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Pain reduction due to novel sensory-motor training in Complex Regional Pain Syndrome I – A pilot study

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HIGHLIGHTS

- Proof-of-principle successfully implemented home-based sensory-motor training in CRPS.
- Home-based sensory-motor self-training leads to a significant reduction pain.
- Pain reduction is correlated with reduction in pain disability and depresivity.

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ABSTRACT

Background and aims: Patients suffering from Complex Regional Pain Syndrome (CRPS) of the upper limb show a changed cortical representation of the affected hand. The lip area invades the former hand area contralateral to the affected hand. This change in cortical representation is correlated to the intensity of ongoing pain in patients with CRPS. Further studies revealed that restoration of the original representation coincides with a decrease of pain. Sensory-motor training protocols can increase and/or relocate cortical somatosensory and motor representation areas of the fingers, as shown, for example, in Braille reading individuals and professional violin players. Further, there is evidence that sensory-motor discrimination training has a beneficial effect on both the intensity of pain and the mislocalization of sensory-motor cortical areas in CRPS patients. Based on these propositions, we developed a novel sensory-motor self-training paradigm for CRPS patients to use in a home-based manner.
Methods: Ten CRPS patients performed the sensory-motor training for 2 weeks. The training consists of a braille-like haptic task with different training modes (bi-manual, speed and memory training). During the training, as well as 1 week before and after, patients were asked to fill out pain diaries. Furthermore, measures of impairment were acquired at baseline and post training.
Results: Patients showed significant pain reduction after the 2 week training period. The overall disability as well as the depression scores showed a trend to improve after the 2 week training. The reduction in pain was correlated with the total amount of training performed.

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Abbreviations: CES-D, Center for Epidemiological Studies – Depression Scale; CRPS, Complex Regional Pain Syndrome; M1, Primary motor cortex; PDI, Pain Disability Index; PT, Physical Therapy; S1, Primary sensory cortex; ST, Sensory-motor Training; tDCS, Transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; VAS, Visual Analogue Scale.

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Conclusions: This is a first proof of principle study of a novel sensory-motor self-training protocol to reduce pain in CRPS patients. The more consistent the patients trained the larger the pain reduction. Sensory-motor training, which can be performed on a regular basis at home might provide a novel interventional strategy to improve symptoms of CRPS.
Implications: Although a larger study needs to be conducted to confirm our findings, including long-term follow-up, the results show, that a sensory-motor home-based training is a strategy worth exploring further for the reduction of pain as well as high frequency training for patients with CRPS.

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition typically affecting one limb, often after minor injury or trauma to that extremity. It is associated with poor quality of life, and considerable healthcare and societal costs with limited success from current treatment strategies [1]. While pain is the main symptom (93% [2]), other symptoms include impairments in sensory and motor performance [3], as well as changes in body perception [4] and tactile acuity [5]. Unfortunately, despite the availability of analgesic medications, no treatment has been found that benefits the majority of individuals with CRPS [6]. As multimodal, interdisciplinary therapy seems to be the most effective treatment, a large part of this approach is physical therapy (PT) to regain mobility. Graded motor imagery may be effective [6], however, therapies in clinical environments are time and cost intensive and achieve only limited treatment frequency. Thus, a cost-effective approach with a high therapy density, in form of a daily training over the course of several weeks or even months, requires self-training at home.

The pathophysiological mechanisms of CRPS are not completely understood [3,7]. Yet, evidence suggests that maladaptive neuroplastic cortical changes, especially in the sensory-motor cortex, may play a role in the development and maintenance of chronic neuropathic pain [8]. Changes in cortical representation and body representation in the primary somatosensory (S1) [9] and motor (M1) [10] cortex in the form of shrinkage of the hand representation were identified in CRPS patients [11–13]. The amount of these neuroplastic changes are correlated with the intensity of ongoing pain [14,15]. Furthermore, restoring the original representation of the hand has been shown to be associated with reduction in pain levels [16].

Sensory-motor training in healthy subjects has been demonstrated to be associated with neuroplastic mechanisms leading to changes in cortical representation, such as an increase of the somatosensory or motor cortical maps (e.g. [17,18]). Learning paradigms, e.g. working with Braille characters, led to enlarged cortical representation of the reading finger [19]. Several studies from Moseley et al. [5,20] demonstrated beneficial effects of sensory discrimination training on pain in CRPS patients. In this study, a tactile discrimination training was compared to tactile stimulation. Whereas the tactile stimulation did not have any effect on pain or two point discrimination, the tactile discrimination training had beneficial effects on both [5]. In a further study, they found an additional beneficial effect when the tactile discrimination training was combined with a mirror training [20]. In further studies, higher pain levels were associated with lower tactile acuity [21] as well as body scheme disturbances [22].

Taken together, this evidence clearly suggests that sensory-motor training can functionally alter cortical representation areas which may result in a decrease in pain.

Our novel sensory-motor self-training (ST) protocol is developed to be used by the CRPS patients in their home environment. The ST is comparable to Braille reading where patients are trying to identify patterns by touch.

The idea behind this treatment is that impairments in the motor and sensory domain will be positively influenced by non-painful tactile differentiation training of the affected hand, with subsequent decrease of pain, enhanced use and mobility of the affected limb. As the fear of pain leads the patients to reduce or even avoid movements of their painful limb, it was crucial to develop a training that can achieve high training density without inducing pain. Thus, we hypothesized in the present study that home-based ST of the hand in patients suffering from CRPS at the upper extremity will lead to a reduction of CRPS symptoms.

2. Materials and methods

2.1. Participants

Ten CRPS I (according to Budapest criteria [23,24]) patients (3 male; age, mean ± standard deviation 58.4 ± 11.23) participated in the protocol after giving their informed consent (see Table 1). All of them were right-handed according to the Edinburgh handedness inventory [25]. Four subjects were affected on the left, six on the right upper limb. Quantitative sensory testing was reported comparing the affected with the unaffected hand (Table 1). The protocol used is the one used by the German Research Network on Neuropathic Pain (DFNS) [26,27]. The mean pain duration was 42.7 ± 79.7 months with a minimum of 2 months pain duration and a maximum of 264 months (22 years). Written informed consent was obtained from all subjects according to the Declaration of Helsinki (www.wma.net/en/30publications) and with approval from the local Ethics Committee of the Medical Faculty of the University of Tuebingen.

2.2. Sensory-motor training (ST)

2.2.1. ST training

The ST was developed by our pain research labgroup at the Medical Psychology in Tuebingen (Fig. 1). The ST is based on the concept of meaningful perceptual discrimination training (pattern recognition). We used Duroplastic discs (diameter 5 cm) with small embedded metallic spheres (diameter 15 mm). The spheres are elevated on the disc, such that they can be recognized by moving a fingertip over them. The shapes we used are one dot, two dots, three dots in a row, a triangle, a square and an arrow (Fig. 1D).

The training was constructed with two different degrees of difficulty, which are represented by different distances between the metallic spheres: “easier” shapes with 5 mm distance and “more difficult” ones with 2.5 mm distance (Fig. 1E).

All CRPS patients were asked if they experienced an increase in ongoing pain during the sensory-motor sessions. No CRPS participant reported an increase in ongoing pain. Furthermore, the movements of the ST are feasible even with reduced strength and may therefore help the patients in regaining function in the affected hand. Recent studies indicated that passive movement training does not improve task performance, cortical organization or CRPS symptoms [13].

Table 1
Description of the 10 patients including affected side, age, sex, pain duration as well as resting pain pre and post training. Further CRPS signs and symptoms are reported as well as the QST changes in the affected vs. the non-affected hand.

Code	Affected hand	Age	Sex	Pain duration (months)	Resting pain pre treatment (VAS)	Resting pain post treatment (VAS)	Spread	Pain	Allodynia/ hyperalgesia	Edema	Temperature changes	Hair/finger nail growth	Motor impairment	QST measures
330	L	54	M	24	6	3	Hand, fingers	Burning	+/+	–	–	–/–	+	Lower HPT, higher CPT, higher PPT, lower MPT
331	R	51	M	12	4	2	Hand, fingers	Stabbing	–/–	+	–	+/+	+	Higher MPT
332	R	57	F	264	5	3	Hand, fingers, lower arm		+/+	+	+, Bluish	–/–	+	Lower PPT, low vib.T, lower MPT, lower HPT, higher CPT
334	R	73	F	24	3	2.3	Hand	Stabbing	–/–	+	–, Redish	–	+	
335	L	55	F	12	2.6	0.8	Hand, fingers	Stabbing	+/+	–	+, Bluish	–/–	+	Thermal testing too painful, lower MPT, aftersensation
336	R	72	F	2	5	4.3	Hand, fingers, wrist, lower arm	Stabbing	–/+	+	+	–/–	+	Lower MPT, lower PPT, higher CPT, lower HPT
337	R	40	F	60	4	4.1	Hand, fingers, lower arm	Stabbing	–/+	+	+, Marbeled	+/+	+	Lower MPT, lower PPT, lower CPT
338	L	48	F	2	7.7	8.7	Hand, fingers, lower arm	Dull, burning	+/+	–	+	+/+	+	
339	L	58	M	3	3.3	3	Hand, fingers	Stabbing, burning	+/+	–	+	–/–	+	Lower HPT, lower PPT
340	R	73	F	24	4.5	3.6	Hand, arms	Stabbing	+/+	+	+	–/–	+	Lower PPT, lower MPT, lower HPT, lower CPT

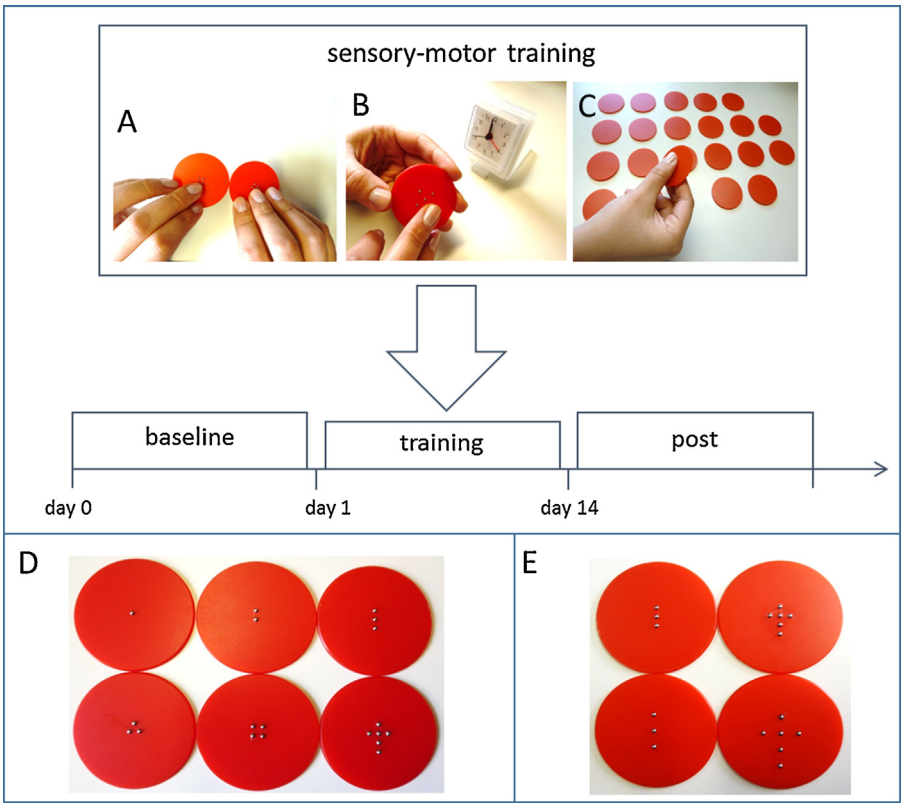

Fig. 1. Time course of experimental design. Patients come in for testing on day 0 for the baseline and day 15 for the post assessment. Day 1 until day 14, the patients are training by themselves at home and fill out their pain and training diary every day. Sensory-motor training: Patients were using three different training modalities provided: (A) bi-manual training, where the participant uses both hands to recognize the same pattern; (B) speed training, where the participant tries to recognize patterns as quickly as possible with the affected hand; (C) Memory Game like training modality where the participant needs to identify two identical patterns just by haptic recognition with the affected hand; (D) all 6 different patterns patients have to recognize (one dot, two dots, three dots in a row, triangle, square and arrow); (E) two different degrees of difficulty, further apart = easier (lower part of the figure), closer together = more difficult (upper part of the figure).

2.2.2. Three training modes (bi-manual, speed and memory training)

The patients performed three different modes of ST over a 2-week period (Fig. 1A–C). The first training mode was the "bi-manual" training (Fig. 1A), where the same pattern was haptically explored with the affected and the non-affected hand at the same time. Therefore, we expected better learning due to intercortical transfer of learning [28,29] and thereby an increased learning effect within the affected hand.

The goal of the second mode of training (speed-training) was to recognize the patterns of all discs as quickly as possible (Fig. 1B). The patients were instructed to use their affected hand to haptically recognize all patterns as quickly as possible. They recorded, using a timer, how many minutes it took them to recognize all the patterns and how many shapes they used to train.

The third mode of training was called "memory" where, like in the game "Memory", pairs of two identical pictures have to be identified by turning two cards at a time. If the two pictures have the same pattern, the person can keep both, if they are different, they need to go back on the table. Here, the patients had to identify two identical patterns using only their haptic sense for the disc recognition (Fig. 1C). To keep compliance high, this training mode could be performed together with a partner (e.g. partner, grandchildren). The patients recorded if they trained by themselves or with a partner.

2.2.3. Training instructions

The patients were instructed how to use the different training modes. Further, they were instructed to start out with the bi-manual training, moving on to the speed-training and the memory training as soon as they felt comfortable (Supplementary Material 1). The patients allocated a different amount of time to the different training modes depending on their abilities and individual state of training. The patients had to monitor how long they trained with each of the different training modes as well as record whether they did any other training with the hand by using a training diary (Supplementary Material 2).

Before and after the 2 weeks of training we assessed different measures of pain and impairments due to the pain (study design: Fig. 1).

2.3. Training and pain evaluation

For evaluating the amount of training and pain the patient experienced, we used a diary where the participants recorded how much they were training in which training modality. They also rated their pain on a visual analogue scale (VAS 10 cm, 0 = no pain; 10 = most pain imaginable). We accumulated additional information about the different modes of training which were performed and the time spent on each mode (in minutes as well as how many patterns were recognized). For the full set of questions see Supplementary Material 2.

2.4. Questionnaires

To evaluate the impairment caused by the CRPS, we used the pain disability index (PDI) [30] to measure impairment before and after the training period. The PDI uses seven items asking about the impairment experienced due to the pain in seven areas of everyday life. We also evaluated depression with the Center of Epidemiologic

Table 2
Display of the training evaluation for each patient in amount of training separated in different training modes as well as time of day (values are expressed as mean ± SD).

Code	Both handed training			Speed training			Memory training		
	Morning	Afternoon	Evening	Morning	Afternoon	Evening	Morning	Afternoon	Evening
330	56.8 ± 8.7	51.6 ± 16.7	50.6 ± 17.6	0	0	0	42.9 ± 13.0	41.5 ± 12.7	42.1 ± 17.1
331	0	0	12.4 ± 7.2	0	0	1.4 ± 3.6	0	0	0
332	0.6 ± 0.5	0.7 ± 0.5	0.4 ± 0.5	5.4 ± 7.7	10.0 ± 5.9	8.2 ± 6.0	0.2 ± 0.4	0.2 ± 0.4	0.4 ± 0.5
334	0	3.6 ± 8.4	2.1 ± 5.8	0.4 ± 1.3	0	0.4 ± 1.3	0	0	0
335	0	2.1 ± 5.4	5.4 ± 7.7	0.4 ± 1.3	0.7 ± 2.7	3.0 ± 5.5	0	0	0
336	0.7 ± 2.7	0.7 ± 2.7	0.9 ± 3.2	3.1 ± 3.5	5.4 ± 3.7	7.6 ± 5.4	5.4 ± 4.1	3.4 ± 4.0	9.6 ± 4.1
337	2.6 ± 2.1	2.9 ± 2.7	7.2 ± 4.7	2.9 ± 3.0	3.1 ± 3.0	5.1 ± 3.8	6.7 ± 6.8	6.1 ± 5.9	7.4 ± 5.6
338	1.9 ± 3.3	0.7 ± 2.7	1.4 ± 3.1	2.6 ± 4.5	0.7 ± 2.7	1.6 ± 3.4	1.8 ± 3.7	0.7 ± 2.7	2.7 ± 6.5
339	1.5 ± 2.9	3.2 ± 5.4	8.2 ± 9.5	0	0.7 ± 2.7	3.2 ± 5.4	0	0.7 ± 2.7	2.2 ± 5.8
340	2.8 ± 5.5	3.9 ± 8.4	0.8 ± 2.0	3.8 ± 5.3	2.9 ± 5.8	1.1 ± 2.9	0	0	0

Amount of training participants performed at different times of day and different modes of training.

Studies Depression Scale short form (CES-D) both before and after training [31].

2.5. Statistics

The statistical evaluation was done using SPSS 22 (IBM SPSS Statistics Base 22, Chicago). The data were tested for normal distribution using the Kolmogorov–Smirnow-Test. For Data that were normally distributed, paired *t*-tests were used to compare before vs. after treatment measures. Pearson correlations were performed. We used one-sided tests as we hypothesize an improvement due to the training. All data that were not normally distributed are marked accordingly. For non-normally distributed data, Wilcoxon signed rank tests and Spearman correlations were used.

3. Results

3.1. Performance

The inter-individual training performance of the patients varied. As the training data are not normally distributed, all statistics regarding the training information are reported with non-parametrical measures. The total average training time per day was between 10.7 min and 285.4 min (median 16.8). The different modes of training were allocated different amounts of training time by the participants (Tables 2 and 3 and Fig. 2).

The bi-manual training was performed by all participants, but less so over time (minimum of 2 days) (Table 2). All but one participant performed the speed training, and the number of patients training with the speed training remained stable over time (minimum of 2 days) (Table 2). The memory training was not used by four of the participants; towards the end of the 2-week training period the memory training was performed less. Four participants reported that they trained every day (14 days), whereas one participant trained five of the days (see Table 3 & Fig. 3).

Only three participants performed the memory training together with a partner, whereas only one of them trained with a partner more than one time during the 2-week training period.

3.2. Pain rating

Pain ratings averaged 4.5 ± 1.52 (mean ± SD) on the 10 cm VAS (Fig. 3a) before the intervention; after the 2 weeks of training the average pain rating was 3.5 ± 2.09 (mean ± SD). The changes in VAS pre-post averaged 1.0 ± 1.19 (mean ± SD) with a range between −1 and +3, which represented a statistically significant decrease ($t(9) = 2.748$, $p = 0.023$). A partial correlation analysis between the total amount of training (in minutes) and the magnitude of pain

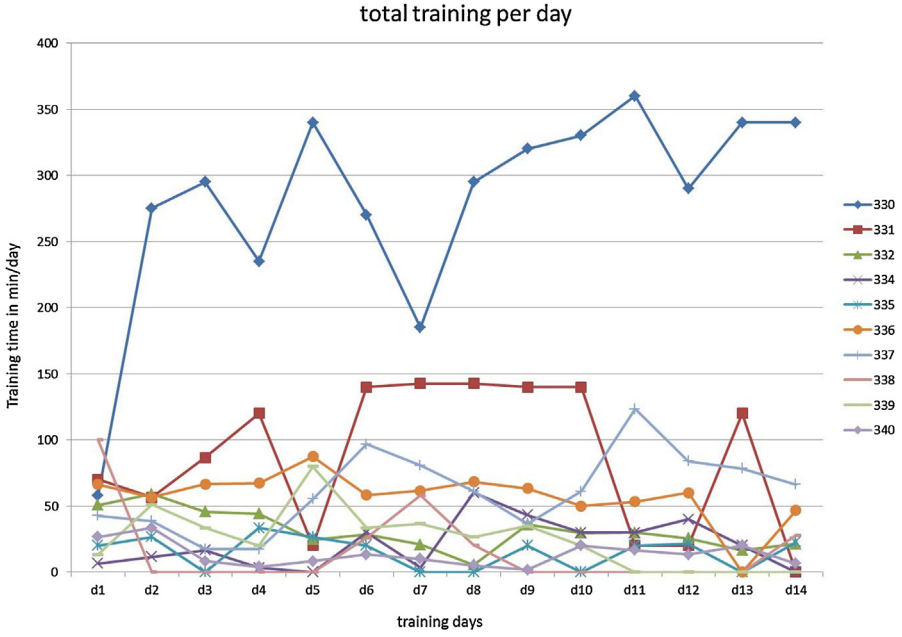

Fig. 2. Total training time per day (all modes of training taken together) for every participant. d1–d14 = day 1–14.

Table 3
Display of days participants did not train.

	d1	d2	d3	d4	d5	d6	d7	d8	d9	d10	d11	d12	d13	d14
330														
331				x									x	x
332														
334	x	x			x	x		x				x	x	x
335	x	x				x		x					x	
336														
337				x										
338		x	x	x	x				x	x	x	x	x	
339											x	x	x	x
340														

Days participants did not train at all.

Fig. 3. Behavioral results: (a) Changes in visual analogue scale (VAS) ratings before and after the 2 weeks of training; please note the significant reduction of pain with training. (b) Changes in pain disability index (PDI) before and after; (c) Changes in Depressivity (CES-D score) before and after. * corresponds to $p < 0.05$.

reduction while controlling for the duration of pain revealed a significant association ($r = .66$, $p = 0.025$).

Furthermore, the amount of reduction in pain shows a tendency to correlate with the regularity of training (days trained), such that the more days the patients trained, the more pain reduction they experienced ($r = .54$; $p = 0.053$, n.s., 1-sided).

3.3. Questionnaires

The baseline ratings for the PDI (Fig. 3b) were on average 37.6 ± 19.36 (mean $\pm$ SD), while after the treatment the ratings were reduced to an average of 25.3 ± 19.77 (mean $\pm$ SD). There was a trend towards lower disability scores (PDI sum) post training ($t(9) = 2.008$, $p = 0.076$, n.s.).

The decrease in pain was significantly correlated with the reduction in pain disability (VAS-PDI, $r = .598$, $p = 0.034$, 1-sided).

Baseline CES-D values (Fig. 3c) averaged 19.2 ± 8.99 (mean $\pm$ SD), where after the 2 week treatment period the scores were reduced to 13.3 ± 10.69 (mean $\pm$ SD); this decrease in depression scores shows a clear trend, however, it did not become statistically significant ($t(9) = 2.191$, $p = 0.056$, n.s.). The decrease in pain (VAS) was statistically significantly correlated to the decrease in CES-D ratings ($r = .84$, $p = 0.001$, 1-sided).

4. Discussion

The present data suggest, that a 2-week home-based, sensory-motor training can significantly reduce the intensity of pain in CRPS I patients.

The ST was designed as a non-painful, meaningful and challenging haptic training with different training aspects, so the patients focus their attention on the material throughout the training period [32]. The training experiences varied among the patients with the amount of training between ~10 min and almost 4 h per day (Fig. 2). Analysis revealed a strong, positive association between training duration and the magnitude of pain reduction. The differences in the amount of training are partly due to the participants' variable capacities for different levels of movement. Some patients mainly trained using one or two of the different modes suggested.

The three different modes of sensory-motor training could be selected by the patients according to their individual capacity to move the hand. The patients were advised to start with the bimanual training. This was especially important in cases, where the movement of the hand was very restricted. However less movement impaired patients focused more on other modes of training.

The social interactions with a second person during the memory mode training did not find favor with the patients. Only three of the patients tried the training with a partner and only one participant repeatedly trained together with another person. This might be due to the lack of a partner to train with, however it is also possible that training with a non-impaired partner results in increased frustration due to lower performance. In the future, this might be circumvented by having two patients with matching degrees of mobility train together.

The home-based sensory-motor training derives from the fact that CRPS-patients experience pain while performing more extended movements. Our training paradigm demands only small and slight movements of the hand and therefore does not exacerbate the patient's ongoing pain. It was important for the training to include aspects which kept attention high, challenged working memory, and thus kept the training meaningful with a clear goal [32].

Furthermore, our results are in line with data from other neurorehabilitative training-based treatments, which also show a clear association between the amount of training and reduction of symptoms [33].

Maihöfner and colleagues (2003) showed that CRPS patients developed cortical changes in the representation of the affected limb [12]. Specifically, the lip representation "invades" the hand area in S1 cortex contralateral to the affected side. These maladaptive changes subside when the pain decreases [34,35] leading to a 'back-to-normal' cortical representation comparable to the

"healthy" side. Based on previous work, one can reasonably hypothesize that comparable maladaptive cortical changes occurred in the present group of CRPS patients as demonstrated before [35]. Given the finding that intensive training leads to cortical plasticity and reorganization, as demonstrated e.g. in violin players [17] and braille language readers [19], it is feasible to suggest that the CRPS patients might show a reversion of the maladaptive cortical plastic changes with the intensive training of the affected upper limb used here. It is mandatory in the future to evaluate the effects of ST on cortical representation with modern neuroimaging techniques, such as MEG or fMRI, to validate these neurobiological hypotheses.

The major limitations of this study are the small sample size and the lack of a placebo control group. Furthermore, we did not assess treatment expectancy and thus we cannot completely rule out an effect due to the participant's expectancy. Most participants who did benefit from the ST however did have pain for a prolonged period of time. The pain ratings of the two participants whose pain duration were only 2 months at the time of study participation did not benefit much from the training. The patient who trained the fewest days showed an increase in pain rating despite the short duration of the condition. The participant who trained the most in the study group achieved the largest pain reduction (3 points on VAS) after the 2 week training.

Further, behavioral measures of the sensory and motor impairments before and after training would have been helpful to quantify the changes in impairment. For measuring impairment in daily life we had used the PDI, which showed a clear trend of improvement (effect size $r = 0.56$). Similar results were found for the CES-D measure of depression (effect size 0.59).

The training resulted in a mean pain reduction (effect size $r = 0.68$) of 1.03 on a 0–10 VAS scale, although individual patients reached a pain reduction of 3 points. The pain reduction over all is not very large and the clinical impact on the symptoms of the patients is moderate.

However, the approach is promising and might have, if applied more intensively or combined with other interventions such as brain stimulation, a clinically significant effect. The training only had a duration of 2 weeks and was performed without supervision from expert staff. For the future, the method might benefit from a more rigid training plan and a longer training period.

The effect of the 2 week sensory-motor training was moderate, however compared to other non-pharmacological treatments, the treatment duration with a period of just 2 weeks is on the shorter side. Other studies, e.g. Moseley [36] used a longer training period of 6 weeks. Compared to other studies using non-pharmacological treatment methods the effect seems moderate but promising. Moseley [36] reach about a ~10 point (of a 100point NRS) pain reduction after 2 weeks of their 6 week total training time; whereas after the total 6 week training a ~20 point pain reduction is shown. A prolongation of the total training period would therefore need to be tested.

In this context it is important to mention that the present study is a proof-of-principle study with a relatively short training period. However, as the training is home-based, it would be feasible to have longer and more intensive training with a more rigorous training plan. This scenario would be expected to lead to a larger magnitude of symptoms improvement and thus clinical impact.

5. Conclusions

In summary, the present work provides first proof-of-principle evidence that home-based sensory-motor self-training can be successfully implemented in CRPS patients and can lead to a significant reduction of CRPS symptoms.

6. Implications

Development of home-based therapeutic regimens is essential for wide-spread application of regular, non-invasive, high-density approaches to chronic pain amelioration. Compared to other studies using non-pharmacological treatment methods we had used a rather short training period where the patients trained at home by themselves, whereas in other training protocols the training took mostly place in a laboratory setting or was performed over a longer training period. To improve on the moderate but promising effects of our sensory-motor training a prolongation of the training would be beneficial.

Other innovative approaches to enhance neuroplasticity include non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) [37–39]. Such approaches can be combined with behavioral training, as has been demonstrated in stroke patients ([40], for review see [41]). Combining non-invasive brain stimulation with the present sensory-motor training to enhance the magnitude of the effects seems potentially valuable. In particular, tDCS can even be applied in a home-based manner, as has been done for other neurological conditions [42]. Thus, to establish this home-based training from proof-of-principle towards clinical application more extensive evaluations and evidence of treatment efficacy is necessary to implement it in regular treatment routines, providing a potentially cost effective and motivating treatment strategy.

Author contributions

All authors discussed the results and commented on the manuscript.

Ethical issues

Written informed consent was obtained from all subjects according to the Declaration of Helsinki (www.wma.net/en/30publications) and with approval from the local Ethics Committee of the Medical Faculty of the University of Tuebingen.

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Conflict of Interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sjpain.2016.11.003.

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