Sex, quality of life and brain function in complex regional pain syndrome

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Chapter 6

Motor cortical activity during motor tasks is normal in patients with Complex Regional Pain Syndrome

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ABSTRACT

Motor dysfunction in complex regional pain syndrome is often considered a functional movement disorder. Earlier studies in patients with functional movement disorders found evidence of cortical inhibition during explicit - but not during implicit - motor tasks, suggesting active inhibition from other brain areas. In this study we explored whether active inhibition occurs in complex regional pain syndrome patients. We compared patients with complex regional pain syndrome with 2 control groups: healthy controls matched for age and sex, and patients whose hand was immobilized to treat a scaphoid fracture. We used transcranial magnetic stimulation to measure corticospinal excitability at rest and during motor imagery (explicit motor task) and motor observation (implicit motor task). Motor corticospinal excitation measured at rest, and during implicit and explicit motor tasks was similar for CRPS patients and healthy controls. Patients with an immobilized hand showed an absence of motor cortical excitation of the corresponding hemisphere during motor imagery of tasks involving the immobilized hand, but not during motor observation.

The normal motor cortical processing during motor imagery and motor observation found in the corresponding hemisphere of complex regional pain patients suggests that the nature of motor dysfunction in this condition differs from that described in literature for patients with functional paresis or under circumstances of limb immobilization.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a debilitating pain syndrome that usually develops after a minor trauma to a limb. The condition is clinically characterized by neuropathic pain, autonomic disturbances and motor dysfunction[1]. Examples of the latter are a loss of voluntary motor control, slowness of movement, weakness and postural abnormalities ('fixed dystonia') of the affected limb[201]. The nature of motor dysfunction in CRPS, particularly 'fixed dystonia', has been a continuous source of debate[59,61,62]. On the one hand, fixed dystonia in CRPS has been viewed as a consequence of maladaptive neuronal plasticity or so-called central sensitization[197], while some, on the other hand, emphasized a resemblance with functional movement disorders (i.e., movement disorders without a demonstrable organic substrate), such as a prior peripheral trauma, the prominent presence of pain, and the occurrence of fixed postures[59,61,62,202].

Given the lack of a gold standard for the diagnosis of functional movement disorders[59,203], Schwingenschuh et. al.[204] attempted to develop laboratory tests to help establish the presence of a functional movement disorder. One such promising technique could be transcranial magnetic stimulation (TMS) during motor imaginary (MI) and motor observation (MO). During MI subjects rehearse a movement mentally without actually executing the movement, while in MO subjects observe someone else moving. In healthy controls both conditions activate similar brain areas involved in motor planning comparable to the actual execution of these movements, without being influenced by nerve or muscle disorders[205–207]. In patients with functional paresis, MI results in reduced primary motor cortex activation while normal activation is seen during motor observation[65,66]. This dissociation of motor cortex activation between the explicit, voluntary MI and the implicit, automatic MO is attributed to inhibitory activity of frontal or limbic brain areas during voluntary motor tasks[66,208].

In view of the clinical resemblance between the movement disorders seen in patients with CRPS and patients with functional movement disorders, this study sought to investigate if CRPS patients also exhibit the different pattern of corticospinal excitability during explicit and implicit motor tasks found in patients with functional movement disorders. In order to accomplish this, we first measured baseline cortical excitability at rest using different intensities of TMS. Next, TMS measurements during MO and MI of weightlifting were performed using two distinct weights, to check the assumption that observed and imagined weightlifting results in a corresponding increase of cortical spinal excitability for heavier weights[209], In addition, an extra control group was recruited consisting of patients who had one hand immobilized for a period of at least four weeks because of cast treatment for a scaphoid bone fracture (SBF) to control for the effects of underutilization of a limb, such as often seen in CRPS patients.

If the discrepancy in corticospinal excitability during explicit and implicit motor tasks is observed in patients with CRPS related motor dysfunction, this condition shares an important characteristic with functional movement disorders, which would require modification of therapeutic strategies.

METHODS

Subjects

Patients followed up at the neurology outpatient clinic of the Leiden University Medical Center (LUMC) in Leiden, the Netherlands, with documented CRPS of an upper limb were contacted by the principal investigator (GAJV) and informed on the purpose and procedures of the study, after which they were asked if they would consider participating in this study. If a patient was interested, a patient information sheet was sent to his or her home 2 weeks before the potential entry in the study. On the study day a neurological examination was performed by the principal investigator and Budapest Criteria [2] were checked to include or exclude a patient. Additional inclusion criteria were loss of voluntary motor control of the affected limb for over 6 months; weakness; slowness of movement, whether or not in combination with decreased active range of motion or fixed dystonia. These characteristics were all evaluated without the use of extra instrumentation. Exclusion criteria were any relevant neurological illness or any other condition with pain or functional impairment of an arm.

Between July 2012 and July 2013 we specifically included patients with a unilateral scaphoid bone fracture (SBF), because in this patient group, as opposed to patients with other forearm and wrist fractures, the pincher grip (first dorsal interosseus muscle, see below) was immobilised for at least 4 weeks. These patients were approached during their immobilisation period and included only if pain was minimal or absent (e.g. ≤ 1 on a numeric rating scale (NRS) ranging from 0 – 10). These patients were evaluated within an hour after cast removal. Lastly, healthy controls (HCs) were age and sex matched to the CRPS patients. These control subjects were volunteers from the hospital staff or relatives of the CRPS patients. Exclusion criteria were pain, neurological disease or any other condition that might affect proper hand function.

The study was approved by the Medical Ethics Committee of the LUMC, and written informed consent was obtained from all patients and control subjects.

Transcranial magnetic stimulation

Subjects sat in an adjustable chair with supports for the head, arms and legs. Subjects rested their hands on a pillow, with the palms downwards. A computer screen was placed before the subjects at eye level (Appendix A).

We used a Magstim Rapid 2 (Whitland, Dyfed, UK) with a figure-of-8 shaped coil supported by a standard. We positioned the coil over the motor cortex and locked the coil on the position where the lowest stimulus intensity was needed to evoke a 100 μV motor evoked potential (MEP). This position was considered as the "motor hotspot". An optical measurement and positioning system (Polis Spectra, NDI, software: ANT ASA 4.7.3, Enschede, the Netherlands) ensured that the position of the coil was held constant.

We recorded and stored MEPs (Medelec Synergy 10, Oxford instruments) from the first dorsal interosseus (FDI) muscle of both hands using 23-mm-diameter Ag/AgCl surface electrodes. MEP amplitudes were measured peak-to-peak with a 30-3000 Hz bandpass filter. All consecutive TMS stimuli were given with an interstimulus interval of 4-6 seconds. The sequence of testing was always: motor threshold, input-output curve, motor observation, motor imagery with a 5 minutes break between the tests. The sequence in which hands were measured during the different tests was determined at random.

Motor threshold

Patients were asked to relax and look in front of them. We defined the motor threshold (MT) as the lowest stimulus intensity needed to evoke MEPs with amplitudes of 50-100 μV in at least 5 out of 10 trials during muscle relaxation[210]

Input-output curve (IO curve)

We first established the stimulus intensity needed to evoke a 1 millivolt MEP at rest (=SI1mV) using the median of 10 consecutive repetitions. Next, we applied in total 60 TMS stimuli on the motor hotspot with 80, 90, 100, 110, 120, and 130% of SI1mV intensity (10 stimuli/intensity). Decreased cortical excitation as reflected by a flatter curve was considered as evidence of centrally active drugs used by the patients[211]. Conversely, a steeper curve has been associated with changes in cortical spatial motor representation[212], extensive use[213] or prolonged disuse[214] of the hand.

Motor observation (MO)

Subjects were ignorant of the purpose of the test. For both hands we screened 8 videos in which a left or right hand lifted either a heavy (1kg) or a light (50g) weight in the air for 15 seconds (pincer grip)[209]. The weight difference could be appraised by object size, inscriptions (1kg; 50g) and apparent strain on arm muscles. Signals added to the videos ensured perfect

timing of 3 TMS stimuli during weight lifting. The sequence of weights (heavy and light) and the order of hand used (right and left) was randomized. To ensure that subjects remained focused while keeping them ignorant about the real purpose of the test to prevent that this knowledge could bias the results, we instructed them to identify one of the used weights in the videos as a (in reality non-existing) phony weight.

Motor imagery (MI)

First, subjects were given the weights to feel the weight in real life. Subsequently they closed their eyes and focused on the examined hand. We then instructed them to imagine lifting either the heavy or light weight, or to imagine the hand at rest (order again randomized). After 2 seconds, 3 consecutive TMS pulses were given. This procedure was repeated 4 times. After each session, subjects rated their subjective performance of imagined movements from 1-5 (1: very good image; 5: no image).

Secondary outcome measurements

In the days before the research-day, patients completed questionnaires measuring pain (McGill Pain Questionnaire, MPQ)[77], manual activity (Radboud skills questionnaire, RSQ)[131], and the ability to perform imagined movements (Vividness of Movement Imagery Questionnaire-2, VMIQ-2)[215], In addition, on the day of examination we collected data on demographic variables, pain severity (NRS), CRPS (CRPS severity score[75]), dystonia (Burk-Fahn-Marsden scale[132]), strength, active range of motion, slowness of movement and pressure pain thresholds. The latter was determined in 3 muscles (first dorsal interosseus, flexor and extensor digitorum), using an electronic algometer (FPX50; Wagner Instruments, Greenwich, CT, USA)[216]. The pressure pain threshold was used as a covariate in the main TMS analysis.

Sample size calculations

Sample size calculation was based on data from Liepert et al[66], patients and healthy controls. With a mean of 74.8±16.4% of MEP amplitude at rest during MI and 128.9 ±15.4% during MO, and considering an alpha of .05 and a power of 0.80, 6 patients would be sufficient. To be on the conservative side we aimed to include 12 patients in every group.

Data analysis

We compared the affected hand of CRPS patients with the dominant hand of healthy controls because insufficient data was collected from the unaffected hand of CRPS patients: 1 patient had CRPS in both hands, 2 others had complaints of pain in the non-affected hand not fulfilling CRPS criteria, and in 3 patients MEPs could not be recorded from the unaffected hand (see limitations). The dominant hand of HCs was chosen because motor imagery of the dominant hand has been shown to yield better EMG results[217]. We analysed TMS results of the SBF group separately, due to the small number of subjects and the strong age

and sex difference with the other two groups. In this group the healthy hand was compared with the immobilized hand.

Statistics

Data were analysed with IBM SPSS statistics version 20.

We checked normality of the data before using t-tests to assess differences in baseline characteristics and MT between CRPS patients and HCs. For the analyses involving SBF patients, nonparametric tests were used (Wilcoxon-signed-rank-test and Friedman-test) due to the small sample size.

In all TMS analyses we used the median of 10 (MT and I0 curve) or 12 (MO en MI) consecutive TMS recordings. Linear mixed models were used for the analysis of the IO curve (fixed factors: "group" (CRPS or HC) and "TMS intensity" (80-130%)) and for the analysis of MO/MI (fixed factors: "group" (CRPS or HC), "task" (MO or MI) and "weight" (rest, light, heavy)). In both analyses "age" and "mean pressure-pain-threshold" were included as covariates[216]. Correlations between VMIQ-2 scores (low scores indicate good ability to perform IM) and MI EMG results were examined with Pearson's correlation coefficient.

RESULTS

Data of CRPS patients and HCs are presented as means ± standard deviation and data of SBF patients as medians with interquartile range.

One-hundred-and-twenty-one patients were considered for inclusion in the study. Of these, 31 did not fulfil Budapest criteria for CRPS of a hand. In addition, 40 patients declined to participate, 28 were excluded because of comorbidities, while 10 patients could not be reached by telephone, mail or email.

Twelve CRPS patients (age: 51 ± 9.5; 2 men) and 12 HCs (age: 52 ± 13.0; 1 man) and 6 SBF-patients (age: 24 (20.5-33.5); 5 men) participated in the study. Age did not differ between CRPS patients and HCs ($t(22)=0.034$, $p=.97$), but did between CRPS and SBF patients ($U=4.5$, $z=-2.95$ $p<.01$), as well as between HCs and SBF patients ($U=5.0$, $z=-2.91$, $p<.01$).

Characteristics of the CRPS and SBF group can be found in Table 1. All CRPS patients had a chronic disease course (88.0 ± 26.9 months) and experienced continuous pain. The immobilization period in the SBF group ranged from 4-10 weeks.

Table 1 Patient characteristics

CRPS patients	Age	Sex	Hand domi-nance	Affected side	Disease duration (months)	CRPS severity score (0-17)	BFM	MD	NRS (0-10)	MPQ (0-63)	RSQ (0-5)	Centrally acting drugs
1	54	F	L	R	120	12	16	we, sl, drm, dyst	5	26	3.68	Tramadol-acetaminophen (Zaldiar), etoricoxib (Arcoxia), pregablaline (lyrica)
2	34	F	R	L	75	9	28	we, drm, dyst	8	41	3.39	Oxycodon (OxyContin) baclofen, temazepam
3	58	M	R	L	75	14	16	we, sl, drm, dyst	9	34	5.00	Amitriptyline
4	58	M	R	L	60	9	9	we, drm, dyst	7	27	2.71	-
5	54	F	R	L	360	13	14	we, sl, drm, dyst	5	27	2.76	Pregabaline (Lyrica)
6	50	F	R	R	89	9	16	we, sl, drm, dyst	8	27	4.24	-
7	58	F	R	L	13	14	12	we, sl, drm, dyst	7	26	3.77	Tramadol, gabapentin
8	36	F	R	R	24	8	0	we, sl	6	30	2.00	Pregabaline (Lyrica), amitriptilyne
9	41	F	R	L	72	11	0	we, sl	9	-	2.63	Amitriptilyne
10	63	F	L	L	120	10	9	we, sl, drm, dyst	7	0	1.76	Amitriptilyne, diazepam
11	55	F	L	R	39	11	28	we, sl, drm, dyst	3	26	4.04	(1/4 months ketamine)
12	43	F	R	1	9	10	0	we, sl, drm	6	21	2.48	-
Mean (±SD)	51 (9.5)				88 (93.3)	10.8 (2)	12.3 (9.6)		6.7(1.8)	25.9(10.0)	3.2(1.0)	

Table 1 Patient characteristics (continued)

CRPS patients	Age	Sex	Hand domi-nance	Affected side	Disease duration (months)	CRPS severity score (0-17)	BFM	MD	NRS (0-10)	MPQ (0-63)	RSQ (0-5)	Centrally acting drugs
SBF patients	Age Sex		Hand dominance		Immobilized hand	Immobilization duration weeks		NRS (0-10)	MPQ (0-93)	RSQ (0-5)		Centrally acting drugs
1	21 F		R		R	9		0	9	1.67		-
2	26 M		R		L	7		0	14	2.78		-
3	50 F		R		L	8		0	1	2.20		-
4	28 M		L		R	4		0	0	1.75		-
5	19 M		R		R	6		1	1	2.33		-
6	22 F		R		L	10		0	0	missing		-
Median (IQR)	24 (20.5-33.5)					7.5 (5.5-9.3)		0 (0-1.0)	5.0 (1.0-12.8)		2.3(1.8-2.7)	

Abbreviations: BFM, Burk-Fahn-Marsden scale; MD, motor dysfunction; NRS, numeric rating scale; MPQ, McGill Pain Questionnaire; RSQ, Radboud Skills Questionnaire; F, female; L, left; R, right; we, weakness; sl, slowness; drm, decreased active range of motion; dyst, fixed dystonia; M, male; SD, standard deviation; IQR, interquartile range. NOTE. All patients exhibited loss of voluntary motor control.

No healthy control reported any pain. Eight of 12 CRPS patients used centrally acting drugs on the day of examination, and one had a ketamine infusion in the previous month.

Mean pressure pain threshold was significantly lower for CRPS patients (1.8 ± 1.2 kilogram force (kgf)) than for HCs (3.1 ± 0.7 kgf ; t(142)=-8.064, p<.001). In the SBF group no difference was seen between the healthy (3.0 [2.2-3.6] kgf) and immobilized hands (2.7 [1.9-3.3] kgf; t=5, z=-1.153, p=.25).

TMS results CRPS patients and healthy controls (Appendix B)

MT did not differ between the `affected` hemisphere of CRPS patients and the dominant hemisphere of HCs (t(22)=-0.416, p=.68). Analysis of the IO curves revealed an expected increase in MEP amplitude with increasing stimulus intensity (F(5,22.2) = 70.1, p <.01), which was similar in both groups (F(1, 38.9) = 0.160, p=.69). There was no interaction between group and intensity (F(5,22.2) = 0.572, p=.72) (figure 1). Neither age (F(1, 18.9) = 3.26, p=.09) nor pain-threshold (F(1, 18.9) = 0.43, p=.52) affected the IO-curves.

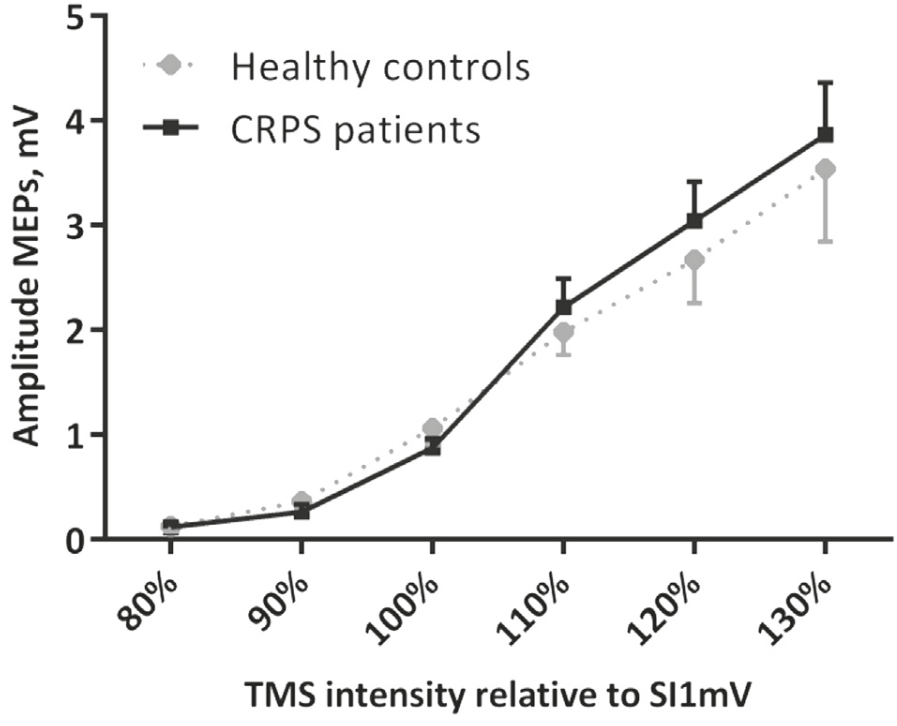

Figure 1
IO curves for CRPS patients and HCs. Bars: means ± standard errors. Note that no significant differences were found between the groups.

MI resulted in significantly higher MEP amplitudes than MO ($F(1, 91.7) = 4.42$, $p=.04$) (figure 2). In addition, increasing weight resulted in higher MEPs ($F(2, 59.6) = 7.65$, $p<.01$) in all occasions, except for 'MI-heavy' in CRPS patients. No difference was found between groups ($F(1, 18.3) = 0.174$, $p=.68$). No significant interaction was found between group and task (i.e. CRPS/HC and MI/MO) ($F(1, 90.5) = 0.843$, $p=.36$) or between group and weight ($F(2, 56.6) = 1.469$, $p=.24$). Notably, only one CRPS patient showed decreased cortical excitability during MI (light or heavy) relative to MO-rest while this occurred in none of the HCs.

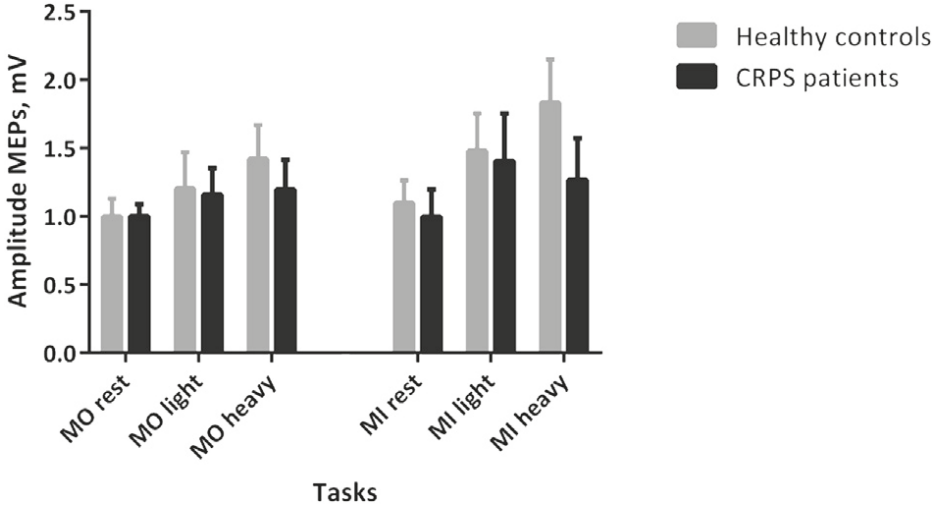

Figure 2

MO and MI results for CRPS patients and HCs. Bars: means ± standard errors. For comparison purposes, data have been transformed to make MO rest precisely 1mV, statistics were performed on original data. Excitation of the primary motor cortex during MO and MI is similar in CRPS patients and HCs.

Influence of age ($F(1, 18.0) = 0.79$, $p=.39$) and pain-threshold ($F(1, 18.0) = 0.78$, $p=.39$) were both non-significant. Post-hoc analyses of MI-heavy resulted in a non-significant difference between CRPS patients and HC's ($T(22) = -1.863$, $p=.09$).

Eight CRPS patients and 8 HCs designated the light weight as the phony weight during MO, whereas a heavy weight was indicated as phony by 3 HCs; 5 subjects (4 CRPS patients, 1 HC) were incapable of identifying the phony weight. The vividness of MI in CRPS patients was significantly worse than in HCs ($T(22) = 3.34$, $p<.01$) and correlated with the EMG-MI results ($r=-0.26$, $p=.03$). Similarly, results of the VMIQ-2 showed that CRPS patients (2.7 ± 1.1) exhibited significantly worse scores for MI of self-performed actions than HCs (1.8 ± 0.6), ($T(21) = 2.5$, $p=.02$).

TMS results scaphoid bone fracture patients

No significant difference in MT was found between the healthy and immobilized hand (T= 5, z=-1.153, p=.31). Increasing TMS intensities resulted in significantly higher MEPs in the healthy hand ($X^2(5) = 28.4$, $p<.01$) and the immobilized hand ($X^2(5) = 24.5$, $p<.01$) (figure 3). No differences between hands were found.

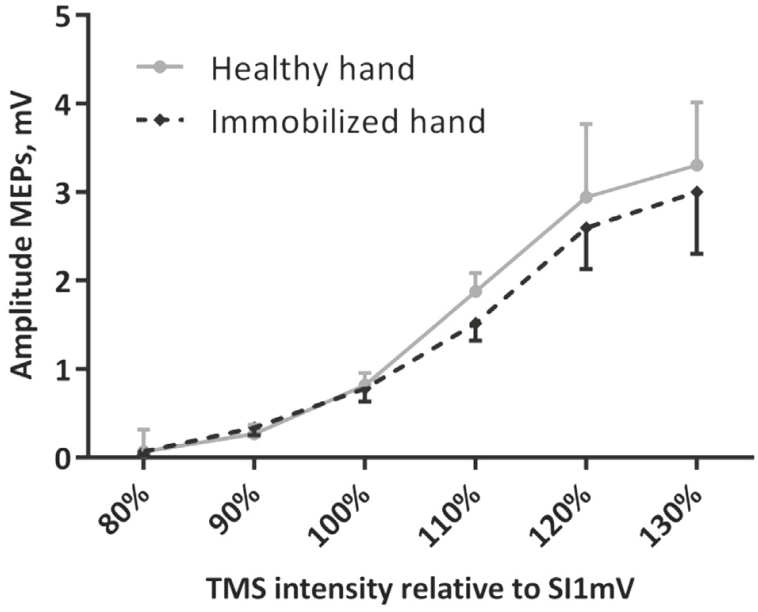

Figure 3
IO curves for SBF patients. Bars: means ± standard errors. Note that no significant differences were found between hands.

MI of the immobilized hand did not result in an increase of MEPs such as seen in MI of the healthy hand (T = 0, z=-2.201, p=.03), or as seen during MO (T=0, z=-2.201, p=.03) (figure 4).

For the healthy hand no difference was observed between MO and MI (T = 7, z=-0.734, p=.56) and MO did not differ between hands (T=2, z=-1.782, p=.09). Vividness of MI was equal for both hands; healthy hand 1.9 [1.3-2.3], immobilized hand 1.6 [1.3-2.5], (T=5, z=-0.680 p=.50).

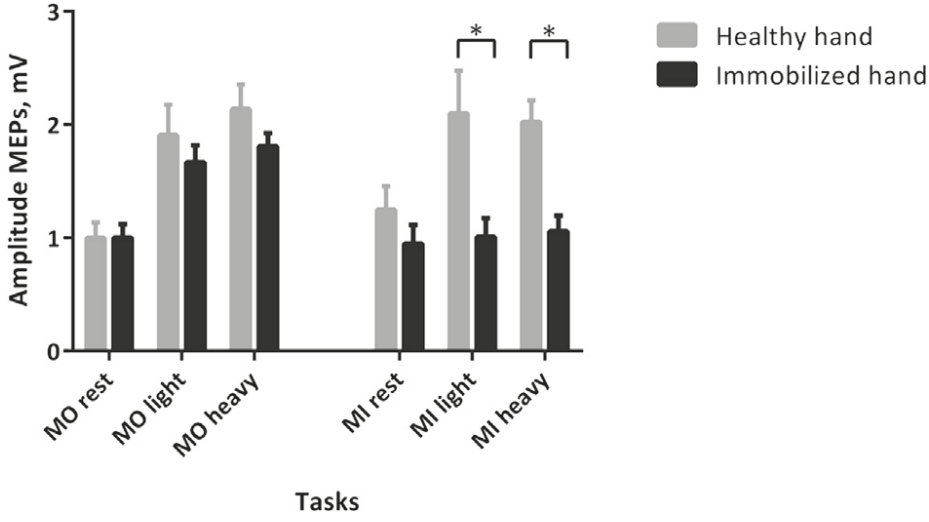

Figure 4
MO and imagery in SBF patients. *P<.05, corrected for multiple comparison. Bars: means ± standard errors. For comparison purposes, data have been transformed to make MO rest precisely 1mV, statistics were performed on original data.

DISCUSSION

Using TMS, we studied corticospinal excitability of the affected hemisphere of CRPS patients with motor dysfunction at rest and during implicit and explicit motor tasks. Our findings show normal motor cortex activation at rest (MT/IO curve) and similar motor cortex excitation in MI and MO in comparison to results obtained from healthy controls, indicating normal motor processing without inhibitory interference from other brain areas such as seen in patients with functional paresis[65,66]. A second important finding is the absence of corticospinal excitation only in the hemisphere corresponding with the affected side during MI, but not during MO, in patients with unilateral hand immobilization due to a fracture.

CRPS patients and healthy controls

The results of MTs and IO curves in CRPS patients are consistent with pooled results in a recent systematic review by Di Pietro et al[124]. and likely suggests that centrally active drugs did not influence our results. Additionally, motor cortical reorganization or an effect of prolonged disuse could not be demonstrated, although, hypothetically, the opposing effects of drugs (reduced excitability[211]). and immobilization (increased excitability in some studies[214]) could have neutralized each other.

The excitation of the primary motor cortex in the "affected" hemisphere during MO and MI in CRPS patients indicates that implicit and explicit motor planning in CRPS patients is similar to HCs. This finding contrasts with the results reported by Liepert et al. who found inhibition of MEP amplitudes during MI in 8 upper limb and 10 lower limb patients with a functional paresis compared to healthy controls, as well as in 2 patients with fixed dystonia[65,66].

Given the partial overlap between clinical features of CRPS and functional paresis patients, similar activation patterns of the motor cortex might have been expected in the 2 conditions. However, previous results from imaging studies already showed that in CRPS patients and functional paresis patients, motor planning involves distinct cortical activation patterns: In CRPS patients *in*creased activation of the primary motor cortex with decreased activation of parietal cortex was seen[40,218], whereas in functional paresis patients *de*creased activation of the primary motor cortex[219,220] basal ganglia and thalamus[221] and increased activation of prefrontal and brain areas associated with emotional regulation[222] was observed.

While these imaging data display spatial differences in cortical activation patterns during motor planning, our data in CRPS, finding no difference in cortical excitability from HCs, and the results from Liepert et al in functional paresis[65,66], finding distinct cortical excitability differences from HCs, show that quantitative changes in cortical excitability differ between the syndromes. Collectively, this suggests that motor processing in CRPS patients with motor dysfunction substantially differs from motor processing in patients with functional paresis.

The question remains why many CRPS patients develop motor dysfunctions. One possible explanation is that the initial adaptation of motor behaviour is aimed at a short-term protection from further pain, injury, or both. In susceptible subjects, the plastic changes associated with central sensitisation may have consequences for motor programming in the long term, rendering it difficult to return to the initial pattern of normal motor behaviour and contributing to the maintenance of motor dysfunctions in CRPS[85,223] Another possible explanation for motor dysfunctions in CRPS could be the disturbed processing of afferent information. Recent data show that impaired central processing of proprioceptive information is related to motor dysfunction in CRPS[55]. Taken together this may suggest that although intrinsic properties of motor processing are intact, altered processing of afferent input is key in the development and maintenance of motor dysfunctions in CRPS patients. Consequently, therapeutic strategies should be focussed on restoring afferent processing, for example by stimulating afferent input in duration, intensity and modality as much possible (e.g. by using the affected limb, touching the skin, using different textures).

It has to be noted that post hoc analysis of the results of "MI of the heavy weight" show a lower excitation than might be expected (figure 2). This could suggest that MI of "heavy" labour is more difficult to perform than MI of light labour. Patient's vividness of MI and the results of VMIQ-2 concur with this trend, which is consistent with earlier reports stating a negative relation between the ability to perform MI and loss of afferent input, a characteristic feature of CRPS[50,55,224].

Scaphoid bone fracture patients

No significant difference in motor excitability at rest was found between the immobilized and healthy hand of SBF-patients. This finding contrasts with that of a previous study showing increased IO curves and reduced MTs after 5 weeks of immobilization[214]. Whether methodological differences between both studies (powering, different TMS coil and different muscles examined) explain the different results remains unclear.

Results of the immobilized hand in the SBF-group showed an absence of increased motor cortical excitability during MI, while patients' subjective vividness of MI was not different from HCs. Of note, these results are different from the motor cortex inhibition seen in patients with functional movement disorder since those patients showed a reduction in excitability relative to rest.

However, these results suggest that underutilization of the affected limb in CRPS patients does not affect motor cortical excitation during explicit motor tasks as present during cast immobilization, as we had anticipated. In addition, we found that immobilization causes a (temporary) inability to activate the primary motor cortex (published before[225,226]), whereas implicit motor observation activates the motor cortex in a classical way. These results are in line with those of a recent study,[227] in which the authors argue that MI is dependent on afferent feedback that continuously updates the state of a limb, while MO can directly activate the motor cortex without knowledge of the state of a limb. This implies that under circumstances of limb immobilization, explicit motor tasks are ineffective in activating the motor cortex.

Limitations

No EMG recordings could be obtained from the unaffected side of three CRPS patients (3, 5 and 9). We have no explanation for this finding and could not find a similar report in the literature. However, discussion with other TMS researchers revealed that it is not unusual to find people unresponsive to TMS stimuli, although a unilateral absent response might be a novel finding. Second, we did not succeed in recruiting the planned 12 scaphoid bone fracture patients with a comparable age and sex as the CRPS patients. In fact, we only found 6 patients, who turned out to be significantly younger. For these reasons a direct comparison of the groups was not possible. Still, the validity of our findings is underscored by the findings

of Bassolino et al.[227], who recently published on 24 HCs who had been immobilized for 10 hours.

In the present article we compared the results of the dominant hand of HCs with the affected hand of CRPS patients because motor imagery of the dominant hand has been shown to yield better EMG results[217]. However, although not reported here, comparisons of the data of the patients´ affected hand with those of the non-dominant hand of HCs showed similar results as those of the dominant hand, indicating that the (arbitrary) choice of the hand of HCs did not alter the conclusions of this paper.

To summarize, we found no evidence for inhibited motor cortical excitation of the hemisphere corresponding with the affected side during motor tasks in CRPS patients, which suggests that the nature of motor dysfunction in CRPS patients differs from that encountered in patients with functional paresis or under circumstances of limb immobilization. This information is important for patients and pain clinicians, to prevent implementation of therapeutic strategies based on the wrong assumptions.

Future studies on motor dysfunction in CRPS patient should focus on structures peripheral to the primary motor cortex.

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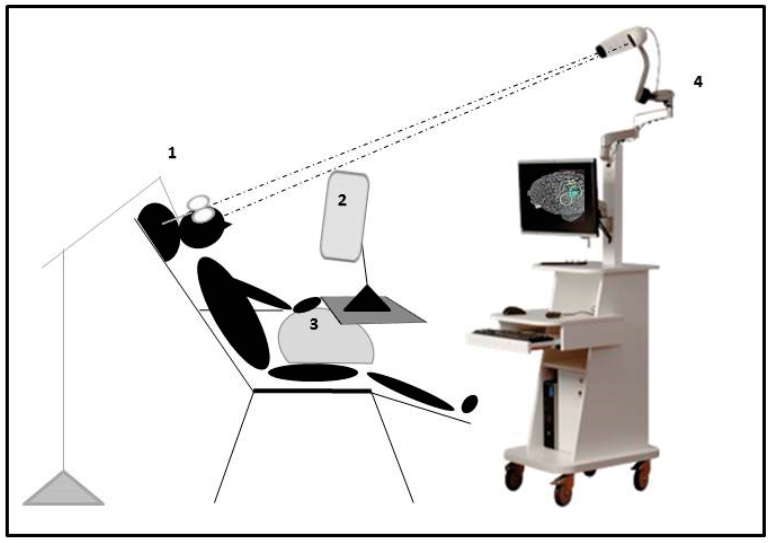
APPENDIX



Appendix A: Setup transcranial magnetic stimulation measurement.
1 = TMS figure-of-8 coil with standard, 2 = Screen for observation tasks, 3 = Pillow, 4 = Brain navigation for accurate TMS stimulation

Appendix B Appendix B: TMS results (MEPs) first dorsal interosseus muscle and vividness of motor imagery

	CRPS affected n=12 mean (SD)	HC dominant hand n=12 mean (SD)	SBF non-immobilized n=6 median, (IQR)	SBF immobilized n=6 median (IQR)
MT	**52.2 (8.3)**	**53.5 (7.4)**	**50.5 (41.8-53.3)**	**50.0 (45.5-56.5)**
80%	**0.1 (0.1)**	**0.1 (0.1)**	**0.1 (0.0-0.1)**	**0.1 (0.0-0.1)**
90%	**0.3 (0.3)**	**0.4 (0.3)**	**0.2 (0.1-0.4)**	**0.4 (0.2-0.5)**
100%	**0.9 (0.3)**	**1.1 (0.6)**	**0.9 (0.4-1.0)**	**0.6 (0.6-1.1)**
110%	**2.2 (0.9)**	**2.0 (0.8)**	**1.8 (1.5-2.3)**	**1.6 (1.3-1.8)**
120%	**3.0 (1.3)**	**2.7 (1.5)**	**2.4 (1.4-4.2)**	**2.8 (1.6-3.5)**
130%	**3.8 (1.4)**	**3.5 (2.1)**	**3.1 (1.7-4.8)**	**3.0 (1.6-4.4)**
MO rest	**0.9 (0.3)**	**1.1 (0.5)**	**0.9 (0.5-1.1)**	**0.7 (0.6-1.1)**
MO light	**1.0 (0.7)**	**1.3 (0.9)**	**1.6 (1.2-2.4)**	**1.3 (1.2-1.8)**
MO heavy	**1.1 (0.8)**	**1.6 (0.8)**	**2.2 (1.5-2.4)**	**1.5 (1.4-1.8)**
MI rest	**0.9 (0.7)**	**1.2 (0.6)**	**1.1 (0.8-1.5)**	**0.7 (0.5-0.9)**
MI light	**1.3 (1.2)**	**1.6 (0.9)**	**1.9 (1.0-2.9)**	**0.8 (0.5-1.0)**
MI heavy	**1.2 (1.1)**	**1.9 (1.1)**	**1.9 (1.4-2.3)**	**1.0 (0.6-1.0)**
VMIQ-2	**3.0 (1.1)**	**1.8 (0.6)**	**1.9 (1.3-2.3)**	**1.6 (1.3-2.5)**

TMS=transcranial magnetic stimulation; MEPs=motor evoked potentials; SD=standard deviation; IQR=interquartile range; CRPS=complex regional pain syndrome; HC=healthy controls; SBF=scaphoid bone fracture (patients); MT=motor threshold; %=percentage stimulus intensity to produce 1mV; MO=motor observation; MI=motor imagery; VMIQ-2=Vividness of Movement Imagery Questionnaire-2