



Differences in Neuronal Representation of Mental Rotation in Patients With Complex Regional Pain Syndrome and Healthy Controls

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Abstract: Spatial integration of parts of the body is impaired in patients with complex regional pain syndrome (CRPS). Because the training of mental rotation (MR) has been shown to be among the effective therapy strategies for CRPS, impairment of MR is also important for the pathophysiological understanding of CRPS. The aim of this study was to evaluate whether differences in the neural representation of MR occur between patients with CRPS and healthy controls (HC). Therefore, we included 15 patients with chronic CRPS and 15 age- and gender-matched HC. We assessed behavioral (accuracy and reaction time for MR of both hands), clinical (Disabilities of Arm, Shoulder and Hand questionnaire) and magnetic resonance imaging (T1-weighted, functional magnetic resonance imaging during MR) data. Reaction times in the patient group were delayed compared with HC without a lateralization effect for the affected hand side. Although both groups showed an activation pattern typical for MR, only HC showed a highly significant contrast for the rotated versus unrotated hands in the right intraparietal sulcus. Patients with CRPS showed a reduction of functional magnetic resonance imaging activation in areas including the subthalamic nucleus, nucleus accumbens, and putamen. Regression analysis for the CRPS group emphasized the importance of putamen and nucleus accumbens activation for MR performance. This study highlights the reduced access of patients with CRPS for mental resources modulating arousal, emotional response, and subcortical sensorimotor integration.

Perspective: This study localized the underlying neural responses for impaired mental rotation in patients with complex regional pain syndrome as a decrease in basal ganglia (putamen) and nucleus accumbens activation.

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Key words: CRPS, mental rotation, body matrix, basal ganglia, nucleus accumbens.

Complex regional pain syndrome (CRPS) affects about 7% of patients after limb trauma⁴ and leads to chronic pain in the affected limb. There is increasing evidence for a pathophysiological involvement of the central nervous system in maintaining CRPS symptoms by altered central sensorimotor processing^{22,53} and pathologic cortical reorganization.^{31,32,43} In

addition, neuropsychological pathologies have been described in CRPS, such as impairment in integrating objects spatially in reference to the own body, and a neglect-like mechanism has been controversially discussed.^{36,56} Patients with CRPS show a generalized delay in mental rotation (MR) decisions without a laterality effect.^{28,44} This MR deficit is part of a disturbance of the

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body matrix, a construct postulated by Moseley et al.³⁵ The integration of external objects into the spatial concept of the body to external objects is processed in the inferior parietal lobe.⁴⁷ In particular, the intraparietal sulcus (IPS) integrates multimodal input into a spatial concept of the body and is crucially involved in MR processes.²⁰ Consequently, it has been postulated that patients with CRPS suffer from a localized functional impairment of the IPS.²⁵

MR of hands—as evaluated via a hand laterality task—involves implicit motor imagery. Subjects are thought to complete the task by mentally simulating a spatial transformation of their own body part,⁴⁰ which involves parietomotor interactions.²⁶ Furthermore, a number of motor areas, such as the premotor cortex and basal ganglia, are involved during tasks of MR of the hands,^{1,13,42} whereas the contribution of the primary motor cortex to the hand laterality task remains a matter of debate.^{11,16} Concurrent motor activation is an important aspect for using MR in the graded motor imagery concept to induce mental movements of the affected limb.³⁰ Consequently, training of MR of the hands has been used for treating patients with CRPS in a behavioral approach.³⁴ However, studies depicting potential differences in neuronal representation during MR in patients with CRPS compared with healthy volunteers are rare and, to date, include the evaluation of only a single case of CRPS.⁵⁵

In addition to spatial integration impairment, patients with CRPS suffer from a number of dysfunctions in motor performance that cannot be solely attributed to immobilization owing to chronic pain.^{3,45} Most patients have postural or action tremor and a high percentage of patients with CRPS develop dystonia of the affected limb (20–30%^{12,8}). Movement disorders, such as dystonia or tremor, are highly suggestive of a profound, possibly widespread, impact of CRPS on the cortical motor system.⁷ For dystonia, the association of symptoms with basal ganglia neuropathology (especially the putamen) has been described for decades.⁶ Because MR of hands and its training involves the putamen,⁵ MR performance impairment might be associated with altered putamen processing in patients with CRPS.

Interestingly, both basal ganglia disturbances, such as essential tremor and dystonia,¹⁰ and chronic neuropathic pain⁹ respond to brain stimulation of the subthalamic nuclei. Together with the thalamus, the cortex, and the subthalamic nuclei, the basal ganglia form a functional pathway³⁷ modulated by long-term depression and potentiation and are thought to be hyperexcitatory in chronic neuropathic pain.²¹ In addition, a decreased activation of the reward system (nucleus accumbens) has been described for these patients, especially during successful performance of cognitive tasks.^{17,49}

The aim of this study was to investigate the neural representation underlying performance differences in MR of the hands in a group of patients with CRPS and healthy controls (HC). We hypothesized that functional magnetic resonance imaging (fMRI) activation in CRPS differs from that of HC in the MR network,

but also in the putamen, thalamus/subthalamus, and nucleus accumbens. In addition, we expected associations between impaired performance and neural processing during MR in patients with CRPS. We, therefore, optimized an fMRI paradigm on MR of the hands, which had been used previously in a longitudinal study⁵ to allow for cross-sectional group comparisons of patients with CRPS and age-matched controls.

Methods

Participant Characteristics

From a previous investigation,⁴³ the reaction time difference for the MR task between HC (average 1,826 ms) and patients with CRPS (average 2,278 ms) showed an effect size (Cohen's *d*) of 1.13. Therefore power analysis (*g**power, version 3.1.3, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), using 1-sided *t*-tests, suggested a sample size of about 18 per group. We here included 15 patients with CRPS (Disabilities of Arm, Shoulder and Hand questionnaire (DASH) average, 54; CRPS severity score = 13; pain intensity 4.4 of 10.0 on a visual analogue scale; age = 58 years; CRPS duration = 21 ± 20 months; Table 1) and 15 age- and gender-matched HC. Education time did not differ between the patients with CRPS and the HC group ($T(28) = 1.80$; $P = \text{NS}$). All participants were free from other neurologic and psychiatric problems as assessed by a neurologist (M.L.). All reported normal or corrected-to-normal vision. Participants were informed that we were investigating functional representations of the limb laterality recognition task. Informed consent was obtained from each study participant for participation in the study.

Measurement of Clinical and Performance Parameters

Handedness of all subjects was measured with the German version of the Edinburgh Handedness Inventory.³⁹ All participants were strongly right handed. The mean laterality quotient in the Edinburgh Handedness Inventory was 90.3 ± 16.9 for the patient group and 93.0 ± 17.6 for the control group. Clinical data were obtained with the German version of the DASH questionnaire.³⁸ This 30-item, self-report questionnaire is an instrument to rate the ability to perform certain daily activities, as well as the severity of symptoms experienced in the preceding week (each item can be scored 1–5). The assigned values were summed and averaged. After the stated analyses protocol, the raw score was then transformed to a 0 to 100 scale, whereby a higher score indicates greater disability. Performance data for the MR task comprised reaction time and decision correctness. The study was approved by the Ethics committee of the Medical Faculty of the University of Greifswald.

Table 1. Overview of Demographic and Clinical Data of Patients With CRPS

PATIENT NO.	AGE	SEX	HANDEDNESS*	AFFECTED LIMB	TIME† OF EDUCATION	GRADUATION‡	INCITING EVENT	CURRENT PAIN (VAS)§	AVERAGE PAIN (VAS)§	CSS	DASH	TIME ONSET¶	MEDICATION
1	76	M	R (100)	L	13	A, B, C	RF	.00	1.0	7	2	72	A
2	44	M	R (70)	R	13	A, B	RF	7.0	7.4	17	59	48	B, D
3	59	F	R (100)	R	12	A, B	RF	1.5	1.5	13	3	4	A
4	58	F	R (90)	R	15	A, B, C	CT	4.1	4.4	12	85	20	B
5	59	F	R (100)	L	13	A, B	RF	2.4	4.3	15	50	22	B, D
6	39	F	R (55)	R	16	A, B, C	RF	2.3	2.4	16	71	8	A, C
7	55	F	R (50)	R	15	A, B	OF	3.0	5.4	15	65	8	—
8	54	M	R (95)	L	12	A, B	CS	5.2	4.8	11	76	42	—
9	59	M	R (100)	R	10	A, B	RF	4.8	7.2	7	69	5	A
10	46	F	R (100)	R	13	A, B	CT	4.9	7.9	14	54	15	—
11	81	F	R (100)	L	8	A	HF	2.9	4.9	14	83	3	A
12	64	M	R (100)	L	16	A, B, C	RF	2.4	2.3	12	41	17	A
13	55	F	R (100)	R	13	A, B	RF	2.0	3.7	6	51	7	—
14	63	M	R (100)	L	18	A, B, C	RF	1.9	4.7	15	57	11	A, B
15	57	M	R (95)	L	16	A, B, C	RF	2.1	4.5	15	52	4	A
Mean	57.9	8F/7M	R (90)	R8/L7	13.53	—	—	3.1	4.4	13	54	19	—
SD	10.5	—	16.8	—	2.56	—	—	1.7	2.0	3.3	24	19.3	—

Abbreviations: VAS, visual analogue scale; CSS, CRPS severity score; DASH: Disability of Arm, Shoulder and Hand Score (higher score = higher disability); M, male; L, left; F, female; R, right; RF, radius fracture; CT, carpal tunnel surgical intervention; OF, olecranon fracture; CS, cervical spine; HF, humerus fracture; SD, standard deviation.

*Edinburg handedness score (all strong right handed)

†Education time in years.

‡Education level: A, middle school; B, high school; C, university.

§Current Pain and Average Pain as measured with a VAS in centimeters (10 = maximum pain).

¶Time from CRPS onset in months

||Medication: A, NSAID, nonsteroidal anti-inflammatory drugs; B, opioid; C, amitriptyline; D, pregabalin.

fMRI Paradigm

During fMRI, we presented pictures of hands in various orientations and participants were asked to decide whether a right or left hand was shown. This design was modified based on 2 previous studies on fMRI investigation on MR of hands^{5,55} (Fig 1A).

For the rotation condition (12 pictures), hands were presented in 3 different orientations (90°, 180°, and 270°; for response time (RT) values see Fig 1B), whereas for the unrotated condition (12 pictures), hands were displayed in their upright position (0°). To balance the scan time between all unrotated and rotated conditions, unrotated hands were shown as often as rotated. RTs rather than error rates were the focus of statistical analysis for the investigation of biomechanical constraints given that previous studies have demonstrated a higher sensitivity of RTs for MR.^{18,41} During scanning, the stimuli were presented using *Presentation* (Neurobehavioral Systems, Albany, California). The task items were backprojected onto a translucent screen and viewed through a mirror affixed to the head coil. The subjects' task was to decide whether the picture on the display represented a left hand or a right hand

(regardless of the orientation). All participants performed 2 runs within the same session. The first run demanded pure MR of hands and did not include a performance control, so participants' hands rested in a standardized immobile dorsal position to avoid motor artifacts. In the second run, the participants had to deliver left/right hand judgments by pressing the respective button on a MR-suitable keypad (LUMItouch, Harvard, Massachusetts) with their right hand. The performance on the keypad was picked up by dual photoelectric barriers and transferred by optical fibers to an electronic processor outside the scanner room. The keystrokes were recorded automatically by the presentation software for RT and accuracy. They were stored in log-files and were evaluated post hoc. For the fMRI experiment, the stimuli were randomly alternated to an event-related design consisting of 48 events per run (24 rotated stimuli intermixed with 24 baseline trials) of the hand laterality task. Images were presented centrally on the screen and remained visible for 5.9 seconds and followed by a resting period varying between 7.9 and 8.9 seconds (fixation cross). The analyses of fMRI data focused on the first run in each session, which did not

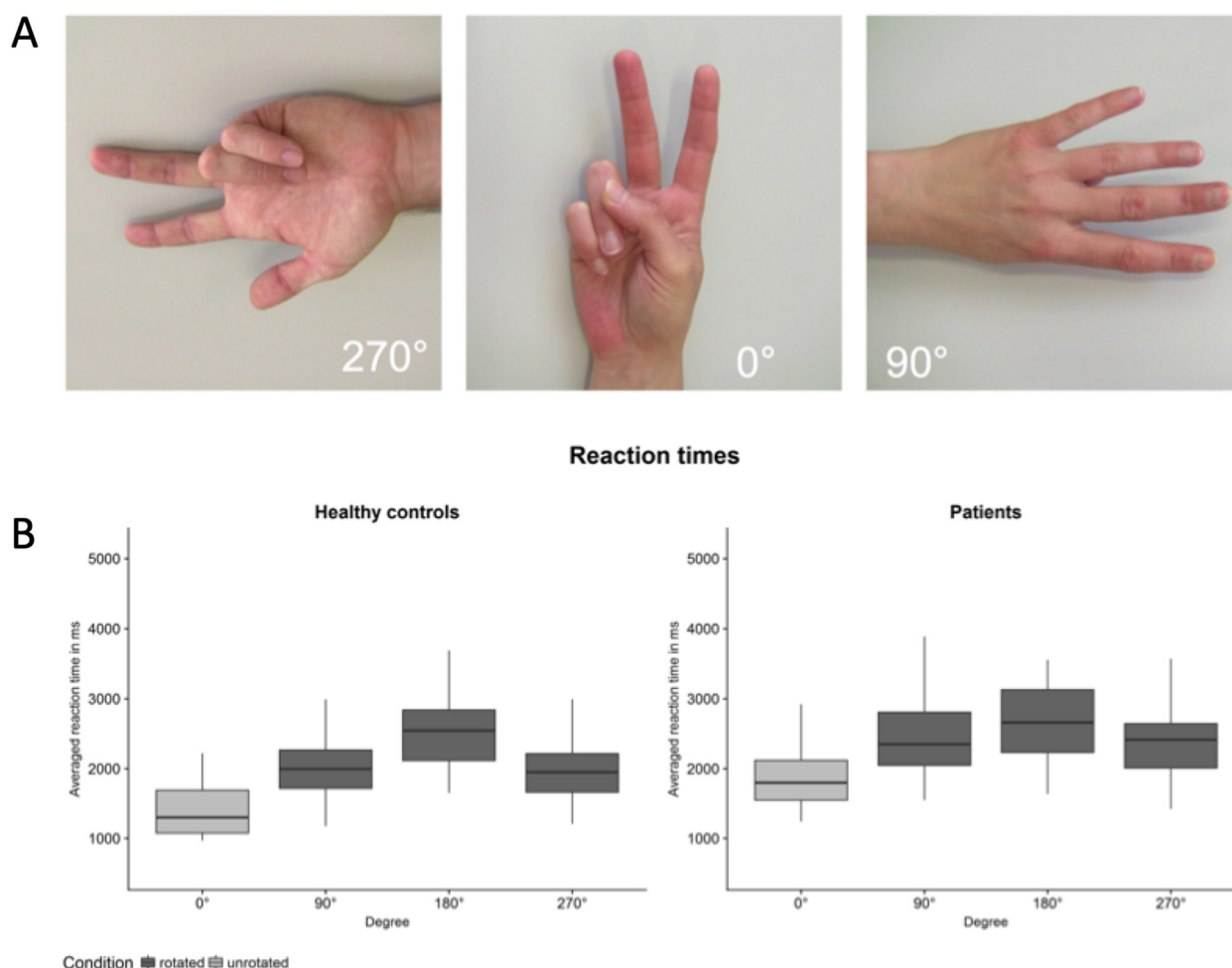


Fig 1. (A) Examples of images in which the patients had to differentiate between right and left hands. An example for an unrotated hand (0°) is shown in the middle. (B) Plotted data for reaction time in milliseconds for MR in HC (left) and CPRS patients (right). For both groups, the reaction time delay with increasing rotation angle from the unrotated (0°) hand picture were present.

include a motor response. Before the scanning session, participants were familiarized with the task outside the scanner. They were not provided with instructions about strategies to use for the MR task and performed 6 trials of left/right hand judgments, which enabled them to perform the task inside the scanner.

Statistical Processing of Behavioral Data

We measured RTs and error rates, which were considered in separate analyses of variance (ANOVAs). Trials in which participants responded incorrectly (error trials: 320/2,580 = 12.40%) and trials with missing responses (33/2,580 = 1.28%) were excluded from RT analyses. Outlier trials for RT were determined separately for each participant and degree condition (0°, 90°, 180°, and 270°): RTs that were 1.5 times the interquartile range above the 75% quantile and below the 25% quantile were defined as outliers and discarded (83/2,580 = 3.21%). Because the total trial number in the rotated (90°, 180°, and 270°) condition matched the trial number in the unrotated condition (0°), the RTs in the rotated condition were averaged. RTs were then analyzed in a $2 \times 2 \times 2$ mixed ANOVA with group (patient/control) as the between-subjects variable and hand (unaffected/affected) and rotation (unrotated/rotated) as the within-subjects variables.

MRI Measurement

MRI was performed with a 3T Magnetom Verio (Siemens, Erlangen, Germany) using a 32-channel head coil. During each of the 2 runs, 433 volumes with 34 slices (1-mm gap) were acquired using echoplanar imaging (repetition time = 2,000 ms; echo time = 30 ms; flip angle = 90°; field of view = 192×192 mm²; matrix size = 64×64 , voxel size = $3 \times 3 \times 3$ mm³). The first 2 volumes in each run were discarded to allow for T1 equilibration effect. T1-weighted structural scans were also acquired (magnetization prepared rapid acquisition gradient echo; repetition time = 1690 ms, echo time = 2.52 ms, flip angle = 9°, matrix size = 256×256 , voxel size = $1 \times 1 \times 1$ mm³). Total imaging time was around 30 minutes.

fMRI Data Preprocessing

fMRI data were analyzed using the SPM 12 software (Wellcome Department of Cognitive Neurosciences, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) running under Matlab (Math Works; Natick, Massachusetts). Spatial preprocessing included realignment to the first scan, unwarping, and coregistration to the T1 anatomic volume images. Unwarping of geometrically distorted echoplanar imaging (EPIs) was performed using the Field Map Toolbox. T1-weighted images were segmented into gray and white matter as well as the cerebrospinal fluid, bias corrected, and spatially normalized using the Segment function of SPM 12. A template normalized image was created with the help of the DARTEL toolbox² and the segmented gray and white matter images from all 30 participants, using linear elastic energy regularization.

This image was then normalized to the Montreal Neurological Institute space using DARTEL's Normalize to Montreal Neurological Institute Space function with the flow fields of the previous step. The same procedure was used to normalize the functional and structural images of every participant. The normalized T1-weighted images were averaged to acquire a structural image representative of the group. Normalized functional images were smoothed using SPM 12 smoothing function with a Gaussian kernel of $6 \times 6 \times 6$ mm³ full width at half maximum to increase the signal-to-noise ratio and decrease intersubject differences.

fMRI Data Statistical Evaluation

Each condition was analyzed using a general linear model with rotated condition (90°, 180°, and 270°) and unrotated condition (0°). Rotated and unrotated conditions were matched for image numbers. Second level fMRI analysis comprised a full factorial model with a $2 \times 2 \times 2$ ANOVA with group (patient/control), condition (unrotated/rotated), and hand (unaffected/affected) as factors. Healthy participants were matched for age, gender, and handedness with patients. The matching of contrast of a right or left presented hand was differentiated for the affected and unaffected hand side. Hereby, for the matched HC, the affected hand side was classified in the same way as in the respective patient. Because no actual movements were executed during the MR task and a specific lateralization effect for the affected side for the MR paradigm was not observed in previous studies, we considered this approach as the most appropriate one. These comparisons were thresholded with a p of $<.05$, applying family wise error correction over the whole brain with additional a cluster threshold of >5 . Relevant results of the ANOVA were followed by t -tests.

For the region of interest analysis, we selected 1) the right IPS, which is essential for cortical integration of visuospatial and motor processes,^{20,54} 2) the bilateral putamen, which is relevant for MR⁵ and symptoms of motor impairment in patients with CRPS,³ and 3) the right nucleus accumbens, showing decreased activation in CRPS⁴⁹ and gray matter atrophy in chronic CRPS.¹⁷

For all these areas (the IPS, putamen, nucleus accumbens) we applied a linear regression analysis, as implemented in SPM 12, to test associations between fMRI activation specific for the MR effect (contrast rotated minus unrotated hand stimuli) and performance in the MR task (RT). Anatomic assignment was performed using ANATOMY (www.fz-juelich.de/inm/inm-1/DE/Home/home_node.html). The subthalamic nucleus mask has been derived from Keuken et al²⁴ and the putamen mask was taken from automated anatomic labeling.⁵¹

Results

Behavioral Data

As expected, correctness of responses (yes–no) was comparable for both groups (Mann-Whitney U test:

$P > .36$). For reaction times, the pattern of delay with increasing rotation effort was observed in both subject groups (Fig 1B). For reaction time, the ANOVA showed main effects of group (HC-CRPS: $F(1,28) = 6.44$; $P = .02$) and condition (unrotated-rotated: $F(1,28) = 251.65$; $P = .0001$), but no main effect for hand (affected-unaffected) ($F(1,28) = 1.86$; $P = .18$). Therefore, for further testing RT values for both hand sides were averaged. We found no significant interactions (Group $\times$ condition: $F(1,28) = 2.96$; $P = .10$; Hand $\times$ Group: $F(1,28) = 2.24$; $P = .16$; Group $\times$ Hand $\times$ Condition: $F(1,28) = .51$; $P = .49$).

Across all stimuli, patients showed longer RTs for decisions than HC (patients: $2,200 \pm 460$ ms; controls: $1,797 \pm 407$ ms; $t(28) = 2.54$; $P = .017$). In more detail, the RT for unrotated hands in patients with CRPS were $1,952 \pm 453$ ms for the unaffected hand side and $1,869 \pm 461$ ms for the affected hand side. For HC, the RTs for the matched hand to the unaffected side was $1,451 \pm 407$ ms and for the matched hand to the affected side $1,493 \pm 398$ ms. The RTs for rotated hands in patients with CRPS were $2,589 \pm 511$ ms for the unaffected hand side and $2,528 \pm 412$ ms for the affected hand side. For HC, the RTs for the matched hand to the unaffected side was $2,264 \pm 489$ ms and for the matched hand to the affected side $2,291 \pm 464$ ms.

Imaging Data: Factor Condition (Rotated vs Nonrotated)

In a factorial design, the factor "condition" (rotated vs nonrotated) showed significant effects for the bilateral IPS, the bilateral premotor cortex, the bilateral middle temporal visual area (MT) (visual area V5), and bilateral insula. A comparison rotated minus nonrotated stimuli revealed a number of frontoparietal effects and V5 (MT; Table 2). The contrast vice versa did not show any significant effect.

Table 2. t-Test: Rotated > Nonrotated Stimuli

REGION	T-VALUE	MONTREAL NEUROLOGICAL INSTITUTE COORDINATE		
		X	Y	Z
SPL le	7.55	-15	-66	52
SPL ri	7.50	24	-63	56
IPS le	6.80	-27	-63	40
IPS ri	7.24	42	-39	44
MT le	6.99	-45	-63	-4
MT ri	6.39	45	-60	-4
dPMC ri	6.99	27	0	52
dPMC le	6.65	-30	3	48
Insula ri	6.36	33	27	-4
Insula le	6.33	-21	21	4
BA 8 ri	6.93	30	3	52
BA 8 le	6.65	-30	3	52
Front inf	6.02	45	30	24
triangular				
Precentral le	5.68	-48	6	32

Abbreviations: SPL, superior parietal lobe; le, left; ri, right; MT, middle temporal visual area; dPMC, dorsal premotor complex; BA, Brodmann area.

Table 3. t-Test: Rotated > Nonrotated Hands for the Healthy Group

REGION	T-VALUE	MONTREAL NEUROLOGICAL INSTITUTE COORDINATE		
		X	Y	Z
IPS ri	5.74	39	-42	48
IPS le	5.48	-15	-66	52
MT le	5.19	-45	-63	-4
dPMC le	5.15	-30	3	48
dPMC ri	6.65	30	3	52

Abbreviations: ri, right; le, left; MT, middle temporal visual area; dPMC, dorsal premotor complex.

We tested the specificity of the stimuli presented for each subject group separately. In the HC group only we found an increased fMRI response for the rotated minus unrotated stimuli in bilateral IPS, left dorsal premotor cortex, and bilateral middle temporal visual area (MT) (Fig 2). No effect was observed in the patient group.

Imaging Data: Factor Group (HC vs Patients with CRPS)

In the factorial design, the factor group showed significant effects for right subthalamic nucleus, left putamen, right nucleus accumbens, left hippocampus, left secondary somatosensory cortex (S2, part OP4), bilateral orbitofrontal cortex, and thalamus. Post hoc t-tests revealed strong effects for HC > patients with CRPS (Table 4; Fig 3), but no significant effect for patients with CRPS minus HC. When investigating only those stimuli with a high cognitive demand on MR (rotated stimuli), we identified an HC minus CRPS fMRI effect in the right subthalamic nucleus ($t = 4.87$; coordinates: 9, -12, -12).

Correlation of Performance, Clinical Scores, and fMRI Activation in Patients With CRPS During MR

In patients with CRPS, the DASH (clinical score) and RT (performance in the MR task) were positively associated ($r = .56$; $P_{\text{corr}} = .03$). The greater the clinical pathology, the worse the performance in MR. In the CRPS patient group, putamen and nucleus accumbens fMRI activation were associated with performance: the faster the MR decision, the higher the fMRI activation in the right putamen ($t = 5.84$; $P_{\text{ROIcorr}} = .01$; coordinates: 12, 9, -4) and bilateral nucleus accumbens (le: $t = 4.29$; $P_{\text{ROIcorr}} = .023$; coordinates: -9, -3, 0; ri: $t = 4.69$; $P_{\text{ROIcorr}} = .013$; coordinates: 12, 6, -4).

Discussion

Herein, we have addressed the neural basis for performance impairments in MR of hands in patients with CRPS of the upper limb. We investigated patients with CRPS and matched controls using an optimized MR/hand lateralization fMRI paradigm. Our paradigm

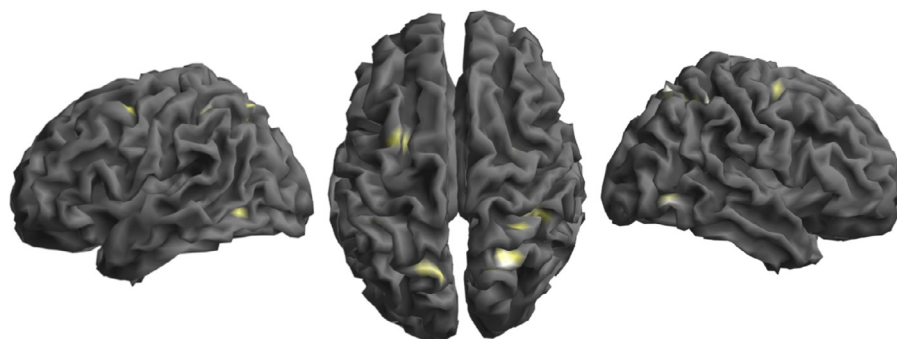


Fig 2. The t-test for HC for the contrast rotated minus unrotated hands showed an increased fMRI activation in bilateral IPS (right > left), bilateral dorsal premotor cortex (dPMC), and left MT ($P_{\text{corr family wise error whole brain}}$). Overall, the stimulus material is highly specific identifying parietal and premotor areas for MR.

robustly identified the well-known premotor–parietal network for MR. Our data showed an overall delay in MR performance in patients with CRPS with no hand laterality effect (affected vs unaffected). Consequently, a hand laterality effect was also absent in fMRI data. Our findings argue against any neglect-like symptoms in patients with CRPS. Patients showed a reduction of fMRI activation during MR in several cortical (orbitofrontal, temporal, inferior parietal/S2), but especially subcortical (subthalamic nucleus, putamen, nucleus accumbens) areas. Our study demonstrated that it is not the MR core network that is decreased in these patients, but rather that there are decreases in the areas modulating arousal, emotional response, and subcortical sensorimotor integration. The modulation aspect of basal ganglia function—especially that of the putamen and the ventral striate—have overall been underestimated in patients with CRPS so far, and should be specifically addressed in future studies.

Across both groups, not only did the known frontoparietal network^{1,13,42} together with the occipital motion-sensitive network show increased fMRI activation during MR, but so did the bilateral insula. Based on

polymodal integration of interoceptive stimuli (pain and temperature regulation, autonomic functions, and somatosensory and vestibular stimuli), the insula is involved in self-awareness of actions and in our sense of limb ownership.²³ This function of the internal monitoring of the body state might be a crucial mechanism in MR tasks. Despite the absence of a motor response in our paradigm, the left precentral gyrus showed a significant increase in activation. However, because this activation was located inferior–anterior to the primary motor cortex hand area, it is probably a more nonspecific premotor contribution.²⁹ Furthermore, the right IPS was maximally involved when contrasting rotated minus nonrotated MR. This finding underlines the special role of this structure, which has been described elsewhere.²⁰

In patients with CRPS, we observed only general effects in comparison with HCs: slower reaction times that were independent of hand side (affected and unaffected) and that were present even for the nonrotated hand stimuli. The general delay in MR decision time observed here is consistent with previous findings.^{28,44} This finding contradicts ideas that suggest a specific impairment of the affected body side, as shown in other spatial tasks (neglect-like syndrome).²⁵ There was no indication for a side-specific neglect³⁶ during MR, which is, therefore, in accordance with the latest findings from Wittayer et al.⁵⁶ This general finding of RT impairment is unlikely to be due to medication use in patients with CRPS. Only 5 patients in our cohort were taking a medication that could explain generalized delay in cognitive tasks, such as opioids or anticonvulsive medication. In a recent study using letters and numbers as control stimuli for MR tasks with different rotation angles, Lee and colleagues²⁷ did not observe a significant delay in reaction times between patients with CRPS and HC.

In addition, we did not observe a between-group effect in areas of the brain that process visuospatial tasks, such as the right parietal lobe and specifically the right IPS. However, in our study the specificity of the right IPS for the rotated minus unrotated task was absent in the group of patients with CRPS. This again points to a more general effect in the patients, for instance, a delay caused by a generally decreased attention to the task, which is supported by the findings that the strongest reaction

Table 4. t-Test: HC > Patients With CRPS

REGION	T-VALUE	MONTREAL NEUROLOGICAL INSTITUTE COORDINATE		
		X	Y	Z
Subthalamic nucleus ri	6.26	9	−12	−12
Putamen ri	6.34	9	−39	12
Putamen le	6.24	−30	−18	0
Midtemp gyrus le	6.15	−62	−57	0
Orbitofrontal le	6.02	−45	30	−4
Fusiform gyrus le	5.47	−21	−45	−16
Secondary somatosensory cortex (S2) le	5.81	−60	−6	16
Nucleus accumbens ri	5.50	9	0	−8

Abbreviations: ri, right; le, left.

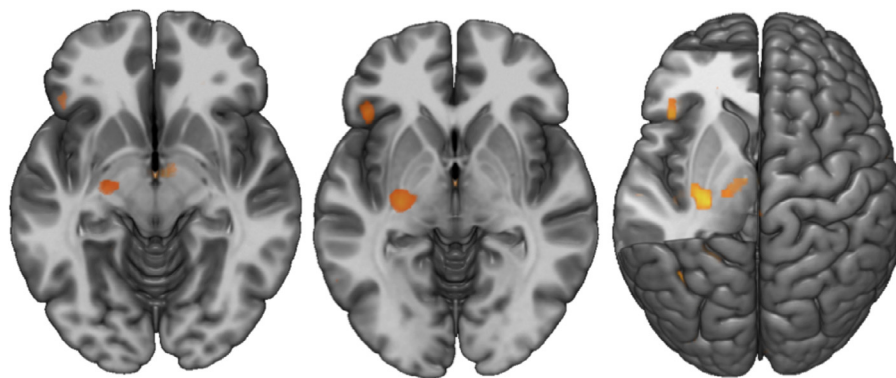


Fig 3. fMRI activation for HC > patients with CRPS (P_{cor} family wise error whole brain) during MR of hands as tested in a 2-sample t-test; fMRI effects are shown in the left putamen, subthalamic nucleus, thalamus, and left lateral orbitofrontal cortex.

time delay observed for the patients in comparison with HC occurred for the unrotated stimuli.

Both the right subthalamic nucleus and bilateral putamen showed the greatest differences in activation between groups. In addition, the right putamen activation was associated with patients' performance (RT in MR). The putamen has been demonstrated to be essential for increasing reaction times during MR also in HC.⁵ In larger CRPS patient cohorts, other investigators have described a high proportion of dystonic symptoms or tremor.^{3,8} It might well be that some of the beneficial effect typically observed during MR training is associated with an improved function of basal ganglia visuospatial and motor integration loops rather than changes in cortical circuits, such as inferior parietal processing. Longitudinal work on MR training in patients with CRPS is essential for further clarification.

The basal ganglia, the subthalamic nucleus, and the thalamus together form a functional pathway³⁷ modulated by long-term depression–like and long-term potentiation–like mechanisms. Their dysfunction may be the reason for hyperexcitability in chronic neuropathic pain.²¹ This hyperexcitability has been described to especially occur in the primary motor cortex^{46,50} in patients with CRPS and has been discussed to be a driver of maladaptive plasticity and chronic pain.¹⁹

For the right nucleus accumbens, patients with CRPS showed a decreased activation during MR that was negatively associated with reaction times. Altered connectivity with prefrontal regions of this area predicts transition to chronic back pain⁵² and its reduced connectivity has also been described in rodent models of neuropathic pain.¹⁴ Pain patients with chronic pain show decreased nucleus accumbens activation during cognitive task performance, pointing to a decrease in the reward cycle in chronic pain.⁴⁸ Furthermore, there is evidence that the nucleus accumbens plays a decisive role in the limbic–motor interface. Based on intensive interconnections to both the limbic (amygdala) and motor systems (prefrontal cortex and basal ganglia), the nucleus accumbens adjusts gain on behavioral output and plays an important role in associative motor learning.³³ As mentioned elsewhere in this article, further work on the role of limbic–motor

integration is necessary to understand the context of chronic pain, MR deficits, and motor deficits in patients with CRPS.

Limitations

This study has some limitations: Although 30 participants have been investigated and there were strong between-group effects and associations between fMRI activation and performance of the patient group, the study would benefit from greater statistical power. In addition, the number of hands presented for the fMRI task ($n = 24$) and for the performance task ($n = 24$) had to be kept small to ensure maximal concentration during task performance. An overall longer RT of patients with CRPS for all stimuli presented necessitates more specific testing with general RTs as a control condition and larger cohorts for enough statistical power to further differentiate stimuli effects. Because years of education, and choice RT are negatively associated,¹⁵ an additional effect of education on RT differences between participant groups cannot be ruled out here. Further studies should carefully control for cognitive and educational effects between samples. In addition, medication might have contributed to a general delay in RTs. However, RTs did not differ between those who received this medication ($2,286 \pm 620$ ms) and those who did not ($2,156 \pm 309$ ms; RT_{all} : $t(13) = .5$; $P = .62$). In larger groups, this factor may become relevant. Furthermore, pain intensity of the present patient cohort was lower than in previous studies investigating MR in patients with CRPS.^{18,43} The low pain intensity may be due to therapeutic intervention before inclusion into the study or a milder form of CRPS.

Conclusions

This study highlights the reduced ability of patients with CRPS to access subcortical resources, such as the subthalamic nucleus, the putamen, and the nucleus accumbens during MR. Because there were no side-specific effects of MR in these patients, this finding speaks against the conceptualization of the symptoms as neglect-like. Likewise, a functional deficit localized in the IPS associated with the representation of the body space in relation to external objects could not be found. Further work is

therefore needed to investigate longitudinal effects of MR, especially in light of the putamen-related changes observed in healthy volunteers. Furthermore, the decrease in fMRI activation in the putamen–subthalamic nuclei–nucleus accumbens circuit is a promising biomarker for predicting the clinical outcome of MR therapy, for example, when MR is implemented in graded motor imagery for therapeutic interventions.

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Supplementary data

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