia, hyperalgesia or even allodynia, have also been linked to pain and somatosensory cortex reorganization (see Henry, Chiodo & Yang, 2011 for a review on chronic pain). Furthermore, it is widely acknowledged that CRPS patients have body representation abnormalities like impaired laterality recognition of the affected limb or lateral bias of the visual subjective body midline (Schwoebel, Friedman, Duda & Coslett, 2001; Moseley, 2005; Reinersmann, Haarmeyer & Blankenburg, 2010). The affected limb can also be felt to be bigger than it actually is (Moseley et al. 2005) and patients may have strange feelings about their limb (Förderreuther, Sailer & Straube, 2004) as if it no longer belongs to them (consciousness that it belongs to the body has disappeared) or that moving it requires intense effort and attention (Galer & Jensen, 1999).

One of the most common and disabling features of CRPS is underuse of the affected limb. This feature of the syndrome has been related to motor neglect (Laplane & Degos, 1983), the clinical description of which is hypokinetic, bradykinetic, and hypometric movements of the affected arm (Galer et al., 1995). The use of the term “neglect-like” to qualify these deficits has led to an ever-increasing number of publications speculating on the parallel between spatial neglect following stroke and body representation disturbances in CRPS patients (Sumitani et al., 2007a; Reinersmann et al., 2012; Förderreuther, Sailer & Straube, 2004; Frettlöh, Hüppe & Maier, 2006;

Acerra, Souvlis & Moseley, 2007; Kolb, Lang, Seifert & Maihofner, 2012; Moseley, Gallace & Spence, 2009; Filippopulos, Grafenstein, Straube & Eggert, 2015). Indeed, spatial neglect includes a variety of symptoms, one of the most striking of which is perceptual neglect i.e. difficulties detecting, responding to, or orienting attention towards stimuli presented on the contralesional side of space (Rode, Pagliari, Huchon, Rossetti & Pisella, 2017 ; Legrain, Bultitude, De Paepe & Rossetti, 2012). For example, after a right hemisphere lesion, patients can fail to eat the food on the left side of their plate, to make up or shave the left side of their face, can bump their left arm when passing through doorways, and exhibit less auditory attention to their left side (Jacquin-Courtois et al., 2010). Despite the fact that CRPS patients have no brain lesion and do not usually exhibit such a severe attentional bias, the parallel between these two syndromes has been repeatedly drawn and several publications have investigated perceptual neglect symptoms in CRPS.

Perceptual neglect in CRPS patients has been explored with specifically-designed subjective questionnaires (Förderreuther, Sailer & Straube, 2004; Galer & Jensen, 1999; Frettlöh, Hüppe & Maier, 2006; Kolb, Lang, Seifert & Maihofner, 2012) as well as with more objective clinical and psychometric tests of tactile attention (Moseley, Gallace & Spence, 2009; Moseley, Gallace & Iannetti, 2012; Reid et al., 2016), visual attention (Bultitude et al., 2017; Filbrich et al., 2017), and egocentric reference frame (Sumitani et al. 2007b, Reinersmann et al., 2012). Studies of visual subjective body midline measurements in CRPS patients have reported a systematic leftward bias regardless of the hand affected by CRPS (Reinersmann et al., 2012), no systematic bias (Christophe et al., 2016) or a bias towards the affected side (Sumitani et al., 2007a). In contrast, using a visual temporal order judgement task, Filbrich et al. (2017) reported a bias towards the *unaffected* limb. A bias towards the unaffected limb finding was also found by Bultitude and colleagues (2017) when targets appeared both on and near the limb (see also Filbrich et al., 2017). In a much larger patient sample (n = 54), however, Halicka et al. (2020b) found no evidence for spatial biases in visuospatial attention (temporal order judgement, Landmark, and greyscales tasks) or mental space representation (Mental Number Line Bisection task). They concluded that a relationship between CRPS pain and body perception disturbance or motor impairment likely exists, but that the presence of spatial biases has likely been overestimated. While their large sample lends support to this conclusion, a close look at the data reveals considerably more variability in the CRPS group than the control group, with a number of patients exhibiting substantial spatial biases. The presence of substantial between-patient variability, a large range of tasks for exploring spatial cognition, each of which potentially taps into a different underlying process, and the inconsistent results of previous studies, all suggest that spatial cognition in CRPS patients has not yet been sufficiently explored.

As mentioned above, at least one study reported a systematic bias in the visual egocentric reference frame towards the affected side (Sumitani et al., 2007a), and in a follow-up study this same group demonstrated that prisms that induce an optical shift *away* from the affected side significantly reduced pain (Sumitani et al., 2007b). The therapeutic effect of adaptation to prisms that induce an optical shift *away* from the affected side was replicated in another patient by Bultitude & Rafal (2010) who reported a positive effect on both pain and range of motion, but only when PA was performed with the pathological hand. A longitudinal follow-up of one patient in the Sumitani et al. study demonstrated the directional specificity of the prismatic deviation, by showing that neutral prisms did not alter pain and that prisms that induced an optical shift *towards* the affected (i.e. that increased the visual reference frame bias) side tended to increase pain (2007b).

On the basis of these results, the neglect-like hypothesis of CRPS has been questioned, and it has been suggested that CRPS patients might have instead an attentional bias towards their affected side that enhances the weight of nociceptive over epicritic stimuli and consequently maintains pain (Legrain, Iannetti, Plaghki & Mouraux, 2011). Another hypothesis proposes that the presence of pain in the affected limb tends to favour protection by increasing visual scanning, and that this explains the presence in some patients of a visuospatial bias towards the painful side (Reid et al., 2016).

Classical prism adaptation (PA) studies in healthy subjects (e.g. Redding et al. 2005) and neglect patients (e.g. Rode et al. 2015) suggest that prisms that induce an optical shift towards the left should produce leftward visual aftereffects and rightward manual/proprioceptive aftereffects (and vice versa for right-shift prisms). If it is assumed that the basic perturbation underlying the spatial cognition bias observed in some CRPS patients lies in the visual coordinate system, then inducing an optical shift in the direction opposite to the bias should reduce the visual bias and reduce pain. This was found to be the case in the 5 patients studied by Sumitani et al. (2007b) who all had a pre-adaptation visual egocentric reference frame bias towards their affected limb that shifted towards their unaffected limb after adaptation using an optical deviation towards their unaffected side. More recently, we replicated the pain–reducing effects of PA with an optical deviation towards the unaffected limb in a group of 7 CRPS patients (Christophe et al., 2016a). Interestingly, these effects were unrelated to visual egocentric reference frame biases, as unlike the patients described by Sumitani et al. (2007b), our patients showed no pre-adaptation bias towards their affected limb and no adaptation-induced shift in their visual egocentric reference frame. These data question the logic behind the idea that patients will only benefit from PA if they have an initial attentional bias towards their affected side that is in turn "corrected" by PA. Thus, despite the existence of data suggesting that prism adaptation with a visual shift towards the unaffected limb can alleviate pain in CRPS patients, there appears to be no clear rationale for the selection of a given optical shift, the use of a given hand to perform the pointing during prism adaptation, nor any precise understanding of the mechanisms involved in PA's therapeutic effects in these patients.

Here we provide a detailed account of the therapeutic follow-up of a CRPS patient described elsewhere (see Christophe et al., 2016b) who, after PA with an optical deviation towards her unaffected side, exhibited clear, long-lasting pain improvement. This patient differed from classical case studies of CRPS patients in that she displayed no signs of neglect of her affected side, but was instead *hyper-attentive* with tests of number representational neglect, motor neglect and extinction as well as measures of visual and manual straight-ahead and line bisection all showing signs of a bias towards her affected (left) hand. In this paper we attempt to better understand the potential cognitive mechanisms involved in PA-induced pain reduction by exploiting the existence of repeated measures of numerous parameters taken in this patient over a two-week PA intervention period and at an 8-month follow-up visit.

METHODS

Patient AZ

In a previous clinical postcard (Jacquin-Courtois et al., 2017) we reported the striking 'anti-neglect' clinical profile of AZ who demonstrated a substantial bias towards her affected side on a number of different measures. At the time of testing, AZ was a 50-year-old woman suffering from type 1 CRPS (with no neurological lesion) on her left hand, due to benign surgery three years earlier. She rapidly developed disproportionately intense pain, with symptoms fulfilling the Budapest diagnosis criteria (Harden et al., 2010). Following several different therapies, none of which produced any long-lasting effects, she presented with permanent pain (ranging from 60 to 80/100 on a visual analog scale), very intense allodynia on the back of her hand, and very cautious protective behaviour towards her pathological hand (she wore a thick fur cuff and was careful not to move her hand). The psychological impact of her disability was such that she had stopped working and her mood and sleep quality were affected. She had no previous history of psychological disorders, but presented with a treated reactive depression and anxiety about her future. AZ spent two weeks as an inpatient at the Henry Gabrielle Hospital (Hospices Civils de

Lyon) and gave written informed consent to participate in an intensive prism adaptation treatment during her hospitalisation.

Spatial cognition outcome measures

Adopting both a prospective and exploratory approach, we carefully tested AZ for spatial neglect before, during and after prism adaptation using sensitive and continuous measures: spatial frames of egocentric reference and manual line bisection. Spatial reference frame measures included visual straight-ahead and manual straight-ahead deviations. Details of all measures are outlined below (for more detail see Christophe et al., 2016a,b):

- Visual straight-ahead (VSA)

  The patient was seated comfortably with her head on a chin rest, and her body aligned with the midpoint of a screen that was either 1 or 2 m in front of her. The experiment was carried out in total darkness. A small red dot (LED) appeared at eye level at approximately 30° to either the right or left of her objective body midline (OM). This dot moved from right to left (or vice versa) in a counter-balanced design at approximately 3° per second. AZ was asked to stop the dot, using a verbal command, when its position crossed her midsagittal plane. Visual straight-ahead (VSA) was evaluated as the deviation between the dot's position and the objective midline position (in degrees of visual angle). A rightward deviation was signed as positive while a negative value indicates a leftward deviation. Ten trials were performed before and after each prism adaptation session (denoted as *Pre* and *Post*). Reported VSA measures are the average of these 10 values.

- Manual/proprioceptive straight-ahead (MSA)

  The patient was seated comfortably at a table with her head on a chin rest which ensured that her trunk remained in an upright position and her head straight. She was asked to point to a position on the table that indicated the “straight-ahead” position, that is, to indicate the position of an imaginary line dividing her body into two equivalent halves. The patient extended her arm without any speed or amplitude constraints and was in total darkness. A metallic thimble on her index finger was used to measure the deviation angle: when the finger touched the table's surface (which was covered with carbon isoresistive paper) the tension between the thimble contact point and the reference electrode was measured and this was used to calculate the angular position (in degrees) relative to the objective sagittal axis with a measurement precision of ± 0.5 degrees. As for VSA, positive values reflect a rightward deviation and negative values a leftward deviation. Ten trials were performed with each hand both before and after PA, and reported measures are the average of these 10 values.

- Open-loop pointing (OLP)

Open loop pointing measurement was carried out under the same conditions as those described above. The luminous visual target was aligned with the patient's sagittal axis and she was instructed to align her right or left index finger with the target as precisely as possible with no time limit to perform the task. Data collection and processing were similar to MSA (10 trials with each hand before and after PA). Open loop pointing is generally considered to be the sum of MSA and VSA (Redding & Wallace, 1988) and is used to assess the combined effect of the visual and proprioceptive systems.

- Manual Line bisection

The patient was seated at a table in front of an A4 sheet of paper on which a centered, 200mm long and 2mm thick line was printed. The midpoint of this line was aligned with her midsagittal axis and she was asked to mark the middle of the line without any computation or external help. The deviation was calculated by measuring the distance in millimeters between the marked point and the objective midpoint of the line. A leftward shift had a negative value and a rightward shift a positive value. Ten trials were performed with each hand both before and after PA and reported measures are the average of these 10 values.

- Prism Adaptation (PA)

PA was carried out using a pair of glasses (http://OptiquePeter.com/) that produced a 15° rightward optical deviation of the visual field - towards the unaffected (right) side of the patient's body. The prismatic lenses were composed of two superimposed, curved, point-to-point lenses fitted with a "glacier" frame containing lateral leather protectors designed to avoid access to non-shifted vision. During prism exposure, the patient executed 80 rapid pointing movements towards visual targets located 10 degrees to the left or to the right of the body midline, in a pseudorandom order. Our patient made rapid, non-corrected movements which resulted in large errors on her initial pointing movements, gradual error reduction, and successful sensorimotor adaptation. Her spontaneous comment at the beginning of exposure revealed that, unlike neglect patients (Rode et al. 2015), she was fully aware of the visual shift.

Experimental time course

We use the term *measurement session* to refer to times when various measures of spatial neglect were made. Since these were taken both before and after each adaptation session there were 4 measurement sessions per day during the intervention period. Prior to the intervention period 2 measurement sessions were conducted in the morning of day 1. This was followed by a break followed by a further measurement session (pre-test), the first adaptation, then a post-test measurement session. This pattern of pre-test measurement session - adaptation session - post-test measurement session was continued over 3.5 days followed by a 3-day break and then repeated in week 2 (see Table 1).

The experiment was divided into five time periods: 1) **baseline** before any prism adaptation composed of up to two measures; 2) **week1: left hand PA:** 7 PA sessions (2 per day for 3.5 days) with 13 measurement sessions; 3) **week 2: right hand PA:** 7 PA sessions (2 per day for 3.5 days) with 14 measurement sessions; 4) **left hand PA:** one session of PA with the left hand at the end of week 2 and 2 measurement sessions (one pre, one post); 5) **long-term follow-up**, eight months after the treatment a final measurement session was performed.

Table 1: Global time course of the experiment. The intervention lasted 2 weeks and included 14 prism adaptation sessions and 28 measurement sessions. A final adaptation session with the left hand was performed on the last day of week 2 and for the purposes of the current analyses was not considered as part of the intervention. Follow-up measurements were made eight months later.

<table>
<tr><th colspan="2">Week 1</th><th colspan="2">Week 2</th><th>+ 8 months</th></tr>
<tr><td rowspan="3">Baseline

2
measurement
sessions</td><td colspan="2">Intervention</td><td rowspan="3">Left
(affected)
hand PA
2
measurement
sessions
1 adaptation
session
0.5 days</td><td rowspan="3">Follow-up

2
measureme
nt sessions</td></tr>
<tr><td rowspan="2">Left (affected) hand PA

13 measurement sessions
7 adaptations
3.5 days</td><td>Right (non-affected) hand PA</td></tr>
<tr><td>14 measurement sessions
7 adaptations
3.5 days</td></tr>
</table>

The first measurement session of the intervention revealed deviations towards the painful (left) side in visual and manual straight-ahead as well as line bisection. That is, neglect of the unaffected side, which contrasts with the widespread idea that CRPS patients neglect their pathological side (Greenspan, Treede & Lenz, 2012; Punt, Cooper, Hey & Johnson, 2013). Although AZ's pattern of reference frame biases was opposite to that observed in Sumitani's patients (see Jacquin-Courtois et al., 2017 for the detailed description), we reasoned that it would be unethical to use a direction of optical deviation that had been shown to increase pain levels, and so we were guided by Sumitani et al. (2007b) in our choice of posology and the use of right shifting prisms (towards her unaffected arm).

Table 1 shows the global time course of the experiment. During her two-week hospitalization AZ performed two PA sessions per day with 15° right-shifting prisms (towards the unaffected side). Each session was separated by at least five hours (e.g., 9 a.m. and 2 p.m.) and there was a 3-day break between the two weeks. Line bisection was measured 9 times throughout the intervention while visual and manual straight-ahead, open loop pointing, and pain were all measured before and after each adaptation session. Following Bultitude & Rafal's (2010) recommendations, AZ performed the pointing during prism adaptation with the left (painful) hand during the first week. We then switched hands and she performed the pointing during prism adaptation with her right hand during the second week. On the last session of the second week, prior to her discharge from the hospital, pointing during prism adaptation was performed with the left (painful) hand, with the aim of maximizing potential long-term pain-reducing effects of adaptation with the left hand. As the patient lived more than 600 km from the hospital we were not able to provide a further detailed follow-up. Nevertheless, she was able to return 8 months later for a follow-up measure of her spatial reference frames and pain level.

Statistical analysis

Despite the fact that the study was exploratory and was therefore not ideally designed for any one particular type of analysis, we used the Single-Case Experimental Design (SCED) approach to analyse our data, i.e. we considered recorded variables as time series and looked for changes in levels or trends during the two intervention weeks. We conducted our analyses using either R software or custom-made Python programs.

- Breakpoint detection and temporal evolution

The evolution of all variables over time was mathematically defined as a superposition of two linear functions reflecting the two different phases of the intervention (see equation (1)). Slopes a_1 and a_2 of the two phases, first session score y_0 and the moment of the transition t_0 between the 2 phases were fitted. This model was applied to Pain, MSA, VSA at 1m, VSA at 2m, OLP and line bisection measurements.

$$y(t)=\begin{cases} a_1 t+y_0 & (t<t_0) \\ a_2(t-t_0)+a_1 t_0+y_0 & (t\geq t_0) \end{cases} \qquad (1)$$

- Pain and straight-ahead data series

Using the R library *dynlm (Zeileis, 2019)*, we applied generalized linear models designed for time series. For more robustness, both pre-adaptation and post-adaptation measurements were taken into account. Since the line bisection series had fewer than ten points in all conditions it was impossible to use generalized linear models with these data. The final model takes this mathematical form:

$$Pain=\beta_1 f_{PP}+\beta_2 f_{LH_{OLP}}+\beta_3 f_{RH_{OLP}} \qquad (2)$$

With $f_{PP}, f_{LH_{OLP}}$ and $f_{RH_{OLP}}$ representing pre/post, OLP deviations of the left and right hands.

The choice of this model was motivated by the fact that our pre/post data are partly auto-correlated due to the repetition of straight-ahead measures before and just after adaptation. The fluctuations generated by the pre/post effect must therefore be "subtracted" (considered as a factor) from the real effects obtained for the right and left hands.

- Significance

We do not interpret our results using the classical rules of statistical significance. These data come from a single patient and we do not intend to extend her pattern of results to all CRPS cases. Instead, with this type of design what counts is to know if, at a certain moment, measures improved, remained stable, or eventually worsened. Thus, when the calculated slope values are known with precision (i.e. when the model fit is good), we present the 95% confidence interval [in square brackets], which gives a good quantitative idea of the rate of improvement (or worsening). On the contrary, when the values obtained by the fit are less precise, we consider only their sign (positive or negative). In these cases, a one-sided test was performed and therefore the 95% confidence intervals only consider the lower limit of the interval, the upper limit (in absolute value) being infinity. The question then becomes "is the slope strictly positive or strictly negative?". This technique allows us to determine whether there was any improvement or worsening, without knowing the exact extent. Only the absolute value of the lower limit of the interval makes it possible to quantify how much the slope differs from zero.

RESULTS

Following recommendations made for SCED (Krasny-Pacini & Evans, 2018) at least 5 points per phase are required to achieve sufficient robustness. Thus, in order to ensure the robustness of our statistics, we only analysed periods containing more than ten points (see Figure 1), namely week 1 and week 2 intervention periods. Data from the other periods are presented for visual comparison.[1]

1. *Temporal evolution of pain, VSA, MSA, OLP and line bisection measurements (all results are shown in Table 2 and Figure 1).*
   - Pain (Figure 1a)

     Unsurprisingly, pain ratings were highly variable. The optimal moment t0 where two slopes could be distinguished was the 23rd session [15.3, 30.7]. The 95% confidence interval for this moment was mainly in the second week, which began at session 16. In the first week pain reduced by approximately 24 pain units and the first week's slope was -1.7 pain units per session [-2.8, -0.5]. The second week's slope was +2.3 pain units per session. This did not reach significance, as the 95% confidence interval was [-3.8, 8.3]. Overall, these analyses show that pain decreased by approximately 30 pain units over a period of time that extended into the second week of the intervention.

   - Manual straight-ahead deviation (Figure 1b)

     Right hand deviations were relatively stable across the two adaptation weeks, fluctuating around -9° (significance was not reached for either of the two slopes, nor for the moment t_0). In contrast, two phases could be identified for left hand deviations. The moment t_0 was found to be at session 19 [12.4, 25.6], slightly after the end of the first week, and the slope of this first phase was 0.9° per session [0.5, 1.3], representing a rightward shift. The slope of the second phase was -0.2° per session but was not significant. These results show that manual straight-ahead deviation with the left hand improved (moved rightwards - towards the

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1 The visible two-order alternating pattern of the results is due to the fact that each day contained two adaptation sessions, each of which was preceded by a "pre" measure and followed by a "post" measure. This alternating pattern represents a short-term effect that is not meaningful in the context of this study in which we were interested in the clinical effects at the time scale weeks.

centre) at the end of the first week, during which adaptation was performed with the left (painful) hand. In contrast, right hand manual straight-ahead measurements remained left-deviated by about 10° across the two weeks. This result differs from that expected after adaptation with prisms deviating the visual field to the right, as *we would have expected (both hands) to show a leftward shift in proprioceptive deviation.*

- Open loop pointing (Figure 1c)

OLP with both hands led to significant “crossed” results. The t_0 moments of the transition between the two phases were found at session 18 for the right hand and session 22 for the left hand, with widely overlapping confidence intervals (see Table 1). The slope of the first phase was -0.4° per session for the right hand and +0.30 per session for the left hand, with widely overlapping confidence intervals (in absolute value). Slopes for the second phase were near zero and non-significant.

These data show that open-loop pointing shifted by approximately 6° for each hand, but this shift was leftward for the right hand and rightward for the left hand. This cross-over pattern occurred during the first week, when adaptation was performed with the left (painful) hand, but open-loop pointing measurements were stable in the second week, when adaptation was performed with the right (unaffected) hand.

- Visual straight-ahead (Figure 1d, 1e)

Visual straight-ahead measurements at 2m did not reveal any significant results. In contrast, for VSA at 1m the moment t_0 reflecting the transition between the two phases was significant at session 14 [6.6, 21.3], near the end of the first week but with a confidence interval that extended into the second week. The slope for the first phase (0.4° per session) was positive (indicating a rightward shift) with a unilateral 94% confidence interval of [0,+∞]. The slope for the second phase was smaller (-0.2° per session) and did not reach significance. The VSA results at 1m during the first week are consistent with what is expected when rightward shifting prisms are used. That is, a shift in the same direction as the visual deviation.

- Line Bisection (Figure 1f)

Line bisection performance with the right hand was relatively stable (around -8°) across the two intervention weeks. In contrast, bisection with the left hand shifted leftward across the two intervention weeks, although the slope was only significant during week two 0.7° [-0.1, 1.5].

- The patient reported a clinically significant event at the 17th session, between the two intervention weeks: the allodynic area on the back of her hand (corresponding to the fifth metacarpal area) changed to become dysesthesic. This change occurred over the week-end, when no experimental measures were conducted.

2. *Study of the link between pain, and pre/post adaptation open-loop pointing deviations using a linear model of pain*

- Open loop pointing (OLP)

Since OLP measures necessarily depend on visual and proprioceptive information, they cannot be independent of VSA and MSA measures. We therefore chose to investigate the effect of OLP on pain using the linear model defined by equation (2). This led to the following results: LH_{OLP}'s slope (β_2 in equation (2)) was -1.4 pain units per degree, for a unilateral 94% confidence interval of [-∞, 0] (94% chance of being negative), RH_{OLP} (β_3, same equation) had a slope of 1.8 pain units per degree, for a unilateral 93% confidence interval of [0,+∞] (93% chance of being positive) and Pre_{Post} showed a difference from pre to post of 13.9 pain units, for a unilateral 95% confidence interval of [0,+∞] (95% chance of being positive). *Therefore we observed a "crossover pattern" for the two hands: the integration of the proprioceptive and visual angular deviations acted negatively on pain when OLP was performed with the right (healthy) hand and positively when performed with the left (painful) hand.*

variable	regression coeff.	value	95% bilat. CI	p
pain	**slope week 1**	**-1.7**	**[-2.8 , -0.5]**	**0.003**
	slope week 2	2.3	[-3.8 , 8.4]	0.224
	t0	**23**	**[15.3 , 30.7]**	**0.000**
MSA left hand	**slope week 1**	**0.9**	**[0.4 , 1.3]**	**0.000**
	slope week 2	-0.17	[-1.0 , 0.7]	0.345
	t0	**19**	**[12.4 , 25.6]**	**0.000**
MSA right hand	slope week 1	-0.8	[-2.6 , 1]	0.181
	slope week 2	-0.1	[-0.3 , 0.2]	0.259
	t0	**8**	**[0 , 16.7]**	**0.035**
VSA 1m	slope week 1	0.4	[-0.1,0.9]	0.063
	slope week 2	-0.2	[-0.4,0.1]	0.081
	t0	**14**	**[6.7,21.3]**	**0.000**
VSA 2m	slope week 1	0.1	[-0.1 , 0.3]	0.171
	slope week 2	0	[-0.5 , 0.5]	0.497
	t0	21	[-15.5 , 57.5]	0.125

OLP left hand	**slope week 1**	**0.3**	**[0.1 , 0.6]**	**0.006**
	slope week 2	-0.16	[-1.2 , 0.9]	0.379
	t0	**22**	**[9.9 , 34.1]**	**0.000**
OLP right hand	**slope week 1**	**-0.4**	**[-0.7 , -0.1]**	**0.002**
	slope week 2	0	[-0.4 , 0.4]	0.490
	t0	**18**	**[8.6 , 27.3]**	**0.000**
Bisec. left hand	slope week 1	-0.5	[-0.3 , 0.4]	0.341
	slope week 2	**0.7**	**[-0.1 , 1.5]**	**0.047**
	t0	9.6	[-4.8 , 24.1]	0.080
Bisec. Right hand	slope week 1	0.06	[-0.3 , 0.4]	0.354
	slope week 2	-0.2	[-0.8 , 0.4]	0.243
	t0	19	[-5.2 , 43.2]	0.053

Table 2: Fitted coefficients for two-slope linear regressions. The two slopes and the transition moment are given for all variables as well as 95% bilateral confidence intervals and p-values. Significant values are in bold.

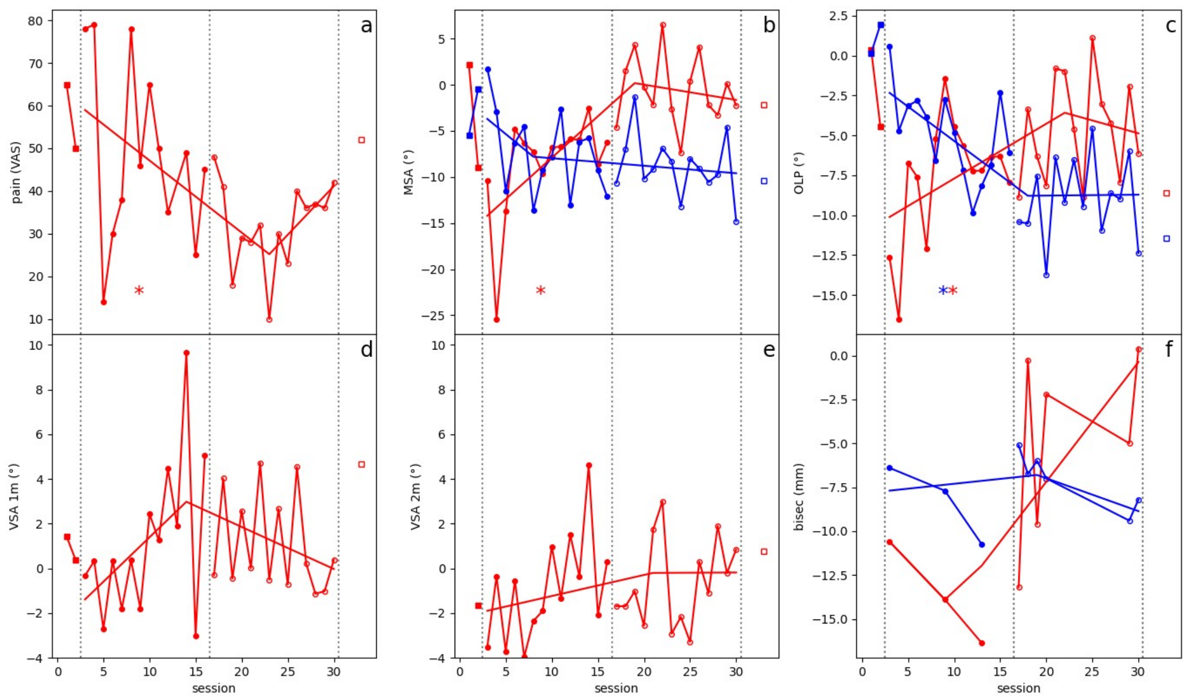

Figure 1: a. *Temporal evolution of pain,* ***d.*** *visual straight ahead (VSA) and* ***b.*** *manual straight ahead (MSA),* ***c.*** *open-loop pointing (OLP) and* ***f.*** *line bisection (bisec) during the baseline, intervention (week 1, week 2) and follow-up. Blue (cyan) lines represent measures taken with the right hand and red lines represent left hand or non-manual measures. Asterisks represent periods in which slopes were significant. Straight lines, either blue or red, show fitted values. For all measures (other than pain) negative values represent deviations to the left (affected) side.*

DISCUSSION

In this exploratory report of a single patient we aimed to retrospectively analyse the potential mechanisms that lead to pain amelioration during prism adaptation treatment. This longitudinal case study was not intended to specifically address the potential therapeutic effects of prism adaptation in CRPS. As a single case study, the question of external validity cannot be addressed. Instead, we wanted to make use of this unique, dense data-set to explore the processes possibly involved in pain reduction during prismatic adaptation. Our results show that the patient reported pain relief (in the form of reduced VAS measurements) throughout the two-week intervention. Figure 1a clearly illustrates a decrease in pain ratings that lasted throughout week 1 and into the beginning of week 2, which was followed by a slight, non-significant increase. At the same time, measurements of manual straight ahead deviations also evolved: deviations either improved by moving towards the centre (left hand manual straight-ahead and open-loop pointing), or they remained stable (right hand manual straight-ahead and open-loop pointing). The temporal profiles extracted by our analysis showed that marked changes appeared at similar times for different parameters: left hand manual straight-ahead and left and right hand open-loop pointing all showed a significant change in slope around the same time (about the 20th session, after the end of the first week). Crucially, this time point also corresponded to a change in the evolution of pain measurements.

It is noteworthy that all the transitions occurred around the end of the first week during which adaptation was performed with the left (painful) hand. During the second week (when the right hand performed the pointing during the adaptation sessions) measures were mostly stable or changed only slightly. Interestingly, our data show that the pain-reducing effect of the first week's adaptation continued beyond the first week until 2 days after the start of the right-hand adaptation sessions. The time course of changes in all relevant variables was very similar: the period of time before a statistically proven transition was longer than the duration of the first week of the intervention. After this time, pain increased slightly, although non-significantly. The time course of our results is consistent with a previous study showing both a time lag between PA introduction (or hand change) and positive effects on pain and a positive effect on pain when PA was performed with the painful hand (Bultitude & Rafal, 2010).

The use of right-shifting prisms meant that, irrespective of the hand used to perform the pointing during the prism adaptation sessions or the hand used to perform the manual straight ahead or open loop pointing, we expected to observe a leftward shift in manual angular deviations and a rightward shift in visual deviation. Our results for the visual deviations and for the manual deviations of the right hand were consistent with this prediction. For the left hand, however, we observed the opposite: manual straight ahead deviations and open loop pointing shifted to the right, improving to almost zero at the end of the first week whereas we expected them to shift to the left.

Crucially, measurements made with the right (unaffected hand) suggest that all the processes normally involved in PA (the direction of angular drifts, the multisensory integration of visual and proprioceptive cues measured by OLP) took place as expected, but this was not the case for the left (pathological) hand. Thus, even though pain improved, there was a non-expected response of the left (painful) hand.

These results may be linked to the hypothesis put forward by Harris (1999) that pain emerges from an incongruence between motor intention and real movement perception. Verfaille and colleagues (2019) also suggested that movement could be hampered by disorganization of the cortical somatotopic representations of the pathological limb due either to the peripheral lesions related to the accident or an initial operation, or to the slow interaction between chronic pain and effective use of the limb. According to this idea, improvement of the left (painful) limb would then be responsible for normalization of movement execution and, according to Harris' hypothesis, for pain relief. This reinforces the existence of a common process involving pain, body representation, egocentric frames of reference and visuomotor spatial attention, and suggests that the links between the various aspects of CRPS must be studied more precisely, and that the concept of “neglect-like” symptoms in CRPS based on the analogy of hemineglect following a stroke is probably too simplistic (Halicka et al., 2020a).

Sumitani (2007a,b) described a clear bias towards the painful limb in visual egocentric reference frame measured at 2m with a reversal of this bias after adaptation with prisms that shifted vision towards the unaffected limb (2007b). In our patient, visual straight ahead measured at both 1 and 2 meters was initially shifted leftwards towards the painful limb. VSA at 2m did not evolve significantly during the intervention and thus did not correlate with changes in pain (Figure 1e) whereas VSA at 1m shifted rightward during the first phase of the intervention. Interestingly, not all studies have reported a consistent bias in VSA towards the affected limb. Reinsersman and colleagues (2010) found a median leftward deviation regardless of the affected side and Kolb and colleagues (2012) found no significant difference between CRPS patients and controls (but with data from left and right pathological sides pooled). This heterogeneity (see also Wittayer et al., 2018 for a description of an association of neglect-like symptoms with pain) suggests that there is large between-patient variability in this parameter. The conclusion made by Halicka et al. (2020b) that attentional deviations in CRPS patients at the group level are likely overestimated should not prevent us taking into account individual patients on a case-by-case basis, some of whom may have substantial biases. Even if CRPS cannot be described in terms of spatial distortion, the close links between egocentric reference frames, body somatotopic representations, and spatial cognition probably leads, at least in some patients - like AZ, to shifts in egocentric reference frames.

CONCLUSION

The aim of this exploratory report was to investigate the potential mechanisms leading to pain improvement after prism adaptation in a patient with chronic CRPS. We observed a significant decrease in pain levels following prism adaptation using a visual shift towards the unaffected hand, but only when adaptation was performed with the painful hand. These results show that prism adaptation can be a possible intervention tool for the treatment of CRPS, even when the painful hand shows an unexpected pattern of spatial behaviour. In order to better understand the mechanisms of pain relief from prism adaptation future these studies should include in a group of patients with lateral egocentric reference frame biases and should pay particular attention to the behaviour of both hands.

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