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Increased motor cortex excitability in chronic complex regional pain syndrome

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ABSTRACT

Objective: To characterize corticospinal excitability and cortical motor representation in complex regional pain syndrome (CRPS) type I and type II, addressing inconsistencies in prior research regarding these mechanisms.
Methods: Fifty-nine CRPS patients (44 type I and 15 type II) underwent TMS and paired-pulse TMS examinations to assess resting motor threshold (RMT), motor evoked potential (MEP) amplitude and latency, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) bilaterally, alongside cortical representation areas of the hands at M1 cortex. Results were compared with 23 healthy subjects.
Results: CRPS patients had lower RMT, higher MEP amplitudes, and lower ICF than healthy subjects. The SICI in CRPS patients showed no interhemispheric differences and did not differ from healthy subjects. MEP latency was shorter to the affected than to the unaffected hand in CRPS type II. Higher pain intensity correlated with higher degree of intracortical facilitation bilaterally, and with smaller motor representation area of the unaffected hand.
Conclusion: Findings of this study suggest increased motor cortical excitability in CRPS patients relative to healthy subjects, with no interhemispheric asymmetry of SICI or ICF observed in chronic CRPS.
Significance: These results provide a comprehensive view of intracortical inhibition, facilitation and corticospinal excitability in chronic CRPS.

1. Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition that may develop following even minor trauma or surgery. It is classified into two subtypes: Type I arising without an identifiable nerve lesion and Type II involving a confirmed nerve injury (Merskey and Bodguk, 1994). The pathophysiology of CRPS is complex, involving both peripheral and central mechanisms (Birklein and Dimova, 2017, Bruehl, 2015). Studies examining central neurophysiological changes in CRPS patients indicate a reduction in the somatosensory cortical representation area corresponding to the affected limb (Juottonen et al., 2002, Maihofner et al., 2003, Pleger et al., 2005) (for *meta*-analysis see Di Pietro et al., 2013). In addition, cortical sensory evoked responses appear to be enhanced and reactivity of spontaneous sensorimotor activity after stimulation to be diminished in the hemisphere representing the affected limb, suggesting cortical disinhibition (Forss et al., 2005, Juottonen et al., 2002, Kirveskari et al., 2010). Research on the cortical motor representation area in CRPS is limited. A transcranial magnetic stimulation (TMS) study investigating CRPS Type I reported larger cortico-motor representation for the unaffected than the affected hand (Krause et al., 2006).

TMS probes corticospinal system and its excitability non-invasively. Paired-pulse TMS (ppTMS), a technique combining two closely occurring stimuli, enables assessing intracortical inhibition and facilitation in detail. In short-interval intracortical inhibition (SICI) paradigm, a conditioning subthreshold stimulus preceding the test stimulus by 1–6 ms

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activates intracortical synaptic inhibition mediated by gamma-aminobutyric acid A ($GABA_A$) (Chen et al., 2008, Kujirai et al., 1993, Rossini et al., 2015). The motor evoked potential (MEP) amplitude in the conditioned SICI paradigm is lower than that following a single test stimulus only. The ratio of these amplitudes estimates the $GABA_A$-mediated inhibition. Paired pulses with interstimulus interval (ISI) of 8–30 ms yield MEPs with higher amplitude than a single test stimulus, representing intracortical facilitation (ICF) (Chen et al., 2008, Kujirai et al., 1993, Rossini et al., 2015).

Previous TMS studies have revealed partially contradictory results about corticospinal excitability in CRPS. They have often had limited sample sizes ($\leq$25 patients) (Eisenberg et al., 2005, Krause et al., 2004, Morgante et al., 2017, Schwenkreis et al., 2003), have studied only patients with CRPS Type I, or have not defined CRPS subgroups. The present study provides a comprehensive assessment of corticospinal excitability and cortical motor representation areas in a large cohort of patients with CRPS. We also consider the two CRPS subtypes, classified by a thorough neurological and neurophysiological examination into those with confirmed nerve lesion (CRPS II) and those without evidence for major neuropathic component (CRPS I).

2. Methods

2.1. Subjects

As part of a multicenter randomized controlled trial assessing the efficacy of therapeutic repetitive TMS for CRPS, 59 patients with chronic CRPS were included in this study. Inclusion criteria were CRPS Type I or Type II in the upper limb, minimum duration of CRPS of 6 months, age $\geq$ 18 years, and mean pain intensity of at least 5 on a numeric rating scale (NRS) from 0 to 10 (at the time of recruitment). CRPS was diagnosed according to the Budapest research criteria (Harden et al., 2007). Type I and Type II were classified on evidence for peripheral nerve damage by clinical assessment, electroneuromyography (ENMG), or quantitative sensory testing (QST, consisting of cool, warm, cold pain, and heat pain detection thresholds with method of limits protocol). Neurological examination and ENMG-investigations of upper extremities were done in detail, according to patient history and good clinical practice standards. Exclusion criteria were epilepsy, psychotic depression, abuse of alcohol, use of strong opioids, and a contraindication for MRI or TMS. Patients were recruited from the Turku University Hospital Pain Clinic, and Helsinki University Hospital Pain Clinic, private clinics, and from a private CRPS patient social media group. Data from 23 healthy participants previously studied in Turku University Hospital formed the control group.

All subjects gave their written informed consent prior to participating in the study. The local ethics committees approved the study protocol.

TMS assessment included ppTMS in affected and unaffected hand motor representations and bilateral mapping of hand motor representation areas. Additionally, the patients recorded their daily pain intensity in a pain diary for two weeks before the TMS examination. For the pain analysis, we calculated the average pain score from the second week of baseline follow-up (the week closer to the TMS assessments). At the same time point, a physiotherapist or an occupational therapist evaluated the motor performance of patients with the 9-Hole Peg Test (Oxford Grice et al., 2003), Box and Block test (Mathiowetz et al., 1985), and JAMAR (JAMAR hand dynamometer, Sammons Preston Rolyan, Bolingbrook, IL, USA). Patient medication was not modified during the study.

2.2. Transcranial magnetic stimulation: equipment

For ppTMS in Turku University Hospital (CRPS patients and healthy subjects), we applied a circular coil (Magstim 200^2, circular 90 mm Remote Control Coil, The Magstim Company Ltd, Carmarthenshire, UK) aligned over the vertex. Current flow in the coil was clockwise in the right, and counterclockwise in the left hemisphere stimulation generating posterior to anterior current direction on the cortex. For ppTMS in Helsinki University Hospital, we used a navigated monophasic figure-of-eight coil (eXimia® 3.2.1, Nexstim Plc, Helsinki, Finland) with a posterior-anterior current direction on the cortex. Both centers used a navigated biphasic figure-of-eight coil (NBS 4, Nexstim Plc) for mapping of the hand motor representation areas in both hemispheres.

2.3. Transcranial magnetic stimulation: paired pulses (ppTMS)

We first identified the motor hotspot of the hand, by searching the location where suprathreshold stimuli elicited the largest-amplitude MEPs in the abductor pollicis brevis muscle of the contralateral hand. Next, we determined the resting motor threshold (RMT), defined as the minimum stimulation intensity that produced MEPs with an amplitude of $\geq$ 50 μV in at least 5 out of 10 trials at the motor hotspot.

Single MEPs were first elicited at the motor hotspot of abductor pollicis brevis with a stimulation intensity set at 120% of RMT. SICI and ICF were then measured with paired pulses, consisting of a conditioning stimulus (CS, stimulus intensity 80% of RMT) and a subsequent test stimulus (TS, stimulus intensity 120% of RMT). The ISI was 2 ms for SICI protocol and 10 ms for ICF protocol, consistent with previous CRPS studies (Eisenberg et al., 2005, Morgante et al., 2017, Schwenkreis et al., 2003). Twenty consecutive MEPs were collected in each protocol (single MEPs, SICI, and ICF) from both hands. We ensured that the hand remained relaxed by continuously monitoring EMG during the TMS session. Trials with baseline noise exceeding 20 μV peak-to-peak amplitude within 100 ms prior to the stimulation were discarded.

2.4. Transcranial magnetic stimulation: motor representation area

To evaluate the hand motor representation area, we first defined the motor hotspot as in the paired-pulse paradigm and assessed the RMT using the motor threshold assessment tool in NBS 4. The vicinity of the motor hotspot and hand knob area, identified from individual MRIs, was then mapped with a stimulus intensity of 110% RMT, until no more MEPs (positive response defined as amplitude $\geq$ 50 μV) were elicited. The locations of each stimulation site and the amplitudes of the MEPs were analyzed with a custom-made MATLAB script (MathWorks Inc., Natick, MA). A motor map consisted, on average, of 74 TMS pulses with a mean distance of 2.6 mm on the cortical surface. The hand motor representation area in each hemisphere was determined as cortical area producing MEPs of at least 50 μV in amplitude, using the spline-interpolation method (Julkunen, 2014).

2.5. Statistical analysis

SICI and ICF values were normalized by dividing the mean of paired-pulse MEP amplitudes by the mean of single-pulse MEP amplitudes. Single-pulse MEP amplitudes were log-transformed and motor representation areas were square-root-transformed to approach normal distribution across the subjects. Normally distributed data were analyzed with mixed ANOVA: 'Side' (levels: 'affected' or 'unaffected') was the within-subject factor, and 'CRPS type' (levels: 'type I' or 'type II') was the between-subjects factor factor when analyzing the CRPS cohort, whereas 'Group' (levels: 'CRPS' or 'control') was the between-subjects factor when comparing the patients and healthy controls. Post-hoc pairwise comparisons were based on estimated marginal means and adjusted with Bonferroni correction for multiple comparisons. Non-parametric tests (Wilcoxon signed rank test and Mann-Whitney *U* test) were used when assumptions for parametric tests were not met. Relationships of clinical data and TMS variables were assessed with Pearson product-moment correlation or Spearman's rank-order correlation, as appropriate. The correlational analyses were not adjusted for multiple comparisons, as they were regarded as exploratory.

Recordings of the healthy control subjects were compared with the patients of Turku University Hospital, as these groups were investigated with the same TMS device. In line with previous TMS studies in CRPS patients (Eisenberg et al., 2005, Morgante et al., 2017), the affected side of the CRPS patients was compared with the dominant side of healthy controls, and unaffected side with nondominant side. Statistical analyses were conducted in R (R Core Team, 2020). Statistical significance level was set to $p < 0.05$.

3. Results

3.1. Subjects

Among the 59 CRPS patients, 44 were classified as CRPS type I and 15 as type II. Table 1 presents the demographics of the subjects. Table 2 provides detailed information on the relevant medications. All patients met the Budapest research criteria, and Table 3 outlines the motor and trophic symptoms and signs. Of the 59 patients, 56 completed the ppTMS session, and 54 underwent motor mapping. Although some patients experienced discomfort during the ppTMS, none opted to withdraw from the study. The missing sessions were due to scheduling difficulties.

3.2. TMS findings in CRPS patients vs. healthy subjects

Fig. 1 shows the main findings for TMS and ppTMS recordings for the CRPS patients and the healthy control subjects. CRPS patients had significantly lower RMT (main effect of 'Group' $p = 0.032$) and higher MEP amplitudes (main effect of 'Group' $p = 0.015$) than healthy subjects. The stimulation side (affected/dominant and unaffected/nondominant) did not affect the results (main effect of 'Side' $p = 0.86$ for RMT and $p = 0.78$ for MEP amplitude), and group and stimulation side did not interact ($p = 0.76$ for RMT and $p = 0.46$ for MEP amplitude). The MEP latencies did not differ significantly between patients and healthy subjects (non-parametric test, affected side, $p = 0.20$, unaffected side $p = 0.41$).

SICI amplitude ratio in healthy subjects did not differ from the patients' SICI on M1 representing the affected or the unaffected hand (non-parametric test, p = 0.85 and p = 0.67, respectively). ICF amplitude ratio was larger in healthy subjects than in patients (main effect of 'Group' p = 0.022) but stimulation side did not affect the results (main effect of 'Side' p = 0.94) (Fig. 1).

3.3. TMS findings in CRPS: side comparisons and impact of CRPS type

Intraindividual interhemispheric differences in ppTMS responses (comparing the affected and unaffected sides) were consistent across the two centers, despite differences in TMS equipment (Supplementary Fig. 1). Therefore, data from both centers were pooled for subsequent analyses focusing on the interhemispheric differences.

Mixed ANOVA revealed a significant effect of side and interaction of side and CRPS type on MEP latency (interaction of 'CRPS type' and 'Side' $p = 0.019$; main effect of 'Side' $p = 0.0017$) and no simple main effect of 'CRPS type' ($p = 0.094$). Post-hoc tests revealed that, in patients with CRPS Type II, MEP latency was longer to the unaffected hand than to the affected hand ($p = 0.0031$). MEP latency did not differ between the sides in patients with CRPS Type I ($p = 0.79$) (Fig. 2).

RMT did not differ between M1 cortices representing the affected and unaffected hands, nor was it influenced by the CRPS type (main effect of 'Side' $p = 0.82$; main effect of 'CRPS type' $p = 0.48$; interaction of 'CRPS type' and 'Side' $p = 0.87$). MEP amplitudes (at 120 % of RMT) in the affected hand (median 926 μV) were slightly higher than in the unaffected hand (median 833 μV), but the difference did not reach statistical significance (main effect of 'Side' $p = 0.058$). CRPS type did not influence the MEP amplitudes (main effect of 'CRPS type' $p = 0.96$; interaction of 'CRPS type' and 'Side' $p = 0.36$).

SICI amplitude ratio on M1 representing the affected side (median 40 %) did not differ from M1 representing the unaffected side (median 35 %, $p = 0.48$). SICI was similar in both CRPS types (M1 representing the affected side: CRPS I 50 % vs CRPS II 34 %, $p = 0.19$; unaffected side: CRPS I 40 % vs CRPS II 31 %, $p = 0.15$). ICF amplitude ratio on M1 representing the affected hand (median 150 %) did not differ significantly from M1 representing the unaffected hand (median 172 %; $p = 0.33$). Type of CRPS did not affect the ICF ratio (affected side: CRPS I 154 % vs CRPS II 149 %, $p = 0.39$; unaffected side: CRPS I 172 % vs CRPS II 179 %, $p = 0.94$).

The size of the hand motor representation area did not differ between the affected and unaffected hands, nor was it influenced by the CRPS type (mixed ANOVA main effect of 'Side' $p = 0.66$, main effect of 'CRPS type' $p = 0.62$, interaction of 'Side' and 'CRPS type' $p = 0.87$).

Table 1
Characteristics of CRPS patients and healthy control subjects. Continuous variables are presented as mean (SD).

	CRPS type I (N = 44)	CRPS type II (N = 15)	Healthy Controls (N = 23)
Age (yrs)	43 (11)	49 (15)	47 (12)
Sex: Female/Male	39/5	11/4	14/9
Duration of CRPS (yrs)	3.0 (3.1)	3.0 (2.8)	N.A.
Handedness: Right/Left/Ambidextrous	41/0/3	11/2/2	20/2/1
Affected hand: Right/Left	30/14	6/9	N.A.
CRPS side: Dominant/Non-dominant/Ambidextrous	29/12/3	6/7/2	N.A.
ENMG: Normal/Abnormal/N.A.	34/4/6	2/12/1	N.A.
Mean pain intensity (NRS)	6.0 (1.4)	5.7 (1.7)	N.A.

SD = standard deviation, CRPS = complex regional pain syndrome, ENMG = electroneuromyography, N.A. = not available, NRS = numeric rating scale.

Table 2
Current use of antidepressants, anticonvulsants, benzodiazepines, and opioids.

	CRPS type I (N = 44)	CRPS type II (N = 15)
Antidepressants*	25 (57 %)	7 (47 %)
TCA	*18 (41 %)*	*6 (40 %)*
SSRI	*5 (11 %)*	*0 (0 %)*
SNRI	*9 (20 %)*	*3 (20 %)*
Anticonvulsants	26 (59 %)	14 (93 %)
Gabapentin	*19 (43 %)*	*4 (27 %)*
Pregabalin	*8 (18 %)*	*10 (67 %)*
Benzodiazepines	4 (9 %)	3 (20 %)
Opioids**	18 (41 %)	4 (27 %)

*TCA: tricyclic antidepressants, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin and norepinephrine reuptake inhibitors. One patient also used mirtazapine and vortioxetine.
**Opioids included buprenorphine, codeine, and tramadol.

Table 3
Motor/trophic symptoms and signs, as defined by the Budapest Criteria for complex regional pain syndrome.

	Symptoms reported		Observed at evaluation	
	CRPS type I	CRPS type II	CRPS type I	CRPS type II
Decreased range of motion	37 (84 %)	11 (73 %)	36 (81 %)	11 (73 %)
Motor dysfunction	43 (98 %)	15 (100 %)	44 (100 %)	15 (100 %)
Weakness	*42 (95 %)*	*14 (93 %)*	*44 (100 %)*	*15 (100 %)*
Tremor	*31 (70 %)*	*9 (60 %)*	*8 (18 %)*	*4 (27 %)*
Dystonia	*24 (54 %)*	*8 (53 %)*	*7 (16 %)*	*2 (13 %)*
Trophic changes	22 (50 %)	12 (80 %)	14 (32 %)	10 (67 %)

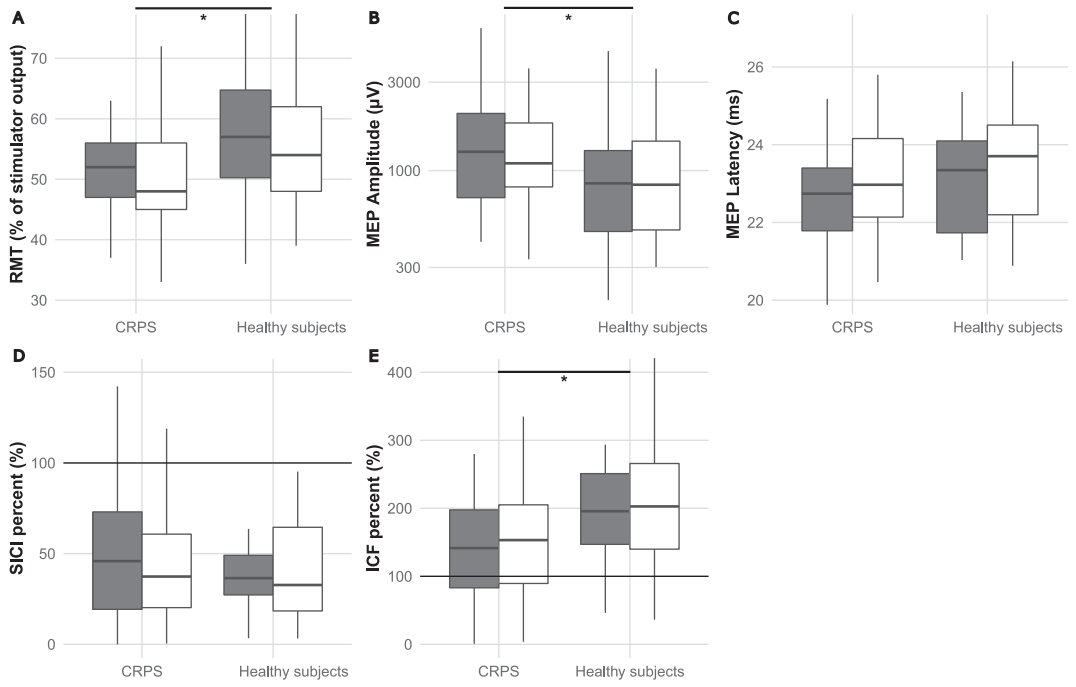

Fig. 1. TMS findings in CRPS patients and healthy subjects. Box and whisker plot, displaying the median (thick line), 25 %–75 % interquartile range (IQR), and the smallest and largest value no further than 1.5*IQR from the hinge (whiskers). Dark grey boxes depict measurements from M1 representing the affected hand (dominant hand in healthy subjects) and white boxes those of the unaffected hand (nondominant hand in healthy subjects). Asterisk denotes p-value < 0.05.

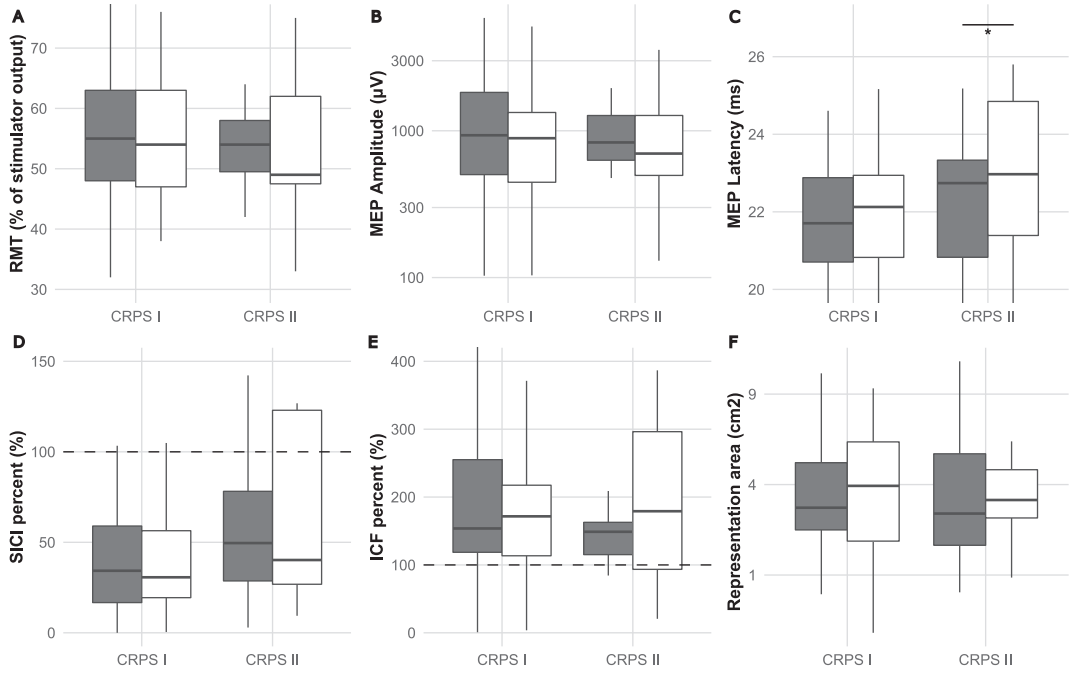

Fig. 2. TMS results in CRPS Type I and II. Dark grey boxes depict measurements with TMS pulses given to M1 representing the affected hand, white boxes to M1 representing the unaffected hand. Asterisk denotes p-value < 0.05 in post-hoc test pairwise comparisons.

3.4. Clinical associations of TMS findings

Pain intensity correlated inversely with the size of the motor representation area of the unaffected hand (r = -0.50, p = 0.0025), with higher pain levels associating with a smaller representation area. A similar but non-significant trend was observed for the motor representation area of the affected hand (r = -0.27, p = 0.089). Pain intensity also correlated with ICF; patients experiencing more intense pain had higher ICF ratios bilaterally (M1 representing the unaffected hand $r = 0.34$, $p = 0.020$; M1 representing the affected hand $r = 0.39$, $p = 0.0073$). We also observed a trend suggesting a correlation between RMT and pain intensity, but this relationship remained at statistical borderline ($\rho = 0.29$, $p = 0.050$ and $\rho = 0.29$, $p = 0.051$). Pain intensity did not correlate with MEP latency, MEP amplitude, or SICI on either side (Table 4).

Manual dexterity correlated with SICI on M1 representing the unaffected hand, where stronger SICI associated with better gross manual

Table 4
Correlation of TMS parameters and clinical data, assessed with Pearson product-moment correlation or Spearman's rank-order correlation. Measurements from affected hand/M1 representing affected hand are marked with italics.

	Pain intensity	Box and Block test	9-Hole Peg Test	Grip
RMT	*ρ = 0.29, p = 0.051*	*r = −0.14, p = 0.32*	*ρ = 0.10, p = 0.46*	*r = 0.06, p = 0.67*
	ρ = 0.29, p = 0.050	**r = −0.28, p = 0.038**	ρ = 0.10, p = 0.45	r = 0.09, p = 0.50
MEP latency	*r = −0.01, p = 0.93*	*r = 0.18, p = 0.18*	*ρ = 0.02, p = 0.91*	*r = 0.17, p = 0.21*
	r = −0.01, p = 0.93	r = −0.11, p = 0.40	ρ = 0.21, p = 0.12	r = 0.22, p = 0.11
MEP amplitude	*r = 0.07, p = 0.64*	*r = −0.07, p = 0.62*	*ρ = 0.10, p = 0.45*	*r = −0.18, p = 0.18*
	r = −0.19, p = 0.20	r = 0.25, p = 0.060	ρ = −0.26, p = 0.052	r = −0.09, p = 0.49
SICI	*ρ = −0.03, p = 0.85*	*ρ = −0.13, p = 0.33*	*ρ = 0.26, p = 0.055*	*ρ = −0.03, p = 0.82*
	ρ = 0.03, p = 0.82	**ρ = −0.32, p = 0.016**	**ρ = 0.36, p = 0.0065**	ρ = −0.02, p = 0.87
ICF	***ρ = 0.39, p = 0.0073***	*ρ = 0.07, p = 0.62*	*ρ = 0.10, p = 0.46*	*ρ = 0.14, p = 0.29*
	ρ = 0.34, p = 0.020	ρ = −0.26, p = 0.053	ρ = 0.25, p = 0.065	ρ = −0.05, p = 0.74
Representation area	*r = −0.27, p = 0.089*	*r = 0.23, p = 0.10*	*ρ = −0.15, p = 0.29*	*r = 0.10, p = 0.51*
	r = −0.50, p = 0.0025	r = 0.16, p = 0.32	**ρ = −0.32, p = 0.038**	r = 0.17, p = 0.29

RMT = resting motor threshold, MEP = motor evoked potential, SICI = short interval intracortical inhibition, ICF = intracortical facilitation

dexterity as measured by the Box and Block test (r = -0.32, p = 0.016) and 9-Hole Peg Test (r = 0.36, p = 0.0065). Better performance in the Box and Block test also associated with a lower RMT on M1 representing the unaffected hand (r = -0.28, p = 0.038). Hand dexterity of the affected hand did not correlate with the TMS results (Table 4).

3.5. Clinical associations of TMS findings

Anticonvulsants, including gabapentin and pregabalin, were commonly used by both CRPS type I (59 %) and type II patients (93 %). Benzodiazepines were used by 11 % of the patients. Because these drugs are known to affect TMS measures of corticospinal excitability (Ziemann et al., 2015), we conducted a post hoc analysis comparing healthy subjects and CRPS patients, including only subjects with no use of anticonvulsants or benzodiazepines. The results were similar as presented in Section 3.1, except for RMT, where the observed difference between patients and healthy controls was not significant (main effect of 'Group' p = 0.13) (Supplementary Fig. 2).

4. Discussion

This study investigated the motor cortical function in patients with CRPS, including both CRPS Type I and Type II patients, confirmed with careful diagnostics. The multicenter study design enabled collection of a substantial patient sample compared to previous studies.

CRPS patients had a lower RMT, higher MEP amplitudes, and reduced ICF compared with healthy subjects, suggesting increased motor cortical excitability in CRPS. On the other hand, in CRPS the SICI tone did not differ between M1 areas representing the affected and unaffected hands, and it did not differ between CRPS patients and healthy subjects. In CRPS Type II, MEP latency was shorter to the affected than the unaffected hand, but did not differ between the patients and the healthy subjects. In addition, higher CRPS pain intensity associated to higher degree of intracortical facilitation bilaterally, and to a smaller size of the motor representation area of the unaffected hand.

4.1. Increased corticospinal excitability in CRPS: insights from RMT and MEP amplitudes

RMT, reflecting the neuronal membrane excitability at M1, varies substantially in healthy subjects (Wassermann, 2002). A considerable between-subjects variability was evident in our data as well (Fig. 1). Despite this, RMT was significantly lower in CRPS patients than in healthy subjects. This contrasts with results of two previous TMS studies indicating no significant difference in RMT between CRPS Type I patients and healthy subjects (Krause et al., 2006, Morgante et al., 2017). However, these studies were limited by relatively small sample sizes (14 and 10 patients). Our larger patient cohort provided more statistical power to detect a difference in RMTs.

The decreased RMT in CRPS patients is compatible with increased membrane excitability of the corticospinal neurons at M1 cortex, and enhanced MEP amplitudes reflecting increased efficacy of excitatory synaptic transmission further support increased cortical excitability in CRPS. However, MEP amplitude is a complex measure, influenced not only by cortical excitability, but also by spinal mechanisms and temporal dispersion of the descending impulse volleys (Groppa et al., 2012). A peripheral nerve lesion, such as that in CRPS Type II, can also affect the MEP amplitude. However, since we observed higher MEP amplitudes in patients than in healthy subjects, a purely peripheral explanation for these findings seems unlikely. Taken together, the findings of decreased RMT and increased MEP amplitudes align to indicate that CRPS is associated with enhanced corticospinal excitability, most likely at the motor cortical level.

4.2. Implications of CRPS on the M1 representing the unaffected hand

Higher pain levels correlated with stronger ICF on M1 representing both the affected and the unaffected hands. Moreover, the size of the motor representation area of the unaffected hand was smaller in those CRPS patients with higher pain intensity. In addition, the MEP latencies induced by TMS from M1 representing the unaffected hand were also longer than those induced from M1 representing the affected hand.

These findings may reflect an imbalance in the reciprocal interhemispheric inhibition. Relative hyperactivity, reflected in increased motor cortical excitability in M1 representing the affected hand could exert an exaggerated inhibition on the contralateral "healthy" M1, leading to reduced motor representation size in patients with higher pain intensity and increased MEP latency to the unaffected hand. Longer MEP latency to the unaffected than to the affected hand is a novel finding in CRPS patients. Subgroup analysis revealed that this latency difference was particularly pronounced in CRPS Type II, where a peripheral nerve lesion is present. A peripheral nerve lesion typically slows down the nerve conduction and should thereby prolong the MEP latency in the affected hand. Thus, the observed shorter MEP latency in the affected hand is most likely due to central mechanisms caused by increased motor cortical excitability within the motor cortex representing the painful hand.

A previous study on CRPS Type I patients reported larger cortico-motor representation area of the unaffected than the affected hand (Krause et al., 2006). Contrary to this, our data did not reveal systematic differences in representation area sizes between the hemispheres. This discrepancy might stem from differences in CRPS duration: in the earlier study, the duration of CRPS was less than 6 months in most patients, whereas we focused exclusively on chronic CRPS (duration of CRPS > 6 months). Unilateral changes in cortico-motor representation area may characterize the acute and subacute phase, but such differences may resolve in the chronic phase, similar to what has been observed in the course of stroke rehabilitation (Liepert et al., 2000a).

The bilaterally symmetrical motor representation areas of the hands may reflect normalization of initially unilateral abnormalities (Krause et al., 2006) or a subsequent, bilateral reduction in motor representation areas. Since we did not map the cortico-motor representation areas of

healthy subjects, the exact trajectory of these changes remains speculative. However, the observed association between smaller corticomotor representation area and higher pain intensity supports the latter hypothesis. This also aligns with prior research linking CRPS to alterations in both the somatosensory (Di Pietro et al., 2013) and the motor (Krause et al., 2006) representation areas.

In our cohort, CRPS was more prevalent in the dominant hand. A previous TMS study involving both CRPS patients and healthy controls found no correlation between handedness and RMT, SICI or ICF in healthy individuals (Eisenberg et al., 2005). When interhemispheric differences in CRPS have been reported, these comparisons typically focused on the differences between the affected and unaffected side (eg. Eisenberg et al., 2005, Krause et al., 2006), without considering hand dominance. Our comparisons were similarly based on this hypothesis, although we acknowledge that hand dominance could potentially influence the results. However, a formal analysis of the effect of handedness would have been underpowered due to the inclusion of only two left-handed patients in our cohort.

4.3. Correlations with hand dexterity

Worse dexterity in the unaffected hand correlated with diminished SICI on M1 representing the unaffected hand. Findings lateralizing to the hemisphere contralateral to the unaffected limb have been reported in CRPS. For example, Di Pietro et al. (2015) challenged the prevailing view of diminished size of the somatosensory representation of the CRPS-affected hand, and suggested that the interhemispheric differences in CRPS are, in fact, due to relative enlargement of the somatosensory representation area of the unaffected hand. In unilateral stroke, the abnormalities can extend to the unaffected hemisphere (e.g. (Liepert et al., 2000b) and the corresponding unaffected limb, manifesting for example as impaired dexterity of the unaffected hand (Nowak et al., 2007). In stroke, this impaired ipsilesional hand function has been attributed to disinhibition of the unaffected motor cortex (Nowak et al., 2007), which parallels our findings of reduced SICI correlating with weaker dexterity of the unaffected hand.

Beyond pain itself, imbalance in daily hand use may contribute to the excitatory and inhibitory dynamics of the motor system. For instance, in motor stroke, several therapies aim to rebalance the cortical excitation and inhibition via interhemispheric connections either by engaging the paretic hand (Boddington and Reynolds, 2017, Wu et al., 2022), or by constraining the use of the healthy hand (Liepert et al., 2000a). This highlights the role of motor cortex plasticity in conditions that involve interhemispheric motor balance and, considering the present findings, extends this plasticity to chronic pain conditions via similar brain-level mechanisms.

4.4. Intracortical inhibition in CRPS

Our results suggest that SICI, thought to reflect $GABA_A$-mediated inhibition, does not differ between patients with chronic CRPS and healthy subjects, nor does it show any hemispheric asymmetry in CRPS patients. CRPS and chronic pain conditions are frequently linked with motor cortex disinhibition and reduced SICI, but findings across studies vary, especially in non-neuropathic pain (e.g. Parker et al., 2016, Schwenkreis et al., 2010). Studies on CRPS also share this inconsistency. Eisenberg et al. (2005) reported a drastically reduced (or even abolished) SICI on M1 representing the affected side but normal intracortical inhibition on the other side. Conversely, Schwenkreis et al. (2003) found no hemispheric asymmetry in SICI among CRPS patients, but a bilaterally reduced SICI compared to healthy controls. A more recent study on 10 CRPS Type I patients suggested reduced SICI on the affected side only (Morgante et al., 2017).

Our findings of no hemispheric asymmetry in SICI align with Schwenkreis' results (Schwenkreis et al., 2003), yet our observation of no difference between patients and healthy subjects contrasts with these earlier studies. Previous studies were limited by small sample sizes (ranging from 6 to 25 patients). In contrast, our larger cohort provides compelling evidence that SICI remains unaltered in CRPS, at least in the chronic phase of CRPS. Additionally, a recent magnetic resonance spectroscopy study detected no changes in GABA concentrations within the sensorimotor cortex of chronic CRPS patients (Lee et al., 2020), supporting our results. In stroke, motor cortical disinhibition is a dynamic process that changes over time (Manganotti et al., 2008). Similarly, CRPS is a dynamic entity, especially in the subacute stages (Birklein and Dimova, 2017). The lack of disinhibition in chronic CRPS suggests that a reduction in GABAergic inhibition, proposed as a cause of chronic neuropathic pain (Canavero and Bonicalzi, 1998), does not underlie the chronic symptoms of CRPS. Given that neuropathic conditions typically show greater motor cortical disinhibition than non-neuropathic conditions (Schwenkreis et al., 2010), our findings support the view that chronic CRPS should not be classified as purely neuropathic pain (Goebel et al., 2021). Thus, in terms of GABAAergic inhibition, chronic CRPS resembles non-neuropathic pain conditions, which might have implications for therapeutic strategies.

4.5. Impact of medications

The use of various medications in our patient cohort is an important confounding factor when comparing their results with healthy subjects (Ziemann et al., 2015). Our ancillary analysis on patients who were not on anticonvulsants or benzodiazepines, however, yielded results consistent with the findings for the entire patient group. The only exception was RMT, where the analysis did not yield significant results, despite a similar trend (Supplementary Fig. 2). This lack of significance is most likely due to the reduced statistical power, because the medications used in our CRPS cohort are unlikely to account for the observed decrease of RMT (Ziemann et al., 2015).

Benzodiazepines have been reported to decrease MEP amplitude; however, contrary to this, our patient cohort exhibited increased MEP amplitudes compared with healthy controls. Anticonvulsants, including gabapentin and pregabalin, were commonly used in our patient group and have been reported to have opposing effect on SICI (Lang et al., 2006, Rizzo et al., 2001). Although we observed a trend consistent with previous literature (data not shown), the effect size was small and non-significant. Gabapentin has also been reported to decrease ICF, a phenomenon not observed in our cohort. As our ancillary analysis, which excluded patients taking these medications, produced consistent results regarding SICI and ICF, we believe that our findings are not significantly confounded by the presence of these medications.

5. Strengths and limitations

This study features a notably larger sample size than previous TMS studies in CRPS. Moreover, patients were carefully examined and diagnosed as CRPS Type I or Type II with appropriate methods. This substantial multicenter cohort, including both CRPS Type I and Type II subtypes, provides valuable insights into the neurophysiological changes associated with the condition. However, due to the limited size of the CRPS II cohort, it is not possible to draw definitive conclusions regarding the presence or absence of differences between the Type I and Type II groups, even in light of the findings from this adequately sized study.

The ppTMS equipment differed between the two study centers. Nevertheless, most comparisons focused on intraindividual, interhemispheric differences, minimizing the impact of differing devices. On the other hand, the consistency of findings across centers and equipment strengthens the reliability of our results (Supplementary Fig. 1). Moreover, prior TMS studies on CRPS have employed both circular and figure-of-eight coils.

A limitation of the study is the use of a consistent target muscle for TMS across all patients, irrespective of specific pain distribution and

location. Especially in CRPS Type II, focusing on a target muscle supplied by the lesioned nerve might have yielded more specific findings, although in a study on chronic neuropathic pain, evidence of cortical disinhibition on TMS parameters could be drawn from muscles supplied by both lesioned and non-lesioned nerves (Schwenkreis et al., 2010). Additionally, a limitation in the mapping of the motor representation areas was the lack of a grid-based or fixed-distance methodology. This may have influenced the accuracy of the present results and restricts the potential for comparing the motor area sizes presented in this study with those mapped with different techniques.

The cross-sectional study design, with no longitudinal follow-up, precludes insights about potential excitatory or inhibitory changes during the acute phase of CRPS. All participants had chronic CRPS with a duration of at least 6 months, which is longer than in most prior TMS studies on CRPS. This difference in disease duration could explain some discrepancies with earlier literature, alongside the larger sample size. TMS parameters, including MEP thresholds and paired-pulse measures, are inherently prone to considerable within-subject variability and experimental error (Wassermann, 2002).

In conclusion, several TMS markers of motor cortical excitability reflected increased corticospinal excitability in chronic CRPS compared to healthy subjects, but mostly no interhemispheric asymmetry. CRPS often manifests as a unilateral disorder initially. Our findings suggest that in its chronic stage, CRPS exerts bilateral effects on the brain which may be emphasized by pain intensity.

6. Data statement

Ethical restrictions imposed by the hospital's research ethics committee prevent the authors from making raw data publicly available without restrictions. However, the relevant summary tables of the data are available from the authors upon reasonable request and with permission of the hospital's research ethics committee, for researchers aiming to reproduce the results.

CRediT authorship contribution statement

Jukka Vanhanen: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Janne Nordberg:** Investigation, Writing – review & editing. **Janika Paavola:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Petro Julkunen:** Formal analysis, Writing – review & editing. **Miguel Munoz:** Investigation, Writing – review & editing. **Jyrki P. Mäkelä:** Conceptualization, Writing – review & editing. **Selja Vaalto:** Conceptualization, Investigation, Writing – review & editing. **Erika Kirveskari:** Conceptualization, Writing – review & editing. **Satu Jääskeläinen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Julkunen reports having received consulting fees from Nestim Plc (Helsinki, Finland) and holds an unrelated patent shared with Nexstim Plc. Dr. Vaalto has been working as end user device tester in Nexstim Plc. The other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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