BRAIN COMMUNICATIONS

Graded motor imagery modifies movement pain, cortical excitability and sensorimotor function in complex regional pain syndrome

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Patients with complex regional pain syndrome suffer from chronic neuropathic pain and also show a decrease in sensorimotor performance associated with characteristic central and peripheral neural system parameters. In the brain imaging domain, these comprise altered functional sensorimotor representation for the affected hand side. With regard to neurophysiology, a decrease in intracortical inhibition for the sensorimotor cortex contralateral to the affected hand has been repetitively verified, which might be related to increased primary somatosensory cortex functional activation for the affected limb. Rare longitudinal intervention studies in randomized controlled trials have demonstrated that a decrease in primary somatosensory cortex functional MRI activation coincided with pain relief and recovery in sensorimotor performance. By applying a randomized wait-list control crossover study design, we tested possible associations of clinical, imaging and neurophysiology parameters in 21 patients with complex regional pain syndrome in the chronic stage (>6 months). In more detail, we applied graded motor imagery over 6 weeks to relieve movement pain of the affected upper limb. First, baseline parameters were tested between the affected and the non-affected upper limb side and age-matched healthy controls. Second, longitudinal changes in clinical and testing parameters were associated with neurophysiological and imaging parameters. During baseline short intracortical inhibition, as assessed with transcranial magnetic stimulation, was decreased only for hand muscles of the affected hand side. During movement of the affected limb, primary somatosensory cortex functional MRI activation was increased. Hand representation area size for somatosensory stimulation in functional MRI was smaller on the affected side with longer disease duration. Graded motor imagery intervention but not waiting, resulted in a decrease of movement pain. An increase of somatosensory hand representation size over graded motor imagery intervention was related to movement pain relief. Over graded motor imagery intervention, pathological parameters like the increased primary somatosensory cortex activation during fist movement or decreased short intracortical inhibition were modified in the same way as movement pain and hand performance improved. No such changes were observed during the waiting period. Overall, we demonstrated characteristic changes in clinical, behaviour and neuropathology parameters applying graded motor imagery in patients with upper limb complex regional pain syndrome, which casts light on the effects of graded motor imagery intervention on biomarkers for chronic neuropathic pain.

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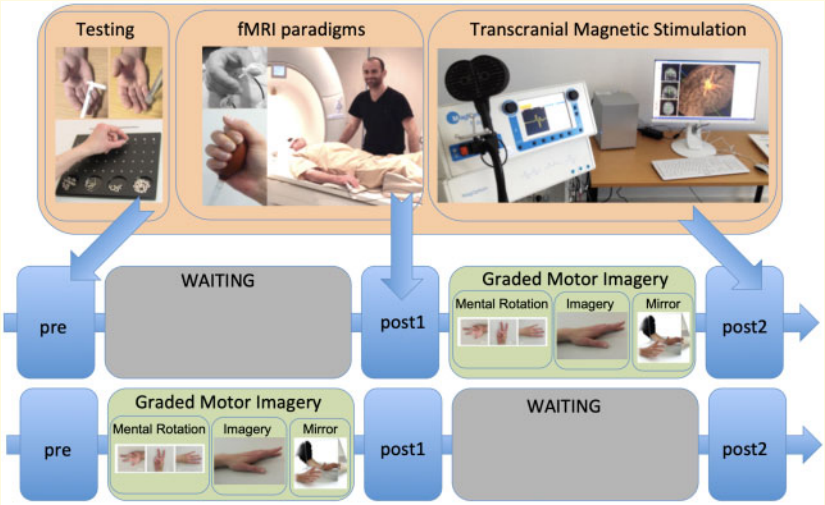
Abbreviations: CRPS = complex regional pain syndrome; CSS = CRPS severity score; CST = cutaneous sensory thresholds as evaluated with vonFreyhair filaments; D1–D5 = thumb to little finger; DASH = disabilities of the arm, shoulder and hand; fMRI = functional magnetic resonance imaging; GLM = general linear model; GMI = graded motor imagery; GOT = grating orientation task as evaluated with domes; M1 = primary motor cortex; rm = repetitive measures; Roeder = Roeder Manipulative Aptitude Test; S1 = primary somatosensory cortex; SPM = statistical parametric mapping; SPSS = Statistical Package for the Social Sciences; STR = spatiotactile resolution (comprises GOT, TPR); TMS = transcranial magnetic stimulation; TPR = two-point resolution.

Graphical Abstract



Introduction

Complex regional pain syndrome (CRPS) affects ~4–7% of patients after limb trauma[1,2] and is characterized by 'unbearable' and 'terrifying' burning or stinging pain, which is difficult to treat.[3] This chronic neuropathic pain is mostly associated with somatosensory, motor and autonomic dysfunctions.[4] Additional perceptual symptoms can include impaired somatosensory discrimination,[5] allodynia,[6] abnormal responses to bodily illusions,[7] distorted limb-specific body image,[8] neglect like signs[9] and symptoms,[10] and problems integrating somatic information during visually guided movements of the limb.[11] Furthermore, there is also evidence that perceptual symptoms are directly linked to the reported intensity of pain levels in these patients.[12] Motor dysfunction may involve dystonic movements,[13] tremor, a reduced motion range, and coordination deficits.[14] Consequently, both the primary motor cortex (M1[15]) and primary somatosensory cortex (S1[16]) show some differences in comparison to healthy controls and/or between the affected and unaffected hemispheres—differences that are not simply explained by decreased use.[17]

A general lack of cortical inhibition of the M1 was observed only for patients with upper limbs CRPS.[18–20] This was reported for M1 contralateral to the affected hand[19–21] or for both hemispheres in comparison to healthy controls.[18] In addition, the somatosensory cortex showed a comparable reduction of intracortical inhibition.[22] Following this, imaging studies revealed that fMRI activation in S1 is markedly increased during movements of the affected hand.[14,23] To what extent reorganization of the sensorimotor system is associated with pain levels has not been consequently reported.

For the S1 representation, some authors reported a decreased representation size of the affected hand as measured in the D1–D5 (thumb–little finger) distance,[21,24] but systematic review and meta-analysis,[16] and a recent investigation[25] appear unsupportive. Most of these controversial results might well be related to methodological issues, since these methods are highly demanding with respect to stimulation techniques avoiding habituation, but also spatial resolution of measurement and data evaluation (for a latest overview of an open-access methods pipeline see Härtner et al.[26]). In addition, neurophysiology might be associated with clinical characteristics, such as pain intensity or duration of the disease, and therefore differences in clinical samples might also explain different findings between studies.

Longitudinal studies are required to better understand associations between clinical and neurophysiological data. However, studies on imaging characteristics for the

affected limb, on neuropathology, on behavioural performance impairment and pain thresholds by treatment, are rare. In a previous study using transcranial magnetic stimulation (TMS), we were able to demonstrate that characteristic neuropathological parameters, such as altered short intracortical inhibition, in CRPS patients can not only be modulated even by short-term interventions, but are also associated with sensorimotor function.[19] Another study using an NMDA-receptor antagonist reported a specific modulation of short intracortical inhibition only for the affected hand side, but no specific effect with regard to intracortical facilitation.[20] Gustin et al.[23] used a placebo-controlled design in a group of subacute CRPS patients to investigate inward physical therapy together with a combination of NMDA-receptor antagonist and morphine versus morphine alone. Those patients who profited from the intervention decreased fMRI activation in the affected S1 when performing fist clenches with their affected hand, over the course of treatment. In a single CRPS case, we reported a comparable effect on S1 going along with an effective relief of pain using graded motor imagery (GMI) intervention over 6 weeks.[27] Group studies investigating biomarkers as assessed by fMRI and TMS are still lacking.

In this study, we used GMI training in a group of 21 patients with chronic CRPS. Clinical trials and meta-analyses support the effectiveness of GMI in CRPS and phantom limb pain,[28,29] but pragmatic cohort audits have produced both corroborative[30] and contrasting,[31] outcomes, pointing to the potential importance of non-treatment related factors in outcomes. GMI is recommended in clinical guidelines and standards statements for people with CRPS in various countries.[32]

GMI has been developed as an attempt to gradually help the patient to move the affected limb. From a behavioural therapy approach, the anticipation of pain and the avoidance of movement can be seen according to a 'fear avoidance model' (overview in Leeuw et al.[33]) that can be effectively treated like phobia with exposure therapy.[34] Gradually increasing the movement provides information about moving without associated pain experience, which might result in extinction of the conditioned response. GMI targets this process through the stepwise use of implicit (mental rotation of hands) and explicit movement imagination and movement observation (mirror therapy) of the mirrored healthy hand side.

The following hypotheses guided the design of this study:

(A) In CRPS patients, characteristic biomarkers will differ for the affected and unaffected hand side (spatial tactile resolution/STR, motor function; D1–D5 distance, fMRI activation in S1 for the motor and somatosensory task, short intracortical inhibition), or in comparison to matched healthy controls.

(B) GMI therapy, but not WAITING, modifies primary (movement pain) and secondary outcome parameters (STR, motor function, D1–D5 distance, fMRI activation in S1 for the motor and somatosensory task, short intracortical inhibition).

(C1) STR and motor performance will be associated with fMRI parameters (fMRI activation in S1 and D1–D5 distance) and TMS biomarkers (short intracortical inhibition) during baseline. We also expected an intact association of STR with D1–D5 distance for the no affected hand side, but a collapse of these associations for the affected hand side. In addition (C2) we expected associations between clinical and behavioural measures (pain, Roeder, STR) after GMI and neurophysiology (S1 activation, D1–D5 distance, short intracortical inhibition).

Materials and methods

Participants

For this randomized controlled crossover study, 26 patients with CRPS of the upper limb were recruited via local pain centres and patients support groups in Northern Germany. An overview of the patient selection process is provided in Supplementary Fig. 1. Only 21 patients finished measurements as planned, because of the onset of SARS-CoV-2 (corona virus) pandemic in March 2020.

Group analysis comprised 21 patients [17 females; age (mean ± SD): 54.71 ± 14.13 years] diagnosed with CRPS following the Budapest criteria.[35] In 16 patients, the right hand was affected, in 5 the left hand and the time after disease onset was averaged to 58.24 ± 43.88 months (range: 4–172 months).

Twenty-one healthy participants matched for age (mean: 52.19 ± 14.76 years) and sex (17 females) were recruited from a local database and via advertisements in local print media. Healthy participants were not included when stating any chronic pain symptoms. Participants were excluded when additional neurological or psychiatric diseases were indicated.

A mental rotation paradigm for fMRI in these patients and in healthy controls, and preliminary cognitive performance data, has been published elsewhere.[36] Here, we report on sensorimotor performance and testing including two fMRI paradigms (somatosensory stimulation and hand grip task; each with the affected and the unaffected hand) and TMS measures (double-pulse paradigms for evaluation of intracortical facilitation and short intracortical inhibition).

All participants gave their written informed consent. The study was approved by the local ethics committee (BB 055/18).

The study protocol was lodged and locked prior to commencement www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00017214.

Study design

We used a wait-list control crossover study design (see Fig. 1A) that allowed differentiating between a therapeutic effect and an effect of time only: participants were randomly assigned to one of two groups; one group

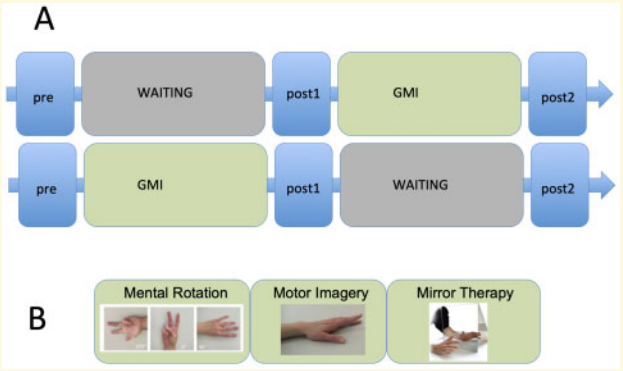


Figure 1 Study design. *Top/A*: Design for the wait list control study including GMI and WAITING periods with 3 different evaluation time points. *Bottom/B*: Time course of GMI intervention: Two weeks of mental rotation were followed by 2 weeks of motor imagery and thereafter 2 weeks of mirror therapy. Training comprised at least 8 sessions per day. Healthy controls were only investigated at baseline.

started the 6-week GMI therapy after the baseline parameters had been collected. After intervention, a 6-week waiting period followed. In contrast, another group started with a 6-week waiting period and continued with the 6-week GMI therapy. Waiting meant that there was no additional treatment but patients went on with their routine treatment as indicated for pharmacological interventions in Supplementary Table 1. Clinical and neurophysiological parameters were assessed before and after each intervention interval. Longitudinal effects of GMI were tested between $_{pre}$GMI versus $_{post}$GMI and those of the waiting period for $_{pre}$WAITING versus $_{post}$WAITING. Effects of intervention order were therefore controlled for by randomization.

Graded motor imagery

GMI[37] consists of three sequential stages (left/right judgments, imagined movements, mirror therapy; see Fig. 1B) each lasting for 2 weeks. The first two stages of the GMI training were performed with the app 'Recognise Hand' (Neuro Orthopaedic Institute, Adelaide, Australia), which displayed pictures randomly and detects the error rate as well as the execution speed for each task, as described below. Patients were encouraged to exercise at least ten minutes every waking hour during the 6 weeks of the GMI training. Patients were asked to keep a pain diary during therapy[38] and were interviewed regularly by the research team via telephone to monitor the task execution, encourage participation and motivation, and to help with any difficulties.

Behavioural testing

Testing was performed in the same way as described before for a group of healthy volunteers who served as controls here[26] and comprised the testing of handedness,[39] clinical parameters [CRPS severity score (CSS)[35]; QuickDASH[40]; rest pain and movement (clenching and unclenching the fist for 5 times) pain of the affected hand side on a 10 cm VAS], somatosensory and motor testing. For somatosensory testing, cutaneous sensory thresholds (CSTs; vonFreyhair filaments) were tested on the tip of the first (D1) and fifth (D5) finger on both hands (additional information provided in the Supplementary methods). For spatial tactile resolution on D1, both two-point resolution (TPR) and the grating orientation task (GOT, Wood Dale, IL, USA) were tested. For each interval, our standardized measurement protocol included pseudorandomized sequences of CST, TPR and GOT. Manual dexterity was assessed using the Roeder Manipulative Aptitude Test (Lafayette Instrument Company, Lafayette, IN, USA) for both hands. All parameters for patients were tested at three time points: pre, post1 (after 6 weeks) and post2 (after 12 weeks).

fMRI measurement, imaging parameters and data evaluation

We used a 3 T MRI scanner equipped with a 32-channel head coil. For the somatosensory stimulation protocol, functional imaging was performed with a multiband EPI sequence of 48 transversal slices oriented along with the subjects anterior commissure–posterior commissure plane with an isotropic resolution of 1.5 mm^3. For the motor performance protocol, we used a standard gradient-echo EPI sequence of 34 transversal slices oriented along the subjects anterior commissure–posterior commissure plane with 3*3 mm^2 in plane resolution. More detailed information on the fMRI methods is provided in the Supplementary methods. In order to improve reliability of the somatosensory task, we applied standardized procedures (available online on github.com/pfannmoe) according to a previous study performed in healthy volunteers.[26] The procedure of the motor task has been used in various protocols before and has been predominantly applied in stroke intervention imaging.[41,42] Here, standardized preprocessing protocols were applied using the SPM12 pipeline (The Wellcome Trust Centre for NeuroImaging, London, UK) following previous published analyses steps.[42] Using the general linear model (GLM), we evaluated statistical maps (first level) of the main condition (fist clenching) and the comparisons between pre and post measurement for each individual. To perform group analysis, corresponding contrast images were compared in a full-factorial GLM random effects analysis. For S1, activation maxima in ROIs (ANATOMY[43]) were extracted as beta-values and evaluated offline using Statistical Package for the Social Sciences (SPSS). Linear regression was calculated to evaluate associations of S1 activation changes over

time with changes in STR (GOT, TPR), movement pain and Roeder test.

TMS short intracortical inhibition and intracortical facilitation measurements

Transcranial magnetic stimuli were provided using a hand-held figure-of-eight coil (C-B60) connected to a MagVenture stimulator. We used a neuronavigation system (LOCALITE® TMS Navigator Germany) for identifying the spot with best muscle response of the first dorsal interosseous muscle (FDI) in M1 of both hemispheres. The paired pulse paradigm consisted of 60 pulses alternating 40 conditioned and 20 non-conditioned test stimuli. Interstimulus intervals of conditioned stimuli were set to 2 and 10 ms to produce inhibition and facilitation, respectively.[44] The conditioned pulse intensity was set to 80% of resting motor threshold (RMT; see Supplementary methods), test pulse was given with 135% RMT, an intensity for which it has been shown in an a priori analysis of our previous CRPS TMS studies, that it is capable to produce motor evoked potential amplitudes of ~1 mv.[19,21] Short intracortical inhibition and intracortical facilitation were calculated as a ratio of the mean motor evoked potentials evoked after single test stimulus.

Further details describing electrophysiological data acquisition have been provided in the Supplementary methods.

Statistics

Statistical comparisons were calculated using SPSS Statistics (IBM), version 21.

Performance data during the fMRI motor task were analysed to confirm stability of performance for force and frequency as mean and standard variation of each participant for side (affected/unaffected hand), treatment (GMI, WAITING) and time (pre/post) using a 2*2*2 rmANOVA followed by *t*-tests for paired samples.

In detail, the following statistical procedures were performed:

Hypotheses A: Differences between hands and groups

(1) within group: paired *t*-tests between affected and non-affected hand side

(2) between groups: two sample *t*-tests for affected hand side and the matched hand side of controls

Hypothesis B: We used repetitive measures (rm) ANOVAs followed by paired *t*-tests corrected for multiple comparisons (p_c) for testing the treatment effect on primary (movement pain) and secondary (GOT, TPR, Roeder, short intracortical inhibition, S1 activation, D1–D5 distance) outcome parameters.

Before, we tested for intervention order (carryover effects in any direction) for the variables 'rest pain' and 'movement pain', as described in the following: The sum of the outcomes of both periods were calculated as (pain_pre_waiting − pain post_waiting) + (pain_pre_GMI − pain_post GMI). These values were then compared with an independent *t*-test for the two groups of patients, who had either GMI first or WAITING first.

Hypothesis C: Associations between testing parameters were performed using Pearson correlations (one-sided and not corrected for multiple comparisons, if effect direction was expected from other studies)

(1) at baseline: for the known association of spatiotactile resolution (STR) and D1–D5 distance in S1 and the assumed association of short intracortical inhibition and Roeder for healthy participants (see Pfannmöller et al.[21]),

(2) for longitudinal changes in clinical (GOT, TPR, Roeder, movement pain), imaging (S1 activation; D1–D5 distance) and neurophysiological (short intracortical inhibition) data.

Data availability

Data used for statistical evaluation can be requested form the corresponding author.

Results

Characterisation of the patient group

The CSS at baseline showed a median of 13.0 (range: 5–17). Pain intensity for the hand during rest was 4.3 ± 2.6 and after movement 6.4 ± 2.5. Pain intensity and duration of the disease were associated; patients with stronger pain intensity indicated a longer duration of CRPS (rest pain: $r = 0.61$; $P = 0.003$; movement pain: $r = 0.50$; $P = 0.021$). The disabilities of the arm, shoulder and hand (DASH) self-assessment of functional impairment was 61.3 ± 19.0.

Hypothesis A: Comparison of behavioural, neurophysiological and fMRI parameters at baseline

(A1) Comparison between the affected and the unaffected hand side in CRPS patients at baseline (Table 1) revealed differences for motor performance [Roeder: $t(18) = 2.27$; $P = 0.036$], short intracortical inhibition [$t(20) = -2.49$; $P = 0.022$], and facilitation [$t(20) = 2.30$; $P = 0.032$] with short intracortical inhibition smaller and intracortical facilitation higher for the affected side. In addition, fMRI activation magnitude in S1 was increased for movement of the affected hand [$t(19) = 2.32$; $P = 0.032$]. There were no differences between hand sides for the somatosensory measures: GOT [$t(18) = 0.39$; n.s.], TPR [$t(18) = 1.21$; n.s.], and CST [$t(19) = 1.07$; n.s.].

(A2) When comparing CRPS patients with HC (affected hand patients against matched hand HCs; Table 2), we found worse performance in CRPS patients for STR [GOT: $t(38) = 2.80$; $P = 0.008$, TPR: $t(38) = 2.49$; $P = 0.017$] and

Table 1 Comparisons baseline between the affected and non-affected hand side

	Parameter	Affected	Non-affected	t-value/ significance
Testing	Roeder	118 ± 108	61 ± 18	2.27/*
	GOT	2.80 ± 0.51	2.74 ± 0.55	0.39/–
	TPR	3.00 ± 1.43	2.60 ± 1.05	1.21/–
	CST	3.39 ± 0.56	3.28 ± 0.53	1.07/–
TMS	SICI	23.53 ± 38.55	43.06 ± 27.77	–2.49/*
	ICF	35.35 ± 23.55	20.03 ± 27.33	2.30/*
fMRI	fMRI S1 motor task	3.33 ± 1.30	2.28 ± 1.70	2.32/*
	fMRI S1 somatosensory	1.10 ± 0.71	1.09 ± 0.70	0.044/–
	fMRI D1–D5 distance somatosensory	18.38 ± 5.50	19.32 ± 5.92	0.067/–

Significance:
*$P < 0.05$;
**$P < 0.01$;
***$P > 0.005$.
CST, cutaneous somatosensory testing; vonFreyhair testing; GOT, graded orientation test; ICF, intracortical facilitation; SICI, short intracortical inhibition; TPR, two-point resolution.

Table 2 Comparisons between affected hand CRPS and matched hand HC

	Parameter	Affected CRPS	Matched HC	t-value/ significance
Testing	Roeder	118 ± 108	44 ± 6	3.11/**
	GOT	2.80 ± 0.51	2.26 ± 0.69	2.80/**
	TPR	3.00 ± 1.43	2.15 ± 0.62	2.49/*
	CST	3.39 ± 0.56	3.28 ± 0.43	0.74/–
TMS	SICI	23.53 ± 38.55	48.23 ± 21.67	2.51/*
	ICF	35.35 ± 23.55	36.78 ± 30.89	–0.16/–
fMRI	fMRI S1 motor task	3.33 ± 1.30	1.81 ± 1.10	2.69/**
	fMRI S1 somatosensory	1.10 ± 0.71	0.76 ± 0.66	1.66/–
	fMRI D1–D5 distance somatosensory	18.38 ± 5.50	20.67 ± 3.60	1.50/–

Significance:
*$P < 0.05$;
**$P < 0.01$;
***$P > 0.005$.
CST, cutaneous somatosensory testing; vonFreyhair testing; GOT, graded orientation test; ICF, intracortical facilitation; SICI, short intracortical inhibition; TPR, two-point resolution.

motor function [Roeder: $t(38) = 3.11$; $P = 0.004$] than in controls. For TMS, short intracortical inhibition was significantly lower in CRPS patients than in controls [$t(39) = 2.51$; $P = 0.016$]. In addition, S1 fMRI activation was significantly increased in patients when compared to HC for movement of the affected hand side [S1: $t(39) = 2.30$; $P = 0.027$]. This was not observed for the unaffected hand side [S1: $t(39) = 0.27$; n.s.].

Again as expected, CST for D1 [$t(39) = 0.74$; n.s.] and intracortical facilitation [$t(40) = -0.17$; n.s.] were not different between CRPS at baseline and HC for the affected hand side. D1–D5 distance in Area 3B was comparable for both subject groups [affected hand side: $t(35) = -1.50$ n.s.; CRPS: 18.38 ± 5.50 mm; HC: 20.67 ± 3.60 mm; unaffected hand side: $t(36) = -0.45$; n.s.; CRPS: 19.32 ± 5.92 mm; HC: 20.13 ± 5.03 mm].

Hypothesis B: Changes over treatment and time in CRPS patients

Controlling for intervention order, there were no significant differences between randomization groups [rest pain: $t(19) = 0.16$, $P = 0.87$; movement pain: $t(19) = 0.03$, $P = 0.98$].

Interaction for time*treatment in the rmANOVA testing movement pain showed a trend for a significant effect when testing pain relief after intervention [$F(1,20)=3.73$; $P = 0.068$]. *Post hoc* *t*-tests revealed a significant change in movement pain after GMI from 6.3 to 5.3 [VAS10; $t(20) = 2.35$; $P = 0.029$], but not for WAITING [from 5.75 to 6.02; $t(20) = -0.61$; n.s.]. Rest-pain showed a significant interaction for time*treatment [$F(1,20) = 6.33$;

$P = 0.021$] with WAITING resulting in increased rest pain over time [$t(20) = -2.41$; $P = 0.026$], whereas GMI showed a trend for a decrease [$t(20) = 1.66$; $P_{one\text{-}sided} = 0.056$].

Follow-up after 6 months did not show any modification of pain compared to baseline [pain rest baseline: 4.33; pain rest follow-up: 4.91, $t(20) = -1.24$, n.s.; pain movement baseline: 6.41; pain movement follow-up: 6.03, $t(20) = 0.83$, n.s.].

The CSS was reduced from 12.0 to 11.0 (median) over GMI (Wilcoxon $Z = -2.1$; $P = 0.034$; non-parametric testing, since the CSS is not interval-scaled), but was unaltered by WAITING ($Z = -0.74$; n.s.).

Quick-dash showed a trend for an interaction for time*treatment [$F(1,20) = 4.24$; $P = 0.054$]. The *post hoc* *t*-test showed that GMI was capable to significantly decrease self-rated functional impairment of the upper limb [$t(20) = 2.18$; $P = 0.041$].

CST using vonFreyhair filaments were not expected to be altered over time.[19] This was confirmed [e.g. for D1 affected hand before GMI: 3.40, after treatment: 3.45; $t(19) = -0.71$; n.s.]. The GOT showed no modification by treatment in the 2*2*2 rmANOVA. However, TPR showed an effect of GMI with $F(1,20) = 13.76$; $P = 0.002$ and a trend for time [$F(1.20) = 4.15$; $P = 0.057$]. *Post hoc* *t*-test revealed an improvement of TPR from 2.83 to 2.37 [$t(18) = 2.19$; $P = 0.042$] after GMI. Roeder test for motor function revealed a positive effect for hand [$F(1,18) = 6.48$; $P = 0.02$], time [$F(1,18) = 4.84$; $P = 0.041$], and a significant interaction hand*time [$F(1,18) = 4.72$; $P = 0.043$]. *Post hoc* *t*-tests for the affected hand side showed a one-sided effect for improvement after GMI [$t(18) = 1.88$; $P_{one\text{-}sided} = 0.038$]. Results for the paired *t*-tests between the pre and post measurements of GMI intervention are depicted in Fig. 2.

Two*two*two rmANOVA for short intracortical inhibition with therapy, time and hand showed a trend for the interaction treatment*hand*time [$F(1,20) = 4.18$; $P = 0.054$]. Short intracortical inhibition for the affected hand side increased from 19.75% to 50.97% after GMI [$t(20) = -3.69$; $P = 0.001$; see Fig. 2]. Intracortical facilitation showed a trend for a treatment*time interaction [$F(1,20) = 3.81$; $P = 0.065$], but no main effect or interaction for hand [$t(20) = 1.73$; n.s.]. For the affected hand, it slightly increased after waiting (from 28.6 to 34.4%) but decreased after GMI (from 37.0% to 31.1%).

Fist clinching (air pressure force, frequency and variability of both parameters) in the MRI scanner was performed as instructed with 33% of maximal force on average (mean for baseline evaluation of the affected hand side: maximal force: 36 674 arbitrary force values; 33%: 12 102). As expected, maximal force of fist clenching with the affected hand was associated with pain intensity [rest pain: $r(20) = -0.55$; $P = 0.012$; movement pain: $r(20) = -0.50$; $P = 0.026$] and CSS [$r(20) = -0.52$; $P = 0.018$]. Importantly, there was no association of fist clenching performance with activation magnitude in S1. For performance during the actual fMRI measurement there was no effect for frequency or force in the 2*2*2 rmANOVA (side, treatment, time); participants' performance did, therefore, not differ systematically between conditions or time and was comparable between the affected and non-affected hand side [e.g. GMI: baseline affected versus baseline non-affected: $t(19) = 1.22$; n.s.]. However, standard deviation (variability) between measurements was increased for the affected compared to the non-affected hand side with respect to frequency [rmANOVA: effect for side: $F(1,18) = 4.82$; $P = 0.04$; baseline GMI: $t(19) = -2.39$; $P = 0.027$], but not to force (rMANOVA: n.s). In a 2*2*2 rmANOVA, we tested fMRI activation magnitude differences in S1 for the fist clenching task. We observed an effect for hand [$F(1,18) = 10.94$; $P = 0.004$] and a time*treatment interaction [$F(1,18) = 7.95$; $P = 0.012$]. *Post hoc* *t*-tests found a decrease in S1 activation after GMI [$t(19) = 2.82$; $P = 0.011$], but not after WAITING [$t(19) = -1.97$; n.s.].

For S1 fMRI activation in the somatosensory task, we found an effect of time [$F(1,18) = 7.86$; $P = 0.012$], but

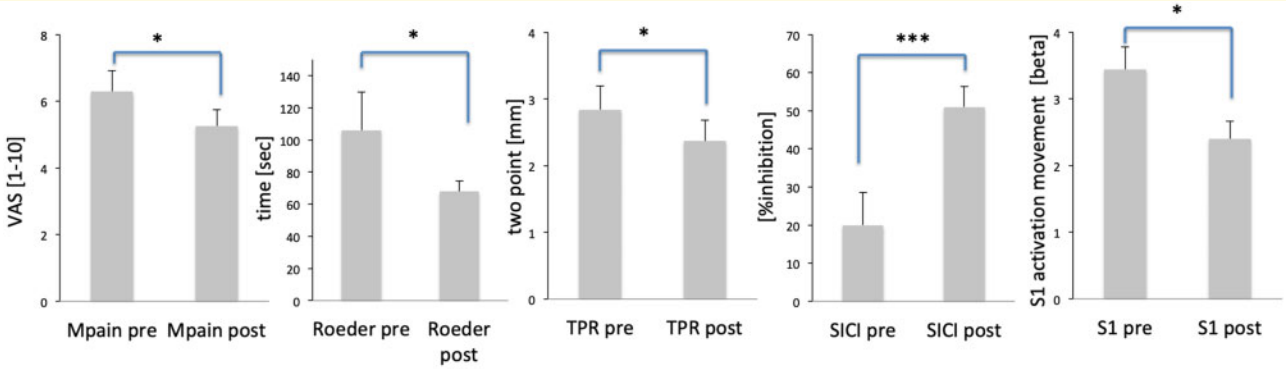


Figure 2 Effect of GMI intervention. Plots of means and standard errors for movement pain (Mpain; shown left), Roeder motor test (shown middle left), TPR (shown middle), short intracortical inhibition (SICI, shown middle right), and fMRI activation in S1 during fist clenching with the affected hand (shown right). Lines on bars indicate standard errors; cramps with stars indicate the significance level for *t*-tests (*$P < 0.05$; ***$P = 0.001$).

no effect of treatment. However, post hoc t-tests showed no significant changes over time [GMI: $t(29) = 1.70$; n.s; WAITING: $t(18) = 0.77$; n.s]. For the distance of D1/D5 finger representation maxima in S1 in Area 3b, the 2*2*2 rmANOVA showed no significant results. Table 3 depicts comparisons over GMI for the affected hand side in CRPS patients.

Hypothesis C1: Associations between clinical parameters and neurophysiology at baseline

The longer the CRPS persisted, the worse the motor performance of the affected hand ($r = 0.41$; $P_{\text{one-sided}} = 0.042$) and the smaller the representation area in S1 [D1–D5 distance; $r(20) = -0.52$; $P = 0.023$]. Increased movement pain of the affected hand was associated with decreased short intracortical inhibition ($r = -0.38$; $P_{\text{one-sided}} = 0.046$) and showed a trend for an association with increased S1 activation ($r = 0.37$; $P_{\text{one-sided}} = 0.053$). Pathologically low short intracortical inhibition was associated with high values in the GOT indicating low STR ($r = 0.43$; $P_{\text{one-sided}} = 0.036$; see Table 4).

No other associations were observed for the affected hand underlining a severe disruption of physiologic associations between cortical representation in S1 and STR (see Fig. 3).

For the non-affected hand, we found a trend for patients for an association between the distance between D1 and D5 in S1 Area 3b and the GOT ($r = -0.41$; $P_{\text{one-sided}} = 0.054$). In contrast, these associations were quite strong in healthy controls (see Fig. 3, for detailed description see Härtner et al.[26]). This underlines a 'nearer to normal' association of cortical distances in S1 and STR for the non-affected hemisphere/hand for CRPS patients.[21]

In Fig. 3, the associations of GOT and D1–D5 distance for the hands of CRPS patients and the matched hand sides for HC were plotted (CRPS affected versus HC corresponding hand: $Z = -2.0$, $P_{\text{one-sided}} = 0.02$; CRPS affected versus unaffected hands: $Z = -1.19$, $P_{\text{one-sided}} = 0.12$; CRPS versus HC unaffected hands: $Z = 0.68$, $P_{\text{one-sided}} = 0.24$).

Hypothesis C2: Associations after GMI treatment

Especially changes in STR (GOT and TPR) over GMI treatment showed associations with fMRI changes. GOT gain after GMI was positively associated with decrease in S1 activation during somatosensory stimulation ($r = 0.49$;

Table 3 Comparisons CRPS over GMI for the affected hand side

	Parameter	Affected GMI pre	Affected GMI post	t-value/ significance
Testing	Roeder	106 ± 107	68 ± 29	1.88/one sided*
	GOT	2.82 ± 0.73	2.67 ± 0.65	1.00/–
	TPR	2.83 ± 1.58	2.38 ± 1.41	2.19/*
	CST	3.40 ± 0.54	3.45 ± 0.55	−0.71/–
TMS	SICI	19.76 ± 37.65	50.96 ± 24.07	−3.69/***
	ICF	37.03 ± 25.73	31.08 ± 37.35	0.74/–
fMRI	fMRI S1 motor task	3.43 ± 1.53	2.40 ± 1.16	2.82/*
	fMRI S1 somatosensory	0.98 ± 0.63	0.71 ± 0.41	1.70/–
	fMRI D1–D5 distance somatosensory	19.48 ± 4.94	19.23 ± 5.17	0.17/–

Significance:
*$P < 0.05$;
**$P < 0.01$;
***$P > 0.005$.
CST, cutaneous somatosensory testing; vonFreyhair testing; GOT, graded orientation test; ICF, intracortical facilitation; SICI, short intracortical inhibition; TPR, two-point resolution.

Table 4 Associations between parameters at baseline

Behavioural	Distance D1–D5 somatosensory	Short intracortical inhibition (SICI)	S1 activity motor task
CRPS duration	$r = -0.52$; $P = 0.023$		
Movement pain		$r = -0.38$; $P_{\text{one-sided}} = 0.046$	$r = 0.37$; $P_{\text{one-sided}} = 0.053$
GOT		$r = 0.43$; $P_{\text{one-sided}} = 0.036$	

GOT, graded orientation test.

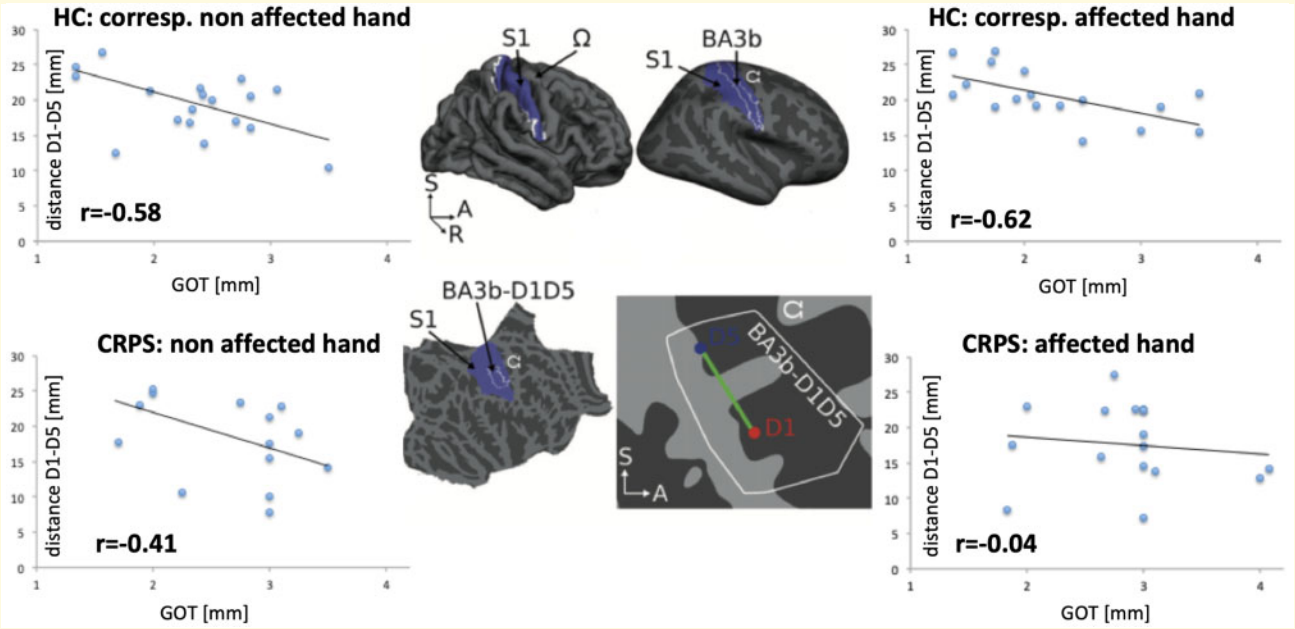


Figure 3 Association of D1–D5 distance and STR of the thumb. Centre: method for evaluating the D1–D5 distance in BA 3b of S1 of each hemisphere. *Top plots*: high association of representation size (D1–D5 distance) and STR as measured with the GOT in healthy volunteers. *Bottom plots*, decrease in these associations in CRPS for the non-affected hand (left) but especially for the affected hand (right). Whereas the non-affected side of CRPS patients barely reached significance, the affected side showed no associations.

$P = 0.04$). As expected, GMI induced changes of somatosensory fMRI parameters (D1–D5 distance, S1-activation magnitude during finger stimulation) were negatively associated: when D1–D5 distance increased, S1 activation during thumb stimulation decreased ($r = -0.52$; $P = 0.019$). In addition, an enlargement of the D1–D5 distance after GMI was associated with movement pain relief, when the duration of CRPS was introduced as a covariate ($r = -0.48$; $P_{\text{one-sided}} = 0.038$).

Discussion

Our study was targeted to discover longitudinal effects of GMI intervention in CRPS with changes in relevant clinical, behavioural, neuroimaging and neurophysiological data. In addition, we intended to test for associations of clinical improvements, sensorimotor performance, imaging and neurophysiological parameters for sensorimotor function in CRPS. Our treatment strategy was effective for the primary outcome parameter movement pain, since we observed a small effect of GMI, but not WAITING on movement pain intensity. In addition, GMI but not WAITING resulted in a decrease of clinical scores (CSS), increased usage of the affected hand side (DASH), and an improvement of motor function (Roeder) and spatiotactile performance (TPR). Intracortical inhibition, known to be decreased in the hemisphere contralateral to the affected hand, increased over treatment, whereas fMRI activation in S1 contralateral to the affected hand during fist movement was initially increased in these patients and decreased over the GMI treatment period. Furthermore, hand representation size in the affected hemisphere, which showed maladaptive disorganization without association to STR initially, was modified, accompanied by movement pain relief. However, there was no relief of movement pain at follow-up after 6 months.

Pathology in CRPS—where to look at?

There are several studies demonstrating CRPS-related pathology. In addition to reduced pain thresholds on the body side of the affected limb (e.g. Ref.45), pathologies included decreased motor function (force, pinch grip, smoothness and aiming[12,14]) and decrease in somatosensory performance on the body side with the affected limb (e.g. for CST and SPR[5,45]). With respect to neurophysiology, decreased intracortical inhibition for M1[18,20,46,47] and S1[22] have been described. Functional imaging results have been reviewed several times already.[15,16] Most consistently, functional activation was increased in M1 and S1 contralateral to the affected side during movement of the affected limb. For the evaluation of representation maxima during somatosensory stimulation of the finger tips contradictory results have been described.[17,21,25,48]

Most of these results had been obtained in cross-sectional studies. There are few studies documenting longitudinal changes in CRPS during intervention and to our

knowledge, there is no other study that comprehensively reports associations between clinical data, behavioural changes, functional imaging data on sensorimotor representation, and data on intracortical facilitation and inhibition. By using these comprehensive measurements longitudinally in the same patient group, we are now able to oversee a much broader picture of CRPS pathophysiology. We will discuss different aspects first as single observations and then as associations of parameters.

Clinical and behavioural outcomes

Apart from a correct diagnosis for CRPS and a scoring of severity (CRSS), movement pain was defined here as the primary outcome consistent with prior findings on effects of GMI in CRPS patients in a randomized trial.[49] In addition, the main purpose of GMI is to bring patients back into movement by gradually increasing usage of the affected hand. Earlier findings highlighted the importance of the duration of symptoms for pain intensity[50] and the development of biomarkers (e.g. grey matter atrophy[51]). We here observed associations of duration of CRPS with the initial motor performance of the affected hand.

Both somatosensory and motor performances are important to control for in studies investigating associations with imaging and neurophysiological parameters, but also for investigating intervention effects. STR is the most specific and sensitive somatosensory parameter for CRPS,[52] since it is highly lateralized and can be modified by intervention (e.g.[19], TPR in our study). In contrast, the CST is not modified by intervention[19] and is also less sensitive for associations with biomarkers such as short intracortical inhibition or D1–D5 distance.[19,21] Accordingly, our study did not observe any relevant effects for CST with respect to lateralization, intervention effect or association with other biomarkers.

For motor performance, especially fine pinch grip manipulations, such as tested here with the Roeder test, are highly associated with STR.[53] We here observed a moderate effect of GMI on motor performance of the affected hand. However, since the Roeder test is associated with the duration of CRPS, this outcome parameter might fail to show a therapy effect, especially for patients with long lasting symptoms. Self-assessments of usage of the affected hand after intervention (DASH) showed a relevant effect indicating that the main purpose of the intervention to decrease movement pain and bring patients back into movement was successful in our investigation.

The validity of imaging and TMS biomarkers for CRPS

Short intracortical inhibition and intracortical facilitation

Whereas there is no doubt about a clear lateralization of pain perception, somatosensory and motor symptoms in unilateral CRPS, there are contradictory results on lateralization of decreased intracortical inhibition. In our previous studies, investigating unilaterally upper limb affected CRPS patients in the chronic stage only, we always found a strict unilateral impairment of somatosensory and motor function in comparison to healthy volunteers, a strict decrease in short intracortical inhibition of the hemisphere contralateral to the affected hand side,[19,21] which had also been reported by others.[20] Early work on short intracortical inhibition in the upper limb of unilaterally affected CRPS patients found decreased short intracortical inhibition compared to HC, but no lateralization.[18] This study included patients with huge differences in duration after diagnosis (2 weeks to 231 months with a mean of 26 months). This inhomogeneity within the patient population might contribute to mixed findings, since for instance pain intensity is related to the duration of CRPS.[50] We therefore conclude that reduced short intracortical inhibition is lateralized to the affected hand side, is associated with clinical parameters at baseline, and also is a sensitive biomarker for intervention induced changes in neuropathic pain (Fig. 4). As a mechanism of decreased intracortical inhibition, a change in thalamo-cortical interaction had been hypothesized[54] which fits well to reports on reduced thalamic grey matter volume in neuropathic pain[55] and altered thalamo-cortical resting state connectivity.[56]

Biomarkers for CRPS

valid	lateralization	intervention sensitive	associations at baseline	associations with outcome
SICI	✔	✔	✔	✗
S1 move	✔	✔	✔	✔trend
D1-D5	✔✗	✗	✔	✔trend
invalid				
S1 sens	✗	✗	✗	✗
ICF	✗	✗	✗	✗

Figure 4 Biomarkers for CRPS. High validity with respect to lateralization (affected versus unaffected) and group specificity (CRPS versus HC) were observed for short intracortical inhibition (SICI), and S1 fMRI activation during movement of hand (S1 move). D1–D5 distance in S1/Area 3B after somatosensory stimulation (D1–D5) showed lateralization in less chronic samples,[21] but not in our patients with extremely long lasting CRPS. Short intracortical inhibition and S1 during movement showed to be intervention sensitive, but D1–D5 was unmodified by intervention in this study. All three parameters showed associations with clinical parameters during baseline, but only S1 move and D1–D5 distance showed a trend for an association with outcome parameters (movement pain). In contrast, invalid parameters were S1 fMRI activation during somatosensory stimulation and intracortical facilitation, which showed no characteristic lateralization, group effect, were not modified by intervention and was not associated with clinical parameters at baseline or over treatment.

In contrast, intracortical facilitation was neither different between the affected and non-affected hand side nor had it been different to normative data, consistent with prior reports in CRPS.[20] We did also not see any modifications of intracortical facilitation by treatment or relevant associations at baseline ore during intervention. Therefore, intracortical facilitation can be excluded as a valuable biomarker for CRPS for all dimensions tested (Fig. 4).

S1 fMRI activation magnitude during somatosensory stimulation

Contrary to Pleger et al.[5] and Stude et al.,[57] we did not see a lateralization for S1 fMRI activation magnitude during fingertip stimulation. Those studies had very small sample sizes (Pleger: $n = 7$; Stude: $n = 5$), which put them at greater risk of bias for underpowered studies than the current work. In addition, S1 activation during somatosensory stimulation did not change relevantly over treatment. However, with respect to somatosensory stimulation, the representation field was related to the response to intervention: movement pain relief and D1–D5 distances changes during GMI were associated negatively, when controlling for the duration of CRPS. This is especially important in our patients, because all patients but one were in the chronic stage of disease (CRPS symptoms for more than 6 months based on the Budapest criteria[35]). We argue that S1 fMRI activation magnitude during somatosensory stimulation is not a valid biomarker for CRPS (see Fig. 4).

Contrarily to our previous group of CRPS patients[21] and reports of others (for MEG[24,58,59]; for fMRI[60]), but in line with other observations,[25] we did not observe differences in S1-hand fingertip representation distances, when compared to the unaffected hand or when compared to those of the matched hand side of HCs. Importantly, average representation maxima distance between S1 D1–D5 were comparable to those of healthy controls in both hemispheres. Besides methodological differences between studies, the most important patient characteristic might well be the onset of CRPS. In our study, on average, 58 months passed since first diagnosis of CRPS. This reflects our recruitment pathway via support groups. In the study of Pfannmöller et al.,[21] for instance, patients with 8 months on average after the first diagnosis were included, because recruitment was performed by the hand surgery ambulance. We found an interaction of the time since diagnosis with D1–D5 distance changes in association to pain relief, which might point to the important impact of persistence of disease, although it might also reflect that more painful CRPS is likely to last longer.

In addition, high variances between S1 D1–D5 distances both in the patient and the HC groups impede their comparison, and might be better suited for investigating intact associations between STR and hand representation distance in an individual approach.

Overall, the most important finding is the loss of associations between the STR and S1 Area 3b representation size. This is related to the duration of CRPS and could also be observed in a lower amount for the non-affected hand, possibly due to effects of altered usage over long time (see Fig. 3). In conclusion, in the light of the extremely diverging methods in evaluating D1–D5 distances in S1 and the methodological demands on spatial resolution, this method might not be ready for a common use as a biomarker for CRPS.

S1 fMRI activation during 33% of maximal force clenching

Contrary to the somatosensory fMRI task, we found a relevant lateralization, a significant group effect (CRPS versus HC) and a relevant modification by intervention for the S1 fMRI activation during the hand movement task. GMI, but not WAITING down-modulated this initially increased S1 activation to the level of the unaffected hand of patients and HCs. It is a fundamental different approach testing somatosensory stimulation of finger tips and performing a voluntary movement in a fist clenching task. Only the active fist clenching includes voluntary movements of the affected limb, which is associated with an increase in pain intensity during task performance. Active fist clenching of the affected hand in patients with CRPS is associated with an increase in S1 activation, which had been modified by intervention in other studies before.[23,27] Therefore, S1 increase for moving the affected hand during baseline and its reduction during intervention seems to be a valid biomarker for CRPS (see Fig. 4). It has to be mentioned here that S1 activation decreased although the actual force during movement post intervention increased until 33% of maximal force was achieved to balance the demand pre and post intervention (see the stroke literature for reference41). Over successful treatment patients are capable of performing more forceful movement with their affected hand resulting in an increase in functional activation magnitude in the contralateral primary sensorimotor cortex (e.g. Ref.61). Therefore, the decrease in S1-activation as observed in our study is remarkable and underlines the validity of this parameter as a biomarker for intervention effects in patients with CRPS. The method balancing performance over time with maximal force is important to consider for future studies.

Limitations

We registered our protocol prior to commencement, which is now considered standard in pain research,[62] but we did not lodge the statistical analysis plan, which limits transparency of reporting. As is almost always the case with such methodologically high demanding studies in

rare patient collectives—our sample was small, especially for a longitudinal wait list control design. Therefore, some parameters that were undetected here might well show relevant effects in larger samples. Also relevant here is our decision *a priori* to not correct for multiple measures, which is considered appropriate if recruiting larger samples presents ethical or logistic challenges.[63] We fully recognize, however, that our while our approach decreases the risk of Type II error, it increases the risk of Type I.[64] That our test results were all consistent and our interpretations do not rest on a single result is reassuring, but the reader is encouraged to evaluate our findings with this limitation in mind.

When using performance of the affected hand in longitudinal designs, there are always issues in controlling performance to avoid systematic changes between the pre and post measurement with fMRI activation. We here used a well-balanced design integrating pre-scanning training (keep 33% of maximal force and 1 Hz frequency) with visual feedback and a monitored and examiner-controlled task performance during scanning. This paradigm allows for post-hoc statistical evaluation of performance data in the fMRI scanner. In addition, the paradigm does not distract the participants by visual adjustment of their force magnitude to a given target.

It has to be mentioned that cognitive issues, which are of interest in these patients (e.g. Ref.65), were not within the scope of the current study, but have been published in a separate manuscript.[36] Finally, we here investigated patients in an advanced chronic stage of disease; effects of treatment and biomarkers may be different in more acute patients.[21,23]

Conclusion

Overall, we demonstrated characteristic changes in clinical, behaviour and neuropathology parameters applying GMI in patients with upper limb CRPS. Particularly (A) S1 activation magnitude during fist clenching and for (B) short intracortical inhibition decrease for distal hand muscles were characteristic biomarkers for CRPS. Less consistent results have been reported for decrease of S1 activation during somatosensory stimulation of the fingertips of the affected hand side and for the D1–D5 distances as a measure for the S1-representation of the affected hand. With the comprehensive knowledge about biomarkers for somatosensory, motor but also cognitive tasks (mental rotation) in cross-sectional and longitudinal studies of CRPS patients, we might now be able to establish a consensus on the most suitable biomarkers, which casts light on the effects of GMI on biomarkers for chronic neuropathic pain.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

GLM receives royalties for books on pain and on graded motor imagery. ML is a paid editor for „Neuroreha“ published by Thieme.

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